EU Risk Management Plan for Pradaxa (dabigatran etexilate)

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RMP version to be assessed as part of this application:

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Rationale for submitting an updated RMP:	Removal of the oral solution formulation for the paediatric population
Summary of significant changes in this RMP:	• Removal of the oral solution formulation for the paediatric population and related update of the indication in Part I, module SI, module SVII, and Part VI • Removal of the related important potential risk "Medication error due to complexity of reconstitution of and dosing with the oral solution (paediatric population below 1 year of age)" in module SVII, module SVIII, Part V, and Part VI • Removal of the human factors study from the pharmacovigilance plan in Part III, Part V, Part VI, and Appendix 2 • Removal of the additional risk minimisation measures related to the important potential risk "Medication error due to complexity of reconstitution of and dosing with the oral solution (paediatric population below 1 year of age)" from Part V, Part VI, and Appendix 6 • Removal of Appendix 7b (prescriber guides) and Appendix 7c (patient alert card) to comply with RMP guidance

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PART I PRODUCT OVERVIEW

PI.Table 1 Product Overview

Active substance (INN or common name)	Dabigatran etexilate mesilate (dabigatran etexilate)
Pharmacotherapeutic group (ATC code)	B01AE07
Marketing Authorisation Holder	Boehringer Ingelheim International GmbH
Medicinal product to which this RMP refers	Pradaxa
Invented name in the EEA	Pradaxa
Marketing authorisation procedure	Centrally authorised product
Brief description of the product	*Chemical class* Direct thrombin inhibitor
	Summary of mode of action Dabigatran, the active moiety of dabigatran etexilate, is a novel, synthetic, non-peptidic, potent, competitive, and reversible direct inhibitor of thrombin developed by BI. Since dabigatran is not absorbed via the oral route, dabigatran etexilate, a pro-drug of dabigatran conveying oral bioavailability was synthesised. Dabigatran etexilate itself exerts no antithrombin activity. After absorption following oral intake, dabigatran etexilate is converted via esterases into the active moiety, dabigatran, which inhibits thrombin. Dabigatran etexilate is available as a capsule and coated granules formulation which ensures adequate absorption of dabigatran etexilate also at elevated gastric pH values.
	Important information about its composition Not applicable
Hyperlink to the Product Information	Module 1.3.1, clean version, current sequence

PI.Table 1 (cont'd) Product Overview

Indications in the EEA	*Current* • Primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery (referred to as **pVTEp** for the purpose of this RMP) • Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF), with one or more risk factors, such as prior stroke or transient ischemic attack (TIA); age ≥ 75 years; heart failure (NYHA Class ≥ II); diabetes mellitus; hypertension (referred to as **SPAF** for the purpose of this RMP) • Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults (referred to as **aVTEt/sVTEp** for the purpose of this RMP) • Treatment of VTE and prevention of recurrent VTE in paediatric patients from the time the child is able to swallow soft food to less than 18 years of age (referred to as **paediatric VTE** for the purpose of this RMP)
	Proposed Not applicable.
Dosages in the EEA	*Current* *pVTEp* 220 mg once daily, 150 mg once daily, or 75 mg once daily *SPAF* 150 mg b.i.d. or 110 mg b.i.d. *aVTEt/sVTEp* 150 mg b.i.d. and 110 mg b.i.d. *Paediatric VTE* The recommended dose of Pradaxa is based on the patient's age and weight as indicated in the SmPC.
	Proposed Not applicable.

PI.Table 1 (cont'd) Product Overview

Pharmaceutical form and strengths	*Current* Capsule for oral use; 75 mg, 110 mg, 150 mg. *For paediatric indication:* • Coated granules: 20 mg, 30 mg, 40 mg, 50 mg, 110 mg, and 150 mg • Capsules: 75 mg, 110 mg, and 150 mg SmPC instructions: • Pradaxa capsules can be used in adults and paediatric patients aged 8 years or older who are able to swallow the capsules whole • Pradaxa coated granules can be used in children aged less than 12 years as soon as the child is able to swallow soft food.
	Proposed Not applicable.
Is/will the product be subject to additional monitoring in the EU?	No

ABBREVIATIONS

ATC	Anatomical Therapeutic Chemical
aVTEt/sVTEp	Treatment of DVT and PE, and prevention of recurrent DVT and PE in adults
BI	Boehringer Ingelheim
DVT	Deep vein thrombosis
EEA	European Economic Area
EU	European Union
DLP	Data lock point
INN	International non-proprietary name
MAH	Marketing authorisation holder
NYHA	New York Heart Association
PE	Pulmonary embolism
pVTEp	Primary prevention of VTEs in adult patients who have undergone

	elective total hip replacement surgery or total knee replacement surgery
QPPV	Qualified person pharmacovigilance
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
SPAF	Prevention of stroke and systemic embolism in adult patients with NVAF, with one or more risk factors, such as prior stroke or TIA; age ≥ 75 years; heart failure (NYHA Class ≥ II); diabetes mellitus; hypertension
TIA	Transient ischaemic attack
VTE	Venous thromboembolic event
NVAF	Non-valvular atrial fibrillation

PART II SAFETY SPECIFICATION

MODULE SI EPIDEMIOLOGY OF THE INDICATIONS AND TARGET POPULATIONS

Pradaxa has been approved for the following indications:

- Primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery (referred to as pVTEp in the following)
- Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF), with one or more risk factors, such as prior stroke or transient ischemic attack (TIA); age ≥ 75 years; heart failure (NYHA Class ≥ II); diabetes mellitus; hypertension (referred to as SPAF in the following)
- Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults (referred to as aVTEt and sVTEp, respectively, in the following)
- Treatment of VTE and prevention of recurrent VTE in paediatric patients from the time the child is able to swallow soft food to less than 18 years of age (referred to as paediatric VTE in the following)

SI.1 pVTEp - THR

SI.1.1 Incidence and prevalence

Prevalence estimates are meaningful for chronic conditions, for surgical interventions incidences are preferred. Crude incidence rates of THR per 100 000 inhabitants per year are provided for several European countries, North America, and Australia (SI.Table 1).

SI.Table 1 Crude incidence rates of THRs per 100 000 inhabitants in Europe, North America, and Australia

	Crude rate of THR	Year/period	Reference
Europe			
Austria	272	2012	[R17-1364]
Belgium	237	2012	[R17-1364]
Bulgaria	19.5	2004	[R10-5335]
Croatia	135	2012	[R17-1364]
Cyprus	15	2012	[R17-1364]
Czech Republic	167	2012	[R17-1364]
Denmark	227	2012	[R17-1364]
England	216*	2013/2014	[R17-1484] [R17-1466]
Estonia	92	2012	[R17-1364]
Finland	237	2012	[R17-1364]
France	230	2012	[R17-1364]
Germany	287	2012	[R17-1364]
Greece	168	2012	[R17-1364]
Hungary	137	2012	[R17-1364]
Iceland	173	2012	[R17-1364]
Ireland	118	2012	[R17-1364]
Italy	164	2012	[R17-1364]
Latvia	105	2012	[R17-1364]
Lithuania	127	2012	[R17-1364]
Luxembourg	217	2012	[R17-1364]
Malta	77	2012	[R17-1364]
Netherlands	216	2012	[R17-1364]
Norway	250	2012	[R17-1364]
Poland	78	2012	[R17-1364]
Portugal	88	2012	[R17-1364]
Romania	53	2012	[R17-1364]
Slovak Republic	95	2012	[R17-1364]
Slovenia	189	2012	[R17-1364]
Spain	102	2012	[R17-1364]

SI.Table 1 (cont'd) Crude incidence rates of THRs per 100 000 inhabitants in Europe, North America, and Australia

	Crude rate of THR	Year/period	Reference
Europe (cont'd)			
Sweden	242	2012	[R17-1364]
Switzerland	292	2012	[R17-1364]
UK	177	2012	[R17-1364]
North America			
US	184	2009	[R17-1484]
Canada	139	2013/2014#	[R17-1362]
Australia	154	2009	[R17-1363]

Includes non-elective THR unless stated otherwise;
*2014/15 Hospital episodes of primary and revision of hip replacement using 2015 population in England
age-standardised rates of all total and partial replacements for population age 20 and older

The incidence rates for THR per 100 000 inhabitants by gender in England, Germany, US, Canada, and Australia are shown in SI.Table 2 below.

SI.Table 2 Incidence rates of THR per 100 000 inhabitants by gender in several countries

	Incidence rates per 100 000 inhabitants				
	England, 2014/2015 [R17-1484, R17-1466]	**Germany* 2008** [R10-5129, R10-5337]	**US* 2005/2006** [Appendix 7a]	**Canada#, 2013/2014** [R17-1362]	**Australia, 2008** [R10-5127, R10-5336]
Men	162	159.2	70.0	127#	92.2
Women	268	222.2	80.0	148#	114.0
Total	216	191.3	75.0	139#	103.2

* elective THR
# age-standardised rates of all total and partial hip replacements for population age 20 and older

The distribution of age and gender specific incidence rates of primary THR per 100 000 inhabitants is presented in SI.Table 3 for the US. The incidences are higher in women compared to men. The highest age-specific incidence rate of THR in the US were seen in the age range of 70 to 74 years in men and 75 to 79 years in women undergoing elective THR.

SI.Table 3 Incidence rates of THR per 100 000 inhabitants by age category and gender for 2005/2006 in the US

Incidence rates per 100 000 inhabitants		
	Elective THR (4495 procedures)*	
Age group [years]	**Men**	**Women**
<40	4	4
40 – 44	44	18
45 – 49	69	65
50 – 54	107	73
55 – 59	179	145
60 – 64	181	161
65 – 69	282	342
70 – 74	408	410
75 – 79	303	430
80 – 84	327	363
85 – 89	258	248
≥90	27	78
Total	70	80

*Weighted for sampling scheme of NHDS.
Data source: Appendix 7a

SI.1.2 Demographics of the population in the authorised indication – age, gender, racial and/or ethnic origin and risk factors for the disease

SI.1.2.1 Demographic profile

THRs are more likely to be performed in women and in the elderly.

The percentage of the female patients undergoing THR was 59% in Germany during 2008 [R10-5129], 62% in England during 2008/2009, [R10-5338, R10-5339] 57% in Canada during 2006/2007 [R10-5128], 56% in Australia during 2008 [R10-5127] and 55% in the US during 2006 to 2011 [R17-1276].

The percentage of patients undergoing THR aged 60 years or older was 80% in Germany during 2008 [R10-5129], 82% in England during 2008/2009 [R10-5338, R10-5339], and 68% in the US during 2006 to 2011 [R17-1276]. The percentage of patients undergoing THR aged 65 years or older was 63% in Canada during 2006/2007 [R10-5128] and 64% in Australia during 2008 [R10-5127].

In the US, about 55% of the patients undergoing THR were 65 years or older. The proportion of THR varied by race: White 64.7%, Black 5.0%, other 1.3%, and not stated 29.0% (see Appendix 7a).

SI.1.2.2 Risk factors for the disease

Gender and age are risk factors for THR. The incidence of THR is higher in women compared to men. Age-specific incidence rates of elective THR increase in men until age 70 to 74 years and in women until age 75 to 79 years are summarised in Section SI.1.1.

SI.1.3 The main existing treatment options

The National Institute of Health and CareExcellence in the UK recommends mechanical VTE prophylaxis at hospital admission for patients undergoing elective hip replacement surgery, with any of the following: anti-embolism stockings, foot impulse devices or intermittent pneumatic compression devices that should be continued until the patient's mobility is no longer significantly reduced [P11-09430]. 1 to 12 hours after surgery they recommend the use of 1 of 4 anticoagulants for 28 to 35 days, provided that there is no contraindication. Those are: dabigatran, fondaparinux (factor Xa inhibitor), rivaroxaban, LMWH or UFH. The starting time of anticoagulants is also of importance. Dabigatran should be started 1 to 4 hours after surgery, fondaparinux 6 hours after surgical closure, provided haemostasis has been established, LMWH (or UFH) 6 to 12 hours after surgery and rivaroxaban 6 to 10 hours after surgery [P11-09430]. The American College of Chest Physicians offers similar recommendations but also recommends VKAs and apixaban as options for anti-thrombotic prophylaxis. Anti-thrombotic prophylaxis with pharmacologic therapies is recommended over intermittent pneumatic compression devices [P12-02756]. Treatment options and optimal use are provided in SI.Table 4.

SI.Table 4 Treatment options for the prevention of VTE in patients undergoing THR

Treatment options	**Optimal use of treatment**
Mechanical VTE prophylaxis[*]	At hospital admission
Anti-embolism stockings[*]	Until the patient's mobility is no longer significantly reduced
Foot impulse devices*	Until the patient's mobility is no longer significantly reduced
Intermittent pneumatic compression devices[*#]	Until the patient's mobility is no longer significantly reduced[*] At least 10-14 days[#]

SI.Table 4 (cont'd) Treatment options for the prevention of VTE in patients undergoing THR

Treatment options		Optimal use of treatment
Anti-coagulants	Dabigatran*#	1 to 4h after surgery and for 28 to 35 days* At least 10-14 days#
	Fondaparinux*#	6h after surgical closure and for 28 to 35 days* At least 10-14 days#
	Rivaroxaban*#	6 to 10h after surgery and for 28 to 35 days* At least 10-14 days#
	LMWH or UFH*#	6 to 12h after surgery and for 28 to 35 days* 12h or more preoperative or 12h or more postoperative and for at least 10-14 days#
	VKAs#	At least 10-14 days #
	Apixaban#	At least 10-14 days#
	Aspirin#	At least 10-14 days#

* Recommended by the NICE in the UK

Recommended by the American College of Chest Physicians

SI.1.4 Natural history of the indicated condition in the population, including mortality and morbidity

SI.1.4.1 Mortality

In-hospital mortality after THR was reported as 0.2% in Germany in 2008 [R10-5129] Inpatient mortality following THR was reported for the US using a nationally representative sample weighted to the national population. The inpatient mortality rate was 0.13% during 2007 to 2008. The mortality rate increased with age (0.04% among age 65-79 and 0.4% among age >80) and was higher among males than females (0.2% vs 0.1%, respectively) [R17-1290].

Mortality was studied using existing data from a district general hospital in the UK reporting 7983 THR surgeries during 2000 to 2012. The overall mortality rate was 0.4% and 0.6% at 42 days and 90 days post-THR. Mortality rates decreased over the study period from 0.5% and 0.9% at 42 and 90 days, respectively in 2000/2001, to 0.2% and 0.3% in 2011/2012 [R17-1275].

Mortality in Sweden following bilateral THR was captured in SHAR during 1992 to 2012. The mortality rate was 0.1% within 30 days after second surgery, 0.3% within 90 days, 1.2% within 1 year, and 14.7% within 10 years [R17-1288].

In the US, the NSQIP 30-day post THR mortality was 0.4% among 17 640 patients from 2006 to 2011 [R17-1276].

In Australia the mortality rate after THR was 2.2 (95% CI: 2.16 - 2.24) per 100 PY during the period of 1999 to 2008 [R10-5127].

SI.1.4.2 Morbidity

Patients undergoing THR are at higher risk of VTE because they are expected to have significant reduction in mobility. The risk is also increased if they have any VTE risk factor present (see Section SI.4) and if the total anaesthetic and surgical time is longer than 90 minutes [P11-09430, R17-1276].

The profile of potential health risks following hip replacement surgery includes perioperative and postoperative complications, complications of medical care and complications affecting specific body systems. The cumulative incidence of procedure-related complications (ICD-9-CM codes 996 to 999) among discharges undergoing THR from 2006 to 2011 is given in SI.Table 5 Postoperative sepsis was the most common major systemic complication (0.47%) followed by PE (0.31%).

Increased BMI, diabetes, cardiovascular conditions, hypertension, pulmonary disease, and rheumatoid arthritis can increase the risk of complications, hospital readmission, and mortality following THR [R17-1299, R17-1276].

SI.Table 5 Incidence of major/minor systemic and local complications within 30 days of THR (17 640 procedures) in the US for 2006 to 2011

	30-day post THR Surgery incidence (%)
Major systemic complications	
PE	0.31
Other system complication	0.29
Postoperative sepsis	0.47
Septic shock	0.12
Cerebrovascular accident	0.17
Acute renal failure	0.07
Cardiac arrest requiring cardiopulmonary resuscitation	0.12
Myocardial infarction	0.24
Minor systemic complications	
Urinary tract infection	1.45
DVT	0.51
Pneumonia	0.42
Renal insufficiency	0.14
Major local complications	
Deep wound infection	0.51
Peripheral nerve injury	0.11
Perioperative fracture	0.12
Graft/prosthesis failure	0.07
Minor local complications	
Superficial wound infection	0.83
Wound dehiscence	0.14

Data source: [R17-1276]

SI.1.5 Important co-morbidities

DVT

Incidence and prevalence of DVT

Thromboembolic events are acute conditions and their occurrence is better described with incidence rates.

Incidences of DVT from several studies are described in SI.Table 6 below.

SI.Table 6 Cumulative incidence in % of DVT after THR

Country **Study period**	**Time period after surgery**	**Cumulative incidence of DVT (%)**	**Reference**
Norway 1989 – 2001	6 months	1.6	[R08-4738]
Scotland 1992- 2001	90 days	2.3*	[R08-4740]
Australia 1995 – 2001	7 days	8.9	[R09-5182]
US 1986 – 1995	30 days	1.3	[R08-4651]
US 2006-2011	30 days	0.5	[R17-1276]

* Includes both DVT and PE.

The incidence of DVT in a nationally representative sample of THR inpatients in the US during 2001 to 2011 is provided in SI.Table 7.

SI.Table 7 Cumulative incidence of DVT in patients undergoing THR from 2001 to 2009

Year	**Incidence of DVT (%)**
2001	0.55
2002	0.45
2003	0.38
2004	0.46
2005	0.42
2006	0.39
2007	0.33
2008	0.34
2009	0.27
2010	0.24
2011	0.24
Data source: [R17-1283]	

In addition, in an observational study based on existing data during 2004 to 2008 in the US 45 203 patients with hip replacement were followed up for a median of 70 days. The incidence per 1000 PY of DVT was 27.8 (95% CI: 24.4 - 31.6) [R11-4338].

Mortality of DVT

In a study based on existing inpatient data from the US NIS during the 2001 to 2011, the rate of inpatient mortality in THR patients with DVT was 1.7% compared to 0.2% in patients without DVT [R17-1283].

Co-medication

The patients after THR or TKR were prescribed LMWH (88%) or warfarin (12%) during the hospital stay, Australia, 1995 to 2001 [R09-5182].

A study on patients aged 65 years or older discharged home after THR or TKR in Canada, between 1997 and 2004, showed that 19% of the patients received thromboprophylaxis at discharge [R08-4652].

Hypertension

Incidence and prevalence of hypertension

Hypertension is a common and chronic co-morbidity and therefore is better described by its prevalence, see below.

The prevalence of hypertension among discharges undergoing THR during 2006 to 2011 in the US was 58.4% [R17-1276]. Among a large healthcare delivery system in the US (Colorado), 20.6% of patients undergoing THR and receiving warfarin during 2005 to 2009 had hypertension [R17-1282]. A study on patients aged 65 years or older discharged home after THR or TKR in Canada, between 1997 and 2004, showed that 41% of the patients had hypertension at baseline [R08-4652].

Mortality of hypertension

No data on mortality from hypertension found in the target population. However, in a follow up of 24 638 patients after THR during 1980 and 1995 in Finland 54% of the deaths were attributed to diseases of the circulatory system [R10-5302].

Co-medication

A retrospective study investigated 285 patients who underwent TKR or THR in Pittsburgh, US between March 2006 and June 2006. 62% of the patients had hypertension and at least one medication prescribed. Of these 32% received diuretics, 29% ACE inhibitors, 26% calcium channel blocker, 45% beta-blocker, and 21% ARBs [R10-5299].

Pulmonary disease

Incidence and prevalence of pulmonary disease

There were no data on incidence of pulmonary disease found in the target population.

The prevalence of pulmonary disease among discharges undergoing THR during 2002 to 2006 in the US was 12% (Appendix 7a) and 4.4% for COPD during 2006 to 2011 [R17-1276].

Mortality of pulmonary disease

No data on mortality of pulmonary disease found in the target population. However, in a follow up of 24 638 patients after THR during 1980 and 1995 in Finland, 5.5% of the deaths were attributed to diseases of the respiratory system [R10-5304].

Co-medication

There were no data on co-medication for pulmonary disease found in the target population.

Diabetes mellitus

Incidence and prevalence of diabetes mellitus

Diabetes mellitus is a common and chronic co-morbidity and therefore is better described by its prevalence, see below.

The prevalence of diabetes mellitus of among patients undergoing THR during 1996 to 2005 in Denmark was 6% [R10-5298]. A study on patients aged 65 years or older discharged home after THR or TKR in Canada, between 1997 and 2004, showed that 13 % of the patients had diabetes at baseline [R08-4652]. The prevalence of diabetes mellitus among discharges undergoing THR between 2006 and 2011 in the US was 11.3% [R17-1276].

Mortality of diabetes mellitus

In a follow up of 24 638 patients after THR during 1980 and 1995 in Finland, 0.6% of the deaths were attributed to diabetes [R10-5304].

Co-medication

There were no data on co-medication for diabetes mellitus found in the target population.

Hypercholesterinaemia

Incidence and prevalence of hypercholesterinaemia

There were no data on the incidence of hypercholesterinaemia found in the target population.

The prevalence of hypercholesterinaemia among discharges undergoing THR during 2002 to 2006 in the US was 9% (Appendix 7a).

Mortality of hypercholesterinaemia

There were no data on mortality of hypercholesterinaemia found in the target population.

Co-medication

There were no data on co-medication for hypercholesterinaemia found in the target population.

Coronary artery disease

Incidence and prevalence of coronary artery disease

There were no data on incidence of coronary artery disease found in the target population but the prevalence of coronary artery disease among discharges undergoing THR during 2002 to 2006 in the US was 10% (Appendix 7a).

Mortality of coronary artery disease

No data on mortality of coronary artery disease were found in the target population. However, in a follow up of 24 638 patients after THR during 1980 and 1995 in Finland, 54% of the deaths were attributed to diseases of the circulatory system [R10-5304].

Co-medication

There were no data on co-medication for coronary artery disease found in the target population.

Obesity

Incidence and prevalence of obesity

There were no data on incidence of obesity found in the target population.

The prevalence of obesity among discharges undergoing THR during 2006 to 2011 in the US was 35.3% for BMI 30-39.90 kg/m^2 and 7% for BMI ≥40 kg/m^2 [R17-1276]. In Canada about

37% of patients undergoing THR in 2006 to 2007 were classified as obese (BMI ≥30 kg/m^2) [R10-5128].

Mortality of obesity

Obesity increases the risk of several other cardiovascular and endocrinological diseases. Please refer to mortality data on the respective co-morbid conditions.

Co-medication

There were no data on co-medication for obesity found in the target population.

SI.2 pVTEp – TKR

SI.2.1 Incidence and prevalence

Prevalence estimates are meaningful for chronic conditions, for surgical interventions incidences are more appropriate. Crude incidence rates of TKR per 100 000 inhabitants per year are provided for selected European countries, North America, and Australia (SI.Table 8).

SI.Table 8 Number of procedures and crude incidence rates of TKR per 100 000 inhabitants in Europe, North America, and Australia

	Crude rate of TKR	Year/Period	Reference
Europe			
Austria	217	2012	[R17-1364]
Belgium	184	2012	[R17-1277]
England	130.7	2008/2009	[R10-5338, R10-5339]
Croatia	48	2012	[R17-1277]
Cyprus	53	2012	[R17-1277]
Czech Republic	116	2012	[R17-1277]
Denmark	171	2012	[R17-1277]
Finland	206	2012	[R17-1277]
France	139	2012	[R17-1277]
Germany	206	2012	[R17-1277]
Hungary	59	2012	[R17-1277]
Italy	104	2012	[R17-1277]
Iceland	90	2012	[R17-1277]
Ireland	47	2012	[R17-1277]
Latvia	46	2012	[R17-1277]
Lithuania	68	2012	[R17-1277]
Luxembourg	173	2012	[R17-1277]
Malta	162	2012	[R17-1277]
Netherlands	118	2012	[R17-1277]
Norway	132	2012	[R17-1277]
Poland	24	2012	[R17-1277]
Portugal	62	2012	[R17-1277]
Romania	17	2012	[R17-1277]
Slovenia	112	2012	[R17-1277]
Spain	105	2012	[R17-1277]
Sweden	140	2012	[R17-1277]
Switzerland	176	2012	[R17-1277]
UK	139	2012	[R17-1277]

SI.Table 8 (cont'd) Number of procedures and crude incidence rates of TKR per 100 000 inhabitants in Europe, North America, and Australia

	Crude rate of TKR	Year/Period	Reference
North America			
US	213	2009	[R17-1363]
Canada	205	2014/2015	[R17-1361]
Australia	158	2009	[R17-1363]

Includes non-elective TKR unless stated otherwise;
*elective TKR# age-standardised rates of all total and partial knee replacements for population age 18 and older
n/a = not provided

The incidence rates for TKR per 100 000 inhabitants by gender in England, Germany, US, Canada, and Australia are shown in SI.Table 9. The distribution of age and gender specific incidence rates of primary TKR per 100 000 inhabitants is presented in SI.Table 10 for the US. The incidences are higher in women compared to men. The highest age-specific incidence rate of TKR in the US was in the age band of 75 to 79 years in men and 70 to 74 years in women undergoing elective TKR.

Incidence rates of TKR have been increasing over time in the US. For adults aged 45 to 64 years, rates of TKR increased from 140 per 100 000 inhabitants during 1995 to 330 per 1000 inhabitants during 2008. Incidence rates for adults aged 65 years and older increased from 520 per 100 000 inhabitants during 1999 to 910 per 100 000 inhabitants during 2008 [R17-1277].

SI.Table 9 Incidence rates of TKR per 100 000 inhabitants by gender in several countries

	Crude incidence rates per 100 000 inhabitants				
	England 2008/09 [R10-5338, R10-5339]	**Germany* 2008** [R10-5129, R10-5337]	**US* 2005/2006** [Appendix 7a]	**Canada 2014/2015** [R17-1361]	**Australia 2008** [R10-5127, R10-5336]
Men	111.2	119.5	131	172#	130.2
Women	149.6	234.5	230	236#	171.4
Total	130.7	178.1	181	205#	150.9

* elective TKR
# age-standardised rates of all total and partial knee replacements for population age 18 and older

SI.Table 10 Incidence rates of TKR per 100 000 inhabitants by age category and gender for 2005/2006 in the US

Incidence rates per 100 000 inhabitants		
	Elective TKR (10 017 procedures)*	
Age group [years]	**Men**	**Women**
<40	2	1
40 – 44	19	40
45 – 49	48	89
50 – 54	130	243
55 – 59	283	488
60 – 64	449	703
65 – 69	686	1187
70 – 74	855	1293
75 – 79	997	1127
80 – 84	651	804
85 – 89	440	429
≥90	256	102
Total	**131**	**230**

*Weighted for sampling scheme of NHDS.
Data source: Appendix 7a

SI.2.2 Demographics of the population in the authorised indication –age, gender, racial and/or ethnic origin and risk factors for the disease

SI.2.2.1 Demographic profile

TKRs are more likely to be performed in women and in the elderly.

The percentage of the female patients undergoing TKR was 67% in Germany during 2008 [R10-5129], 58% in England during 2008/2009 [R10-5338, R10-5339], 64% in Denmark, 70% in Norway and 63% in Sweden during 1997 to 2007 [R11-4743], 65% in the US during 2005 to 2010 [R17-1315], 61% in Canada during 2006/2007 [R10-5128] and 57% in Australia during 2008 [R10-5127].

The percentage of patients undergoing TKR aged 60 years or older was 87% in Germany during 2008 [R10-5129], 86% in England during 2008/2009 [R10-5338; R10-5339]. The percentage of patients undergoing TKR aged 65 or older was 77% in the US during 2005 to 2010 [R17-1315], 64% in Canada during 2006/2007 [R10-5128], and 66% in Australia during 2008 [R10-5127].

In the US during 2005/2006 the proportion of TKR varied by race: White 64%, Black 6%, other 2%, and unknown 28% (see Appendix 7a).

SI.2.2.2 Risk factors for the disease

Gender and age are risk factors for TKR. The incidence of THR is higher in women compared to men. Age-specific incidence rates of elective THR increase in both men and women until age 70 to 75 years are summarised in Section SI.2.1.

SI.2.3 The main existing treatment options

The National Institute of Health and CareExcellence in the UK recommends mechanical VTE prophylaxis at hospital admission for patients undergoing elective knee replacement, with any of the following: anti-embolism stockings, foot impulse devices or intermittent pneumatic compression devices that should be continued until the patient's mobility is no longer significantly reduced. 1 to 12 hours after surgery they recommend the use of 1 of 4 anticoagulants for 10 to 14 days, provided that there is no contraindication. Those are: dabigatran, fondaparinux (factor Xa inhibitor), rivaroxaban, LMWH or UFH. The starting time of anticoagulants is also of importance. Dabigatran should be started 1 to 4 hours after surgery, fondaparinux 6 hours after surgical closure, provided haemostasis has been established, LMWH (or UFH) 6 to 12 hours after surgery and rivaroxaban 6 to 10 hours after surgery [P11-09430]. The American College of Chest Physicians offers similar recommendations, but also recommends VKAs and apixaban as options for anti-thrombotic prophylaxis. Anti-thrombotic prophylaxis with pharmacologic therapies is recommended over intermittent pneumatic compression devices [P12-02756]. Treatment options and optimal use are provided in SI.Table 11 with VKA instead of dabigatran and without rivaroxaban [R08-2897].

SI.Table 11 Treatment options for the prevention of VTE in patients undergoing TKR

Treatment options		**Optimal use of treatment**
Mechanical VTE prophylaxis*		At hospital admission
Anti-embolism stockings*		Until the patient's mobility is no longer significantly reduced
Foot impulse devices*		Until the patient's mobility is no longer significantly reduced
Intermittent pneumatic compression devices*		Until the patient's mobility is no longer significantly reduced
Anti-coagulants	Dabigatran*#	1 to 4h after surgery and for 10 to 14 days
	Fondaparinux*#	6h after surgical closure and for 10 to 14 days
	Rivaroxaban*#	6 to 10h after surgery and for 10 to 14 days
	LMWH or UFH*#	6 to 12h after surgery and for 10 to 14 days# 12h or more preoperative or 12h or more postoperative*
	VKAs#	At least 10-14 days
	Apixaban#	At least 10-14 days

* Recommended by the NICE in the UK

Recommended by the American College of Chest Physicians

SI.2.4 Natural history of the indicated condition in the population, including mortality and morbidity

SI.2.4.1 Mortality

In hospital mortality after TKR was reported as 0.1% in Germany in 2008 [R10-5129] and 0.2% in the US during 2002 to 2006 (see also Appendix 7a).

In the US, the NSQIP 30-day post TKR mortality was 0.18% among 15 321 patients from 2006 to 2010 [R17-1315].

In Australia the mortality rate for TKR was 1.9 (95% CI: 1.83 - 1.90) per 100 PY during the period of 1999 to 2008 [R10-5127].

SI.2.4.2 Morbidity

Patients undergoing TKR are at higher risk of VTE because they are expected to have significant reduction in mobility. The risk is also increased if they have any VTE risk factor present (see Section SI.4) and if the total anaesthetic and surgical time is longer than 90 minutes [P11-09430, R17-1315]).

The profile of potential health risks following knee replacement surgery includes peri-operative and post-operative complications, complications of medical care and complications affecting specific body systems. The cumulative incidence of procedure related complications (ICD-9-CM codes 996 to 999) among discharges undergoing TKR from 2006 to 2010 are given in SI.Table 12. PE was the most common major systemic complication of TKR with 0.78%.

SI.Table 12 Incidences of major/minor systemic and local complications within 30 days of TKR (15 321 procedures) in the US for 2006 to 2010

	30-day post THR Surgery incidence (%)
Major systemic complications	
PE	0.78
Other system complication	0.46
Postoperative sepsis	0.44
Septic shock	0.13
Cerebrovascular accident	0.11
Acute renal failure	0.10
Cardiac arrest requiring cardiopulmonary resuscitation	0.09
Minor systemic complications	
Urinary tract infection	1.49
DVT	1.34
Pneumonia	0.37
Renal insufficiency	0.12
Major local complications	
Deep wound infection/organ space infection	0.30
Peripheral nerve injury	0.10
Minor local complications	
Superficial wound infection	0.79
Wound dehiscence	0.27

Data source: [R17-1315]

SI.2.5 Important co-morbidities

DVT

Incidence and prevalence of DVT

Thromboembolic events are acute conditions. The occurrence is better described with incidence rates. Incidences of DVT after TKR from several studies are described in SI.Table 13 below.

SI.Table 13 Cumulative incidence in % of DVT after TKR

Country	Study period	Time period after surgery	Cumulative incidence of DVT (%)	Reference
Norway	1989 - 2001	6 months	1.5	[R08-4738]
Scotland	1992 - 2001	90 days	1.8*	[R08-4740]
Australia	1995 - 2001	7 days	25.6	[R09-5182]
US	2005 - 2009	90 days	0.7#	[R17-1281]

* Includes both DVT and PE

includes patients with DVT and DVT concurrent with PE

A downward trend in the incidence of DVT was observed over the 2001 to 2011 time period in a nationally representative sample of TKR inpatients in the US (SI.Table 14).

SI.Table 14 Cumulative incidence in % of DVT in patients undergoing TKR from 2001 to 2011

Year	Rate of DVT (%)
2001	0.86
2002	0.82
2003	0.64
2004	0.84
2005	0.66
2006	0.55
2007	0.56
2008	0.57
2009	0.47
2010	0.41
2011	0.45
Data source: [R17-1283]	

In addition, in an observational study based on existing data during 2004 to 2008 in the US 97 469 patients with knee replacement were followed up for a median of 70 days. The incidence per 1000 PY of DVT was 39.2 (95% CI: 36.45 - 42.1) [R11-4338].

Mortality of DVT

In a study using existing data from the US NIS during the 2001 to 2011, the rate of inpatient mortality in TKR patients with DVT was 0.4% compared with 0.1% in patients without DVT [R17-1283].

Co-medication for DVT in TKR is described in Section SI.1.5.

Hypertension

Incidence and prevalence of hypertension

Hypertension is a common and chronic co-morbidity and therefore is better described by its prevalence.

The prevalence of hypertension among discharges undergoing TKR during 2002 to 2006 in the US was 58% (Appendix 7a). A study on patients aged 65 years or older discharged home after THR or TKR in Canada, between 1997 and 2004, showed that 41% of the patients had hypertension at baseline [R08-4652]. Using existing data from a large healthcare delivery system in the US (Colorado) during 2005 to 2009, 59.5% of patients undergoing initial TKR

and receiving warfarin had hypertension [R17-1281]. In the NIS during 2007, the prevalence of hypertension in 516 745 patients undergoing TKR in the US was 67.8% [R17-1302].

Mortality of hypertension

No data on mortality of hypertension were found in the target population. However, in a follow up of 57 979 patients after TKR during 1980 and 2002 in Sweden 54% of the deaths were attributed to diseases of the circulatory system [R10-5300].

Co-medication

See Section SI.1.5.

Pulmonary disease

Incidence and prevalence of pulmonary disease

There were no data on incidence of pulmonary disease found in the target population.

The prevalence of pulmonary disease among discharges undergoing TKR during 2002 to 2006 in the US was 11% (Appendix 7a).

Mortality of pulmonary disease

No data on mortality of pulmonary disease found in the target population. However, in a follow up of 57 979 patients after TKR during 1980 and 2002 in Sweden, 5.5% of the deaths were attributed to diseases of the respiratory system [R10-5300].

Co-medication

There were no data on co-medication for pulmonary disease found in the target population.

Diabetes mellitus

Incidence and prevalence of diabetes mellitus

Diabetes mellitus is a common and chronic co-morbidity and therefore is better described by its prevalence, see below.

The prevalence of diabetes mellitus among discharges undergoing TKR during 2002 to 2006 in the US was 17% (Appendix 7a). A study on patients aged 65 years or older discharged home after THR or TKR in Canada, between 1997 and 2004, showed that 13 % of the patients had diabetes at baseline [R08-4652]. Using existing data from a large healthcare delivery system in the US (Colorado), 14.5% of patients undergoing initial TKR and receiving warfarin during 2005 to 2009 had diabetes mellitus [R17-1281]. In the NIS during

2007, the prevalence of diabetes in 516 745 patients undergoing TKR in the US was 20.0% [R17-1302].

Mortality of diabetes mellitus

In a follow up of 57 979 patients after TKR during 1980 and 2002 in Sweden, 2.1% of the deaths were attributed to diseases of the endocrine/metabolism [R10-5300].

Co-medication

There were no data on co-medication for diabetes mellitus found in the target population.

Hypercholesterinaemia

Incidence and prevalence of hypercholesterinaemia

There were no data on incidence of hypercholesterinaemia found in the target population. The prevalence of hypercholesterinaemia among discharges undergoing TKR during 2002 to 2006 in the US was 9% (Appendix 7a).

Mortality of hypercholesterinaemia

There were no data on mortality of hypercholesterinaemia found in the target population.

Co-medication

There were no data on co-medication for hypercholesterinaemia found in the target population.

Coronary artery disease

Incidence and prevalence of coronary artery disease

There were no data on incidence of coronary artery disease found in the target population. The prevalence of coronary artery disease among discharges undergoing TKR during 2002 to 2006 in the US was 11% (Appendix 7a).

Mortality of coronary artery disease

No data on mortality of coronary artery disease were found in the target population. However, in a follow up of 57 979 patients after TKR during 1980 and 2002 in Sweden 54% of the deaths were attributed to diseases of the circulatory system [R10-5300].

Co-medication

There were no data on co-medication for coronary artery disease found in the target population.

Obesity

Incidence and prevalence of obesity

There were no data on incidence of obesity found in the target population.

The prevalence of obesity among discharges undergoing TKR during 2002 to 2006 in the US was 10% (Appendix 7a). The NIS reported the prevalence of obesity among inpatients undergoing TKR increasing annually to 20.1% in 2009 [R17-1306].

In Spain, the prevalence of obesity among patients undergoing TKR at one clinic during 2009 to 2011 was 54.7%. Among 922 patients undergoing TKR, 36% had BMI between 30 and 34.9 kg/m^2 and 18.7% had BMI ≥ 35 kg/m^2 [R17-1298].

In Canada, about 54% of patients undergoing TKR in 2006 to 2007 were classified as obese (BMI ≥30 kg/m2) [R10-5128].

Mortality of obesity

Obesity increases the risk of several other cardiovascular and endocrinological diseases. Please refer to mortality data on the respective co-morbid conditions.

Co-medication

There were no data on co-medication for obesity found in the target population.

SI.3 SPAF

SI.3.1 Incidence and prevalence

Incidence of AF

The incidence rate of AF is strongly associated with age, gender and the presence of cardiovascular co-morbidities. The overall incidence rate of AF was 9.9 per 1000 PY (95% CI: 9.0, 10.9) among adults aged ≥55 years in the Netherlands during 1990 to 1999 [R09-4875]. In the UK, the standardised incidence rate of AF was 6.7 (95% CI: 6.7 – 6.8) per 1000 PY among patients aged 45 and older during 2001 to 2013 [R17-1303] and 0.9 per 1000 PY among patients of all age in primary care practices in Scotland, 2001 to 2002 [R10-4270]. In Denmark, the annual age- and sex-standardised incidence of AF increased from 2.0 per 1000 PY in 1980 to 4.5 per 1000 PY in 1999 [R09-2457]. In Quebec, Canada, the population-based incidence of NVAF during 2004 was 3.28 per 1000 population (95% CI: 3.27 - 3.29) [R17-1322]. Using existing data from I3/Innovus, a 5% sample of commercial or

Medicare advantage health plans in the US during 2001 to 2008, the age and sex-adjusted incidence rate was 3.5 per 1000 PY in 2007, up from 2.2 per 1000 PY in 2002 [R17-1285].

Incidence of AF by gender and age

The incidence rate of AF is higher among men than women. In the UK, based on data from the CPRD, incidence in men was 6.6 per 1000 PY (95% CI: 6.5 -6.6) and 5.9 per 1000 PY (95% CI: 5.9 -6.0) in women [R17-1303]. In Germany, the incidence rate of AF based on data from 2 statutory health insurance funds during 2008 was 4.4 per 1000 PY among men and 3.9 per 1000 PY among women [R17-1316].

Incidence of AF increases with age and markedly increases after about age 50.

- In Quebec, Canada incidence rates of NVAF rise from 0.9% (95% CI: 0.9 – 0.9) at age 40-49 to 31.7% (95% CI: 31.5 – 32.0) at age ≥80 [R17-1322].
- In the UK, based on data from a CPRD study, incidence rates increased from 0.6 per 1000 PY (95% CI: 0.5 -0.6) among people aged 45–49 years to 25.1 per 1000 PY (95% CI: 24.8 -25.4) at age 80–89 years and 40.6 per 1000 PY (95% CI: 39.8 - 41.4) in age ≥90 years [R17-1303].
- In Germany, the incidence rate of AF increased with age from 13.2 per 1000 PY (95% CI: 12.8 -13.6) in adults aged 65-69 years to 67.7 per 1000 PY (95% CI: 61.8 -74.2) in age group ≥ 90 years [R17-1307].

The incidence rates of AF by age and gender in a community- based study in Minnesota, US are in SI.Table 15. No temporal trends were seen in age adjusted incidence rates per 1000 population from 2000 (2.99 per 1000 population [95% CI: 2.61 – 3.38]) to 2010 (3.23 per 1000 population [95% CI: 2.89 – 3.58]) [R17-1280].

SI.Table 15 Gender and age-specific incidence rates (95% CI) of AF per 1000 population

Country	US (Minnesota, Olmsted County)	
Study period	2000-2010	
Age group [years]	Women	Men
18 – 59	0.4 (0.3 – 0.4)	0.9 (0.8 - 1.0)
60 – 69	3.9 (3.4 – 4.4)	7.4 (6.7 – 8.2)
70 – 79	10.7 (9.7 – 11.8)	15.2 (13.9 - 16.6)
≥80	23.4 (21.8 – 25.1)	25.6 (23.3 – 28.1)
Data source: [R17-1280]		

The Framingham Heart Study followed participants in the US from 1958 to 2007 assessing trends in AF incidence. Age-adjusted incidence rates of AF increased in both men and women. The age-adjusted incidence rate in men increased from 3.7 per 1000 PY in the cohort from 1958-1967 to 13.4 per 1000 PY in the 1998-2007 cohort. In women, the age-adjusted incidence rate increased from 2.5 per 1000 PY in the cohort from 1958-1967 to 8.6 per 1000 PY in the 1998-2007 cohort [R17-1326].

The incidence rates of AF by age and gender in 2 population-based studies in the Netherlands and in the US are shown in SI.Table 16 below.

The incidence increases with age and is higher in men than in women, as well as in Whites than in Afro-Americans in each age group [R09-4875, R10-4274].

SI.Table 16 Gender and age-specific incidence rates (95% CI) of AF per 1000 PY by country and study period

	Rotterdam Study [R09-4875]		ARIC Study [R10-4274]			
Country	Netherlands		USA			
Study period	1990 to 1999		1987 to 2004			
Race	NA		Whites		African-Americans	
Age group [years]	Women	Men	Women	Men	Women	Men
45 – 49			0	1.4	0.4	0.7
50 – 54			0.7	2.3	0.5	0.9
55 – 59	--	2.6 (0.7 - 7.0)	1.7	3.7	1.2	1.4
60 – 64	2.1 (1.1 - 3.7)	4.9 (2.9 - 7.6)	3.3	5.8	2.5	4.1
65 – 69	4.7 (3.1 - 6.8)	6.6 (4.5 - 9.3)	6.1	8.8	4.2	5.8
70 – 74	10.1 (8.3 - 14.1)	12.4 (9.2 - 16.4)	9.3	12.3	10.5	10.9
75 – 79	11.5 (8.7 - 15.1)	19.9 (15.7 - 25.9)	15.5	21.0	11.1	10.9
≥80	18.2* (14.1 - 23.8)	25.5* (18.1 - 34.8)	33.1	47.5	29.3	41.1
≥85	16.2 (11.9 - 21.7)	25.4 (15.6 - 39.2)				

* 80 - 84 years

Prevalence of AF

The estimated prevalence of AF in the general population was 7.7% (95% CI: 7.0 -8.3) among adults aged ≥55 years in the Netherlands during 2002 [R17-1293], 0.95% (95% CI: 0.94% -0.96%) in the US during 1996 to 1997 [R03-1233], 0.4% to 1.4% in Japan in 2003 among adults aged 40 or more [R10-0649], 3.2% in Sweden during 2010 among adults aged ≥ 20 years [R13-3858], and an age-standardised prevalence of 0.7% was shown in China in 2003 [R09-4870].

The prevalence of AF increases with advancing age. AF is uncommon before 50 years of age, but the prevalence increases markedly thereafter, afflicting about 9% and nearly 18% in people 85 years and older in the US during 1996 to 1997 [R03-1233] and Netherlands during 2000 [R17-1293].The estimated age and sex-standardised prevalence of AF was 4.4% (95% CI: 3.8% -5.1%) in Spain during 2011, was similar among women and men, and increased

from 4.6% (95% CI: 3.4 -5.9) among patients aged 60-69 years to 17.7% (95% CI: 14.1 - 21.3) among patients aged 80 and older [R14-3859].

In Denmark, the prevalence of AF in men aged ≥50 years increased from 1.4% in 1976 to 1978 to 3.3% in 1991 to 1994 while the prevalence in women aged ≥50 years remained between 1.0% and 1.4% [R09-2458]. In the US, from 1992 to 2002 and for adults aged ≥65 years the prevalence of AF increased from 3.2% to 6.0% [R06-2145]. In the UK from 1994 to 2003 all-ages prevalence of active AF increased from 0.8% to 1.3% in men and from 0.8% to 1.2% in women [R09-2459].

The above mentioned Framingham Heart Study also assessed trends in AF prevalence from 1958 to 2007. Age-adjusted period prevalence of AF increased in both men and women. The age-adjusted prevalence in men increased from 20.4 per 1000 PY in the cohort from 1958-1967 to 96.2 per 1000 PY in the 1998-2007 cohort. In women, the age-adjusted prevalence rate increased from 13.7 per 1000 PY in the cohort from 1958-1967 to 49.4 per 1000 PY in the 1998-2007 cohort [R17-1326].

In Germany, the prevalence of AF was 2.1% based on data during 2008 from 2 statutory health insurance funds. Prevalence rates increased from 0.5% in men aged 45-49 up to 17.7% in men aged 85-89 and decreased to 16.5 among men aged >89 years. Prevalence rates increased from 0.2% in women aged 45-49 up to 14.0 in women aged 85-89 and decreased to 11.8% among women aged >89 years [R17-1316]. The gender standardised prevalence of AF in Germany was 10.3% among adults aged 65 and older based on existing data from the GePaRD during 2007 [R17-1307].

The lifetime risk of developing AF in the Netherlands is 22% to 24% for men and women at age 55 years [R09-4875], and 23% to 26% for men and women of 50 years and older in the US [R09-4884].

In 2007, AF is estimated to affect a total of 6.3 million people aged ≥40 years in the US, Japan, Germany, Italy, France, UK, and Spain. The number of diagnosed prevalent cases is expected to increase to 7.5 million by 2017 primarily due to the aging population [P09-13748].

Age- and gender-specific prevalences of AF in the US, Europe, and Asia are displayed in SI.Table 17, confirming the AF prevalence increase with age and male gender.

SI.Table 17 Age-specific prevalence (%) (95% CI) of AF in females and males by country

Country	Netherlands [R17-1293]		USA [R03-1233]		Mainland China [R09-4870]	
Study period	2002		1996 to 1997		2003	
Age group [years]	Women	Men	Women	Men	Women	Men
<55			0.1	0.2		
55 - 59	1.7 (0.7, 4.0)	1.3 (0.4, 3.6)	0.4	0.9	0.55 (0.3, 1.0)	0.46 (0.2, 0.9)
60 - 64	1.3 (0.6, 2.7)	1.9 (0.9, 3.6)	1.0	1.7	1.00 (0.6, 1.6)	1.08 (0.6, 1.7)
65 - 69	2.7 (1.8, 4.2)	5.5 (4.0, 7.8)	1.7	3.0	1.27 (0.7, 2.0)	1.84 (1.2, 2.7)
70 - 74	5.1 (3.8, 6.9)	7.3 (5.7, 9.6)	3.4	5.0	2.58 (1.5, 4.1)	3.02 (1.9, 4.5)
75 - 79	9.6 (7.6, 11.9)	12.5 (9.8, 15.8)	5.0	7.3	2.60 (1.1, 5.1)	4.82 (2.8, 7.6)
80 - 84	12.2 (9.7, 15.1)	16.1 (12.4, 20.4)	7.2	10.3	7.00 (2.8, 14.4)	5.00 (1.9, 10.6)
≥85	16.1 (13.1, 19.4)	24.2 (18.5, 30.7)	9.1	11.1	8.57 (1.8, 23.6)	15.38 (5.9, 30.5)
All	7.1 (6.3, 7.9)	8.6 (7.6, 9.7)			1.33 (1.1, 1.7)	1.73 (1.4, 2.1)

SI.3.2 Demographics of the population in the authorised indication –age, gender, racial and/or ethnic origin and risk factors for the disease

SI.3.2.1 Demographic profile

Demographic profiles of registries and studies in selected countries are provided in SI.Table 18.

SI.Table 18 Demographic Characteristics of Registries and Selected Studies of patients with AF

Study	35 ESC member countries on AF [P05-12151].	RECORD AF [R10-4267].	CPRD study [R14-0464]	J-RHYTHM registry	Swedish National Patient Registry [R17-1273]
Country	35 ESC member countries	Worldwide in 21 countries across Europe, America, and Asia	UK	Japan	Sweden
Study Periods	2003 to 2004	2007 to 2008	2005 to2010	1995-2008	1995-2008
Female (%)	42%	43%	48%	29%	44%
Mean age in years (SD)	Paroxysmal AF: 64 (14) Permanent AF: 71 (11)	66 (12)	74 (12)	69.8(10)	72.3 (10.9)
Race White Black Asian Other	NA	 86% 2% 10% 3%	NA		

SI.3.2.2 Risk factors for the disease

The risk of developing AF increases with age, male sex, structural cardiovascular disease, such as myocardial infarction, congestive heart failure, valve disease and rheumatic heart disease, hypertension, renal function [R17-1308, R17-1297, R17-1317], and diabetes mellitus [R13-0094, R03-1228, R11-1465, R03-1233]. Recent data suggests that genetic predisposition [R13-0175], inflammation [R13-0096], metabolic syndrome [R13-0090], excessive alcohol consumption, [R13-0091, R17-1296, R17-1325] obesity [R13-0176, R17-1289, R17-1291] and weight loss and gain[R17-1289], may also increase the risk of developing AF, especially in otherwise healthy individuals.

SI.3.3 The main existing treatment options

The ESC recommends balancing the risk of stroke and the risk of haemorrhage using the CHA_2DS_2-VASc score to identify low-risk and high risk patients for stroke and the HAS-BLED score to assess the risk of haemorrhage [P17-04830]. In men with atrial fibrillation and a CHA_2DS_2-VASc score of 1 or more, or women with atrial fibrillation and a CHA_2DS_2-VASc score of 2 or more, oral anti-coagulation is recommended. Patients with a HAS-BLED score of ≥3 should be treated with caution and should not be automatically excluded from

receiving anticoagulants as evidence does show clinical benefit. Conventionally VKAs (targeted to an INR 2-3) were the treatment of choice, as aspirin had a low efficacy in stroke prevention but the same risk for major bleeding. Non-VKA OAC including dabigatran, apixaban, edoxaban, and rivaroxaban are now deemed appropriate alternatives to VKAs for stroke prevention in AF. Antiplatelet monotherapy and combination with clopidogrel and/or aspirin is no longer recommended for stroke prevention in AF patients due to the increased bleeding risk. Treatment options and optimal use are provided in SI.Table 19.

SI.Table 19 Treatment options for the prevention of VTE in patients with AF

Treatment options		**Optimal use of treatment**
Oral Anti-coagulants	Dabigatran	Recommended in men with atrial fibrillation and a CHA_2DS_2-VASc score of 1 or more, or women with atrial fibrillation and a CHA_2DS_2-VASc score of 2 or more [P17-04830]
	Apixaban	
	Edoxaban	
	Rivaroxaban	
	VKAs	
Oral Anti-platelets	Clopidogrel	No longer recommended as monotherapy nor combination therapy
	Aspirin	

SI.3.4 Natural history of the indicated condition in the population, including mortality and morbidity

SI.3.4.1 Mortality

AF has a significant impact on longevity and is significantly associated with an increased risk of death. Causes of death include coronary heart disease, stroke and other cardiovascular diseases.

SI.Table 20 Estimates of AF-related mortality

Study	Country	Year	Population	Mortality
R14-0464	UK	2005-2010	Patients with AF from a study using CPRD data	**Rate per 100 PY (95% CI)** 8.9 (8.6 - 9.3)
P07-12708	Sweden	2002-2006	Patients with paroxysmal AF	**Age-and sex-adjusted rate per 100 PY:** 5
R09-2455	Scotland	1972-1996	Patients from The Renfrew/Paisley Study (7052 men and 8354 women) aged 45-64 at enrollment	**Adjusted odds ratio (95% CI) for death with AF compared to non-AF at 20 year follow-up** Men: 1.5 (1.2 - 2.2) Women: 2.2 (1.5 - 3.2)
P05-12151	35 ESC member countries	2003-2004	Patients with AF enrolled in Euro Heart Survey on Atrial Fibrillation	**Mortality:** 5.3%
R09-4872	US	1948-1988	Patients from the original Framingham Heart Study cohort followed for 40 years	**Adjusted odds ratio (95% CI) for death with AF compared to non-AF** Men: 1.5 (1.2 -1.8) Women: 1.9 (1.5 -2.2) **Mortality within 30 days after AF diagnosis**: 15% **Mortality between 1 month and 1 year**: 15% - 18%
R10-0675	US	1980-1998	US population using death certificates	**Deaths with AF as underlying cause of death on death certificate:** 1980: 8.3% 1998: 11.6%
R17-1280	US	2000-2010	Olmsted County, Minnesota residents with incident AF identified by the Rochester Epidemiology Project (n=3344)	**Adjusted HR (95% CI) for death** 0.96 (0.71 - 1.32)
R11-4340	US	1993-2010	Healthy middle-aged women participating in the Women's Health Study in the US (n = 34 722)	**Rate per 100 PY (95% CI) for all-cause mortality**: AF: 1.08 (0.81 - 1.35) Without AF: 3.1 (2.9 - 3.2) **Adjusted HR (95% CI) for all-cause mortality for women with AF compared to women without AF** 1.70 (1.30 - 2.22)

SI.Table 20 (cont'd) Estimates of AF-related mortality

Study	Country	Year	Population	Mortality
R10-0598	US	1996-1999	Patients in the ATRIA study in Northern California, US (n=11 526)	**Rate per 100 PY** On warfarin: 4.46 Without warfarin:5.33
R17-1273	Sweden	1995-2008	Patients with incident AF from the Swedish National Patient Registry (n=272 186)	**Rate per 100 PY** <65 years: 2.5 65-74 years: 6.4 75-85 years: 15.2 Mortality rates for AF were lower in all three age categories for women compared to men
R17-1284	England	1995-2010	Population in England studied using death registration data	**AF as underlying cause of death in adults aged ≥45 years:** 0.25% of 192 770 deaths **Mortality rate for AF per million (age ≥45) (AF indicated as the primary cause of death among all listed causes of death on the certificate)** England 1995: 55.1 England 2010: 88.8 **Age standardised mortality rate for AF per million (age ≥45) (AF indicated as a cause of death on the certificate but not required to be the primary cause of death on the certificate)** England 1995: 202.5 England 2010: 554.1
R17-1324	Spain	Pub-lished 2013	Patients with stable AF	Rate per year: 4.35

SI.3.4.2 Morbidity

AF is associated with an increased long-term risk of heart failure and stroke. Furthermore, tachycardia/bradycardia, or sometimes a “brady-tachy syndrome”, can be associated with AF.

The clinical appearance of AF can be heterogeneous. AF is frequently associated with a fast rhythm that may require medication. However, in some cases the heart rate is not accelerated because of intrinsic AV nodal disease. AF can trigger a malignant arrhythmia if it occurs in the presence of an accessory pathway (e.g. WPW) and conduction is preferential down that accessory pathway. This situation leads to an extremely fast ventricular response that can degenerate into ventricular tachycardia.

SI.3.5 Important co-morbidities

Hypertension

Hypertension is considered a risk factor for AF [R08-4873].

Incidence and prevalence of hypertension

Hypertension is a common and chronic co-morbidity and therefore is better described by its prevalence (SI.Table 21). Prevalence of hypertension in patients with AF ranged from 24% to 76%.

SI.Table 21 The prevalence of hypertension in patients with AF

Study	Country	Design	Year	Population	Prevalence of Hypertension
P05-12151	35 ESCmember countries	Pro-spective survey	2003-2004	Patients with AF enrolled in Euro Heart Survey on Atrial Fibrillation baseline assessment	Defined as systolic blood pressure >160 mmHg, diastolic blood pressure >90 mmHg or receiving blood pressure lowering drugs)**:** 64%
R10-4267	21 countries across Europe, America, and Asia	Pro-spective survey	2007-2008	Patients with AF enrolled in the registry on cardiac rhythm disorders assessing the control of AF (RECORD AF)	Defined as systolic blood pressure >140/90 mmHg,**:** 68%
R12-2026	Germany	Cross-sectional	2007 till n=5000	Patients with AF (age 63.2±9.5 years, 31.8% women) (n=161) First 5000 recruited patients from the population-based Gutenberg Health Study	71.6%
R10-4269	Germany	Pro-spective registry	2004-2006	Patients with AF participating in the German Competence Network on Atrial Fibrillation study (AFNET)	Paroxysmal AF: 24.1% Permanent AF: 45.2%
R12-0729	Italy	Pro-spective cohort		AF patients enrolled in EPICA study aged ≥80 years who started VKA treatment after 80 years of age (n=3015)	Defined as taking medication to lower blood pressure): 75.6%
R17-1280	US	Population-based Pro-spective cohort	2000-2003 and 2008-2010	Patients with incident AF in Olmstead County Minnesota	2000-2003: 63.1 2008-2010: 71.1%

SI.Table 21 (cont'd) The prevalence of hypertension in patients with AF

Study	Country	Design	Year	Population	Prevalence of Hypertension
R14-0464	UK	Population-based cohort study	2005-2010	Patients with AF from a study using CPRD data	49.1%
R11-1463	Netherlands	Cross-sectional	1996	AF patients aged 60 and older (n=1234) and controls (n=11 288) identified as part of the PATAF trial screening	AF patients: 42.6% Non-AF controls: 22.0%
R17-1273	Sweden	Case-control study	1995-2008	Patients with incident AF patients from the Swedish National Patient Registry (n=272 186) and controls (n=239 818)	AF patients: 25.4% Non-AF controls: 6.8%
P17-04025	Japan	Cross-sectional	2011-2012	AF patients in the community from the Fushimi AF Registry representing a typical urban community (n=3183)	60%
R17-1292	Japan	Pro-spective cohort	Published 2015	Elderly patients with NVAF (mean age 69.8±10 years)) from specialty cardiology institutions enrolled in the J-RHYTHM Registry (n=7406)	60%

Mortality of hypertension

Please refer to the mortality data of myocardial infarction, stroke, and heart failure.

Co-medication

In the baseline observation of 35 ESC member countries on Atrial Fibrillation , overall 48% of patients received ACE inhibitors, 12% angiotensin II antagonists, 14% beta-blocker (not for anti-arrhythmic indication), 12% dihydropyridine calcium channel blocker, and 51% diuretics [P05-12151].

During the baseline observation of the RECORD AF between 2007 and 2008 overall 60% of patients received ACE inhibitors or angiotensin II receptor antagonists, 17% calcium channel blockers, 39% diuretics, and 3% other hypertensive drugs [R10-4267].

In a population-based cross-sectional study conducted in Germany, 70.9% of the male AF patients (n = 115, age (range) 66.0 years [57.0 to 70.0]) and 67.0% of the female AF patients

(n = 46, age (range) 66.0 years [56.8 to 71.6]) received antihypertensive medication. Of all AF patients (n = 161, age 63.2±9.5 years, 31.8% women), 36.4% received ACE inhibitors, 18.4% angiotensin II antagonists, 17.8% dihydropyridine, and 43.0% diuretics [R12-2026].

In the baseline data of a CPRD study, 65.1% of AF patients in the UK during 2005 to 2010 were receiving antihypertensives [R14-0464].

In the annual National Health and Wellness Survey in 2009 representing a national US sample, among 1297 adults with AF 66% reported hypertension and 64% reported use of prescription medication for hypertension [R13-0111].

In the US, the baseline data of the Framingham Heart Study showed that the prevalence of hypertension treatment in patients with incident AF was 22.1% in the cohort from 1958-1967 and increased in each consecutive cohort with 59.2% receiving baseline treatment for AF in the 1998-2007 cohort [R17-1276].

Diabetes mellitus

Incidence and prevalence of diabetes mellitus

In the follow-up of 16 513 patients with a first record of AF a retrospective cohort study from 2005 to 2010 in England yielded an incidence of diabetes of 8.3 (95% CI: 7.9 - 8.6) per 100 PY [U10-1959-02].

SI.Table 22 provides the prevalence of diabetes mellitus from multiple studies in patients with AF. The prevalence of diabetes mellitus among patients with AF ranged from 12% to 27%.

SI.Table 22 The prevalence of diabetes mellitus in patients with AF

Study	Country	Design	Year	Population	Prevalence of Diabetes Mellitus
P05-12151	35 ESC member countries	Pro-spective survey	2003-2004	Patients with AF enrolled in Euro Heart Survey on Atrial Fibrillation	18%
R10-4267	21 countries across Europe, America, and Asia	Pro-spective survey	2007-2008	Patients with AF enrolled in the registry on cardiac rhythm disorders assessing the control of AF (RECORD AF)	16%
R12-2026	Germany	Population-base cross-sectional	2007 until n=5000	Patients with AF (age 63.2±9.5 years, 31.8% women) (n=161)	12.2%
R10-4269	Germany	Pro-spective registry	2004-2006	Patients with AF participating in the German Competence Network on Atrial Fibrillation study (AFNET)	Overall: 21.7% Paroxysmal AF: 15.8% Permanent AF: 27.6%
R14-0464	UK	Population-based cohort study	2005-2010	Patients with AF from a study using CPRD data	Overall: 15.3% Women: 13.9% Men: 16.6%
R12-0729	Italy	Pro-spective cohort	Pub-lished 2011	AF patients starting VKA treatment at ≥80 years of age (n=3015)	18.3%

SI.Table 22 (cont'd) The prevalence of diabetes mellitus in patients with AF

Study	Country	Design	Year	Population	Prevalence of Diabetes Mellitus
R11-1463	Netherlands	Cross-sectional	1996	AF patients aged 60 and older (n=1234) and controls (n=11 288) identified as part of the PATAF trial screening	AF patients: 16.5% Controls: 9.0%
R17-1280	US	Population-based pro-spective cohort	2000-2003; 2008-2010	Patients with incident AF in Olmsted County, Minnesota	2000-2003: 18.5% 2008-2010: 25.6%
R17-1273	Sweden	Case-control	1995-2008	Patients with incident AF patients from the Swedish National Patient Registry (n=272 186) and controls (n=239 818)	AF patients: 13.4% Controls: 5.2% AF men: 13.8% AF women: 12.8%
P17-04025	Japan	Cross-sectional	2011-2012	AF patients in the community from the Fushimi AF Registry representing a typical urban community	23.2%
R17-1292	Japan	Pro-spective cohort		NVAF elderly patients (mean age 69.8±10 years) from specialty cardiology institutions enrolled in the J-RHYTHM Registry (n=7406)	18.3%
R17-1326	US	Pro-spective cohort	1998-2007	Patients with incident AF from the 1998-2007 time period of The Framingham Heart Study	19.6%

Mortality of diabetes mellitus

In the US among persons with AF aged 45 years or older, 2% to 4% of deaths depending on age group were reported to have diabetes as underlying cause of death during 1994 to 1998 [R10-0675].

Co-medication

In the baseline observation of the Euro Heart Survey on Atrial Fibrillation, conducted 2003 to 2004 in 35 ESC member countries (including Egypt, Israel, Tunisia), overall 13% of patients received antidiabetic drug therapy [P05-12151].

In a population-based cross-sectional study conducted in Germany, 5.0% of all AF patients (n = 161, age 63.2±9.5 years, 31.8% women) received insulin and 6.5% oral antidiabetic medication [R12-0729].

In a CPRD study, 9.1% of AF patients in the UK during 2005 to 2010 received antidiabetic medication. Oral antidiabetics were received by 7.9%, insulin by 2.2% and other injectable antidiabetics received by <1% of AF patients [R14-0464].

In the 2009 National Health and Wellness Survey, 29% of 1297 adults with AF reported diabetes mellitus and 24% reported use of prescription medication for diabetes mellitus [R13-0111].

Stroke

Incidence and prevalence of stroke

SI.Table 23 provides the incidence of stroke from multiple studies in patients with AF. The incidence of stroke among patients with AF ranged from 1.6% to 2.1%. The incidence rate of stroke reported varied in the type of stroke, medication use, and whether the AF was persistent or paroxysmal. The incidence rate ranged from 0.2 to 2.9 per 100 PY.

SI.Table 23 The incidence of stroke in patients with AF

Study	Country	Design	Year	Population	Incidence of Stroke
R10-4268	35 ESC member countries	Pro-spective survey	2004-2005	Patients from the Euro Heath Survey on Atrial Fibrillation study (n=3890)	**Ischemic stroke after 1 year** Overall: 1.6% Persistent AF: 1.2% Paroxysmal AF: 1.9%
R10-4273	Sweden	Pro-spective cohort	2002-2006	Patients from the Stockholm Cohort of Atrial Fibrillation (n=1981)	**Rate per 100 PY of ischemic stroke** Persistent AF: 2.9 Paroxysmal AF: 2.6
R10-4276	Denmark	Pro-spective cohort	1980-2002	Patients with a hospital diagnosis with AF or atrial flutter (n=140 000)	**Rate per 100 PY** 2.9
R14-0464	England	Retro-spective cohort	2005-2010	Patients with first recorded AF (n=16 513)	**Rate per 100 PY (95% CI)** Hospitalised: 2.3 (2.1, 2.5) Haemorrhagic: 0.2 (0.2, 0.3) Ischemic: 1.5 (1.4, 1.6)
R10-0598	US	Retrospect ivecohort	1996-1999	Patients in the ATRIA study in Northern California, US (n=11 526)	**Rate per 100 PY (95% CI) of ischemic stroke** On warfarin: 1.1 (0.9, 1.3) No warfarin: 1.9 (1.7, 2.1)
R06-2834	US	Pro-spective cohort	Pub-lished 2003	Patients with new-onset AF in the Framingham cohort (n=705)	**Rate per 100 PY (95% CI) of ischaemic or haemorrhagic stroke** 2.9 (2.3, 3.5)

SI.Table 23 (cont'd) The incidence of stroke in patients with AF

Study	Country	Design	Year	Population	Incidence of Stroke
R17-1287	France	Non-interventional study using claims data	2008-2010	Adult patients with AF identified from the French National Hospital Claims system (n=61 582)	**Rate per 100 patients with AF during 2 year follow-up** Any: 32.1 Ischaemic: 20.4 Haemorrhagic: 8.0 Unspecified: 5.4
R11-2945	21 countries across Europe, America, and Asia	Prospective registry	1992-2002	Patients with AF enrolled in the registry on cardiac rhythm disorders assessing the control of AF (RECORD AF) (n=5171)	**Stroke or TIA:** 2.1%
R17-1324	Spain	Prospective	Published 2013	Consecutive stable anticoagulated AF patients from an outpatient anticoagulation clinic (n=978)	**Stroke:** 1.7% per year

SI.Table 24 provides the prevalence of stroke from multiple studies in patients with AF and ranged from approximately 4% to 20%.

SI.Table 24 The prevalence of stroke in patients with AF

Study	Country	Design	Year	Population	Prevalence of Stroke
P05-12151	35 ESC member countries	Prospective survey	2003-2004	Patients participating in the Euro Heart Survey on Atrial Fibrillation	**Stroke:** 5.6%
R10-4267	21 countries across Europe, America, and Asia	Prospective survey	2007-2008	Patients with AF enrolled in the registry on cardiac rhythm disorders assessing the control of AF (RECORD AF)	**Stroke:** 6%
R10-4269	Germany	Prospective registry	2004-2006	Patients participating in the German Competence Network on Atrial Fibrillation study (AFNET)	**Stroke** First detected AF: 3.7% Permanent AF: 8.5%
R14-0464	UK	Population-based cohort study	2005-2010	Patients with AF from a study using CPRD data	**Stroke:** 11.2%
R12-2026	Germany	Population-based cross-sectional	Published 2012	AF patients (n=161)	**Stroke:** 9.8%

SI.Table 24 (cont'd) The prevalence of stroke in patients with AF

Study	Country	Design	Year	Population	Prevalence of Stroke
R12-0729	Italy	Pro-spective cohort	Pub-lished 2011	AF patients enrolled in EPICA study aged ≥80 years who started VKA treatment after 80 years of age (n=3015)	**Stroke:** 19.6%
R11-1463	Netherlands	Cross-sectional	1996	AF patients (N=1234) and control patients (N=11 288) without AF	**Stroke** AF patients: 7.0% Non-AF controls: 2.2% **TIA** AF patients: 4.8% Non-AF controls: 2.1%
R17-1273	Sweden	Case-control with pro-spective follow-up	1995-2008	Patients with hospitalised with incident AF (n=272 818) and controls (n=239 818) Identified through the Swedish national Patient Registry	**Stroke** AF patients: 11.5% Non-AF controls: 3.3% Men with AF: 10.8% Women with AF: 12.3%
P17-04025	Japan	Cross-sectional	2011-2012	AF patients in the community identified from the Fushimi AF Registry	**Stroke** Overall: 19.4% Ischemic: 17.8% Haemorrhagic: 1.8% Unknown: 0.3% **TIA:** 2.4%
R17-1292	Japan	Pro-spective cohort	Publis hed 2015	Elderly patients with NVAF (mean age 69.8±10 years) from specialty cardiology institutions enrolled in the J-RHYTHM Registry (n=7406)	**Stroke/TIA:** 13.8%

Mortality of stroke

In the follow up of 16 513 patients with a first record of AF, a study from 2005 to 2010 in England yielded an incidence of fatal stroke of 0.3 (95% CI: 0.2 - 0.4) per 100 PY, where fatal stroke was defined as death within 30 days after the hospitalisation due to stroke [R14-0464].

In the follow up of 3890 patients of the Euro Heart Survey on Atrial Fibrillation, conducted 2004 to 2005 in 35 ESC member countries (including Egypt, Israel, Tunisia), the mortality in patients with an ischaemic stroke was 21% [R10-4268].

Co-medication

In the baseline observation of the Euro Heart Survey on Atrial Fibrillation, conducted 2003 to 2004 in 35 ESC member countries (including Egypt, Israel, Tunisia), overall 64% of patients received oral anticoagulation, 29% received aspirin, and 12% received other antithrombotic medication (clopidogrel, ticlopidine, dipyridamole, heparin or non-specified) [P05-12151].

During the baseline observation of the RECORD AF conducted worldwide in 21 countries across Europe, America and Asia between 2007 and 2008, overall 52% of patients received VKAs and 42 % received antiplatelet agents [R10-4267].

In a population-based cross-sectional study conducted in Germany, 37.1% of the AF patients (n = 161, age 63.2±9.5 years, 31.8% women) received OAC, 23.1% platelet inhibitors, and 0.5% heparin [R12-2026].

In the baseline of a GPRD study conducted in AF patients in the UK during 2005 to 2010, overall 49.3% received antiplatelets, 46.0% aspirin, 4.9% clopidogrel, 1.9% other antiplatelets, and 11% anticoagulants [R14-0464].

In the annual National Health and Wellness Survey in 2009 representing a national US sample, among 1297 adults with AF, 13% reported prior stroke and 7% reported use of prescription medication for prior stroke [R13-0111].

Heart failure

Incidence and prevalence of heart failure

In the follow-up of 3890 patients of the Euro Heart Survey on Atrial Fibrillation conducted 2004 to 2005 in 35 ESC member countries (including Egypt, Israel, Tunisia), overall 5% of the patients developed new heart failure after 1 year. The incidence varied by AF type between 3.0% (persistent AF) and 6.8% (first detected AF) [R10-4268].

In the follow up of 5171 patients in the RECORD AF, conducted worldwide in 21 countries across Europe, America, and Asia, the incidence of hospitalisation or prolongation of hospitalisation for congestive heart failure was 3.4% [R11-2945].

In the baseline observation of the Euro Heart Survey on Atrial Fibrillation conducted 2003 to 2004 in 35 ESC member countries (including Egypt, Israel, Tunisia), overall 33% of patients had heart failure [P05-12151].

SI.Table 25 provides the prevalence of heart failure from multiple studies in patients with AF. Prevalence of heart failure generally ranged from 18% to 29% but as low as 3.5%. Prevalence of cardiac failure and congestive heart failure where lower ranging from 6% to 14%.

SI.Table 25 The prevalence of heart failure in patients with AF

	Country	Design	Year	Population	Prevalence of Heart Failure
P05-12151	35 ESCmember countries	Pro-spective survey	2003-2004	Patients enrolled in the Euro Heart Survey on Atrial Fibrillation	**Heart failure:** 33%
R10-4267	21 countries across Europe, America and Asia	Pro-spective survey	2007-2008	Patients enrolled in the RECORD AF study	**Heart failure** (defined as New York Heart Association class I, II, III, or IV): 26%
R10-4269	Germany	Pro-spective registry	2004-2006	Patients from the German Competence Network on Atrial Fibrillation (AFNET)	**Heart failure** (defined as New York Heart Association class II - IV): 29%
R14-0464	UK	Population-base cohort study	2005-2010	Patients with AF from a study using CPRD data	**Congestive heart failure:** 8.2%
R12-2026	Germany	Population-based cross-sectional	Pub-lished 2012	AF patients (age 63.2±9.5 years, 31.8% women) (n=161)	**Cardiac failure:** 6.3%
R12-0729	Italy	Pro-spective cohort	Pub-lished 2011	Patients enrolled in the EPICA study with AF at ≥80 years of age who started VKA treatment after 80 years of age (n=3015)	**Heart failure** (defined as presence of signs and symptoms of right and/or left ventricular failure confirmed by evidence of cardiac dysfunction)**:** 27.4%
R13-0094	US	Pro-spective cohort	Pub-lished 1982	Participants enrolled in the Framingham study (n=2325 men and n=2866 women)	**Cardiac failure** Overall: 14.3% Male controls: 0.8% Female controls: 2.0%
R17-1280	US	Population-based Pro-spective cohort	2000-2003; 2008-2010	Incident AF patients in Olmsted County, Minnesota	**Heart failure** Incident cases 2000-2003: 24.0% Incident cases 2008-2010: 18.7%
R17-1273	Sweden	Case-control with pro-spective follow-up	1995-2008	Hospitalised AF patients from the Swedish National Patient Registry (n=272 818) and controls (n=239 818)	**Heart failure** AF patients: 24.8% Controls: 2.9% Men: 25.0% Women: 24.5%
	Japan	Cross-sectional	2011-2012	AF patients in the community from the Fushimi AF Registry representing a typical urban community	**Heart failure:** 19.4% **Hospitalisation for heart failure:** 16.8%

SI.Table 25 (cont'd) The prevalence of heart failure in patients with AF

	Country	Design	Year	Population	Prevalence of Heart Failure
R17-1292	Japan	Pro-spective cohort	Pub-lished 2015	NVAF elderly patients (mean age 69.8±10 years) from specialty cardiology institutions enrolled in the J-RHYTHM Registry	**Heart failure:** 27.7%
R17-1326	US	Pro-spective cohort	1998-2007	Patients with incident AF from the most recent cohort of The Framingham Heart Study	**Heart failure:** 3.5%

Mortality of heart failure

No data on mortality of heart failure in the target population found.

However, in the follow up of 3890 patients of the Euro Heart Survey on Atrial Fibrillation conducted 2004 to 2005 in 35 ESC member countries (including Egypt, Israel, Tunisia), overall 2.3% of the patients died due to cardiovascular reasons within 1 year. The mortality varied by AF type between 1.3% (paroxysmal AF) and 3.6% (permanent AF). Mortality due to cardiovascular reason was defined as myocardial infarction, heart failure, sudden cardiac death (all sudden deaths without any other known reason), stroke, or rupture of an aortic aneurysm [R10-4268].

The association between incident AF and mortality was studied in 34 722 initially healthy middle-aged women participating in the Women's Health Study in the US [R11-4340]. During a median follow-up of 15.4 years (1993 to 2010), incidences per 100 PY among women with and without AF were 0.43 (95% CI: 0.26 - 0.60) and 0.06 (95% CI: 0.05 - 0.06) for cardiovascular mortality. The adjusted HR for cardiovascular mortality was 2.57 (95% CI: 1.63 - 4.07) for women with AF compared to women without AF.

In the follow up of 5171 patients in the RECORD AF conducted worldwide in 21 countries across Europe, America, and Asia, the incidence of cardiovascular death was 1.7% [R11-2945].

Co-medication

Please refer to data on co-prescribed medications for hypertension.

Coronary artery disease

Incidence and prevalence of coronary artery disease

In the follow up of 3890 patients of the Euro Heart Survey on Atrial Fibrillation conducted 2004 to 2005 in 35 ESC member countries (including Egypt, Israel, Tunisia), overall 2.4% of

the patients developed new coronary artery disease after 1 year. The incidence varied by AF type between 1.7% (persistent AF) and 2.8% (permanent AF). Coronary artery disease was defined as myocardial infarction (new or presumed new ST-segment elevation in 2 or more contiguous leads of ≥0.2 mV in leads V1, V2, or V3, and ≥0.1 mV in other leads, and/or presumably new left bundle branch block, and/or cardiac enzyme rise more than 2 times the upper values), or unstable angina [R10-4268].

Among 1835 NVAF patients visiting the Skinken Cardiovascular Institute in Japan during 2004 to 2010, 6% had coronary artery disease defined as history of percutaneous coronary intervention or coronary artery bypass graft or documented ≥50% coronary stenosis. During follow up, the incidence of a coronary event defined as hospitalisation for myocardial infarction, unstable angina, or stable angina was 1.9% per year [R13-4723].

In the baseline observation of the Euro Heart Survey on Atrial Fibrillation conducted 2003 to 2004 in 35 ESC member countries (including Egypt, Israel, Tunisia), overall 33% of patients had coronary artery disease [P05-12151].

During the baseline observation of the RECORD AF conducted worldwide in 21 countries across Europe, America, and Asia between 2007 and 2008, overall 18% of patients had coronary artery disease [R10-4267].

In the baseline of the EPICA study, a prospective Italian cohort study on 3015 AF patients at ≥80 years of age who started VKA treatment after 80 years of age, 24.4% of patients had a medical history of coronary artery disease/peripheral artery disease [R12-0729].

During the baseline observation of the AFNET registry study, conducted in Germany between 2004 and 2006, overall 28.1% of patients had coronary artery disease [R10-4269].

In a GPRD study conducted in AF patients in the UK from 2005 to 2010, overall 16.8% of patients had a history of coronary artery disease [R14-0464].

In the Fushimi AF Registry, a community-based survey of AF patients during 2011 to 2012 representing a typical urban community in Japan, 15.0% of AF patients (n=3183) had coronary artery disease. Prevalence by type in the population included 6.4% had previous MI, 7.6% previous PCI, and 2.8% previous CABG [P17-04025].

Mortality of coronary artery disease

Please refer to the mortality data of myocardial infarction.

Co-medication

Please refer to data on co-prescribed medications for hypertension, hyperlipidaemia, and stroke.

COPD

Incidence and prevalence of COPD

COPD is a common and chronic co-morbidity and therefore is better described by its prevalence, see below.

In the baseline observation of the Euro Heart Survey on Atrial Fibrillation conducted 2003 to 2004 in 35 ESC member countries (including Egypt, Israel, Tunisia)overall 13 % of patients had COPD [P05-12151].

In Minnesota, US the prevalence of COPD was 19.5% among incident AF patients from 2000-2003 and significantly decreased to 11.9% among incident AF patients from 2008-2010 [R17-1280]. The prevalence of COPD at baseline among 272 186 patients hospitalised in Sweden with incident AF was compared to a control group free of in-hospital diagnosis of AF (n=239 818) during 1995 to 2008 using the Swedish National Patient Registry. The prevalence of COPD was 4.9% in incident AF patients compared with 1.4% in controls. The prevalence of COPD in AF was 4.8% in women and 5.0% in men [R17-1273].

During the baseline observation of the AFNET registry study, conducted in Germany between 2004 and 2006, the prevalence of COPD increased from 10.2% in paroxysmal AF patients to 13.5% in permanent AF patients [R10-4269].

Mortality of COPD

In the US among persons with AF aged 45 years or older, 2% to 5% of deaths depending on gender and race were reported to have COPD as underlying cause of death during 1994 to 1998 [R10-0675].

Co-medication

No data on co-prescribed medications for COPD in the target population found.

Valvular heart disease

Incidence and prevalence of valvular heart disease

No data on incidence of valvular heart disease in the target population found. However, valvular heart disease is considered a risk factor for AF [R08-4873].

In the baseline observation of the Euro Heart Survey on Atrial Fibrillation conducted 2003 to 2004 in 35 ESC member countries (including Egypt, Israel, Tunisia), overall 26% of patients had a history of valvular heart disease. The prevalence varied by AF type between 19% (paroxysmal AF) and 40% (permanent AF) [P05-12151].

During the baseline observation of the RECORD AF conducted worldwide in 21 countries across Europe, America, and Asia between 2007 and 2008, overall 19% of patients had a history of valvular heart disease [R10-4267].

In the Fushimi AF Registry, a community-based survey of AF patients during 2011 to 2012 representing a typical urban community in Japan, 18.1% of AF patients (n=3183) had prior stroke. Prevalence of mitral stenosis was 1.4% and of valve surgery 4.6% [P17-04025].

Mortality of valvular heart disease

There were no data on mortality of valvular heart disease found in the target population. Please refer to the mortality data of AF.

Co-medication

Please refer to the data on co-prescribed medications for hypertension and stroke.

LVH

Incidence and prevalence of LVH

No data on incidence of LVH in the target population were found.

In the baseline observation of the Euro Heart Survey on Atrial Fibrillation conducted 2003 to 2004 in 35 ESC member countries (including Egypt, Israel, Tunisia), overall 19% of patients had LVH on ECG [P05-12151].

During the baseline observation of the Canadian Registry on Atrial Fibrillation conducted in 1097 patients from 1990 to 1994, overall 13% of female and 18% of male patients had LVH on ECG [R10-4632].

In a publication from 2001, a cohort of 15 406 men and women aged 45–64 years from the UK was assessed after 20 years of follow-up and 100 AF cases were identified [R13-3833]. Patients with AF had an increased adjusted odds ratio of 4.2 (95% CI: 1.5 to 12.3) for LVH compared to the non-AF population.

In the Atrial Fibrillation Registry for ARAPACIS enrolling NVAF patients during 2010 to 2012 , 52% of 1087 patients with NVAF had LVH [R17-1301].

In the US, The Framingham Heart Study enrolled participants from 1958 to 2007. At baseline, the prevalence of LVH in patients with incident AF was 12.9% in the cohort from 1958-1967 and decreased in each consecutive cohort to a prevalence of 2.9% at baseline in the 1998-2007 cohort [R17-1326].

Mortality of LVH

Please refer to the mortality data for heart failure and myocardial infarction.

Co-medication
Please refer to the data on co-prescribed medications for hypertension.

Thyroid disease

Incidence and prevalence of thyroid disease

No data on incidence of thyroid disease in the target population were found. However, thyroid disease is considered a risk factor for AF [R09-4891].

In the baseline observation of the Euro Heart Survey on Atrial Fibrillation, overall 9% of patients had thyroid disease [P05-12151].

During the baseline observation of the RECORD AF between 2007 and 2008, overall 9% of patients had thyroid disease [R10-4267].

During the baseline observation of the AFNET registry study, conducted in Germany between 2004 and 2006, the prevalence of overall thyroid disease was distributed equally in all clinical types of AF (11.8% - 12.8%), and the same was true for hypothyroidism (5.0% - 5.7%) and subclinical hyperthyroidism (2.5% - 2.5%). The range for overt hyperthyroidism was somewhat wider, with a minimum of 3.3% in patients with paroxysmal AF, and a maximum of 5.1% for patients with persistent AF [R10-4269].

Mortality of thyroid disease

No data on mortality of thyroid disease in the target population were found.

Co-medication

In the baseline observation of the Euro Heart Survey on Atrial Fibrillation conducted 2003 to 2004 in 35 ESC member countries, overall 6% of patients received thyroid therapy [P05-12151].

In a population-based cross-sectional study conducted in Germany, 16.5% of all AF patients (n = 161, age 63.2±9.5 years, 31.8% women) received thyroid hormone therapy [R12-2026].

Other cardiac arrhythmia

Incidence and prevalence of other cardiac arrhythmia

No data on incidence of other cardiac arrhythmia in the target population were found.

In the baseline observation of the Euro Heart Survey on Atrial Fibrillation conducted 2003 to 2004 in 35 ESC member countries (including Egypt, Israel, Tunisia), overall 5% of patients had concomitant sick sinus syndrome [P05-12151].

During the baseline observation of the RECORD AF conducted worldwide in 21 countries across Europe, America and Asia between 2007 and 2008 overall 13% of patients had a history of arrhythmia other than AF [R10-4267].

Mortality of other cardiac arrhythmia

No data on mortality of other cardiac arrhythmia in the target population were found.

Co-medication

In the baseline observation of the Euro Heart Survey on Atrial Fibrillation conducted 2003 to 2004 in 35 ESC member countries (including Egypt, Israel, Tunisia), overall 84% of patients received anti-arrhythmic or rate control medication including bepridil, cibenzoline, disopyramide, procainamide, quinidine, flecainide, propafenone, beta-blocker for anti-arrhythmic indication, amiodarone, sotalol, diltiazem, verapamil, digoxin, or digitoxin [P05-12151].

During the baseline observation of the RECORD AF conducted worldwide in 21 countries across Europe, America, and Asia between 2007 and 2008, overall 55% received a rhythm-control strategy at inclusion and 2528 (45%) a rate-control strategy [R10-4267].

Hyperlipidaemia

Incidence and prevalence of hyperlipidaemia

No data on incidence of hyperlipidaemia in the target population found.

In the baseline observation of the Euro Heart Survey on Atrial Fibrillation conducted 2003 to 2004 in 35 ESC member countries, overall 35% of patients had hyperlipidaemia [P05-12151].

During the baseline observation of the RECORD AF conducted worldwide in 21 countries across Europe, America, and Asia between 2007 and 2008, overall 42% of patients had dyslipidaemia, defined as low density lipoprotein >155 mg/dL and high density lipoprotein <40 mg/dL in men and <48 mg/dL in women [R10-4267].

During the baseline observation of the AFNET registry study, conducted in Germany between 2004 and 2006, the prevalence of hyperlipidaemia ranged from 44.7% in persistent AF patients to 48.3% in first detected AF patients [R10-4269].

In the Fushimi AF Registry, a community-based survey of AF patients during 2011 to 2012 representing a typical urban community in Japan, 42.4% of AF patients (n=3183) had

dyslipidemia defined as total cholesterol >220 mg/dL, low-density lipoprotein>140 mg/dL, triglyceride >150 mg/dL, high-density lipoprotein <40 mg/dL, or statin use [P17-04025].

Mortality of hyperlipidaemia

There were no data on mortality of hyperlipidaemia found in the target population.

Co-medication

In the baseline observation of the Euro Heart Survey on Atrial Fibrillation conducted 2003 to 2004 in 35 ESC member countries (including Egypt, Israel, Tunisia) overall 25% of patients received statin therapy [P05-12151].

During the baseline observation of the RECORD AF conducted worldwide in 21 countries across Europe, America and Asia between 2007 and 2008 overall 38% of patients received prescriptions for lipid lowering drugs [R10-4267].

In a population-based cross-sectional study conducted in Germany, 34.9% of all AF patients (n = 161, age 63.2±9.5 years, 31.8% women) received statins [R12-2026].

In the 2009 National Health and Wellness Survey, among 1297 adults with AF, 57% reported a diagnosis of hyperlipidemia and half (50%) reported use of prescription medication for its treatment [R13-0111].

Renal impairment

Incidence and prevalence of renal impairment

No data on the incidence of renal impairment in the target population were found.

Incidence and prevalence rates of renal impairment depend strongly on disease definition. Frequently used terms include e.g. renal disease, renal dysfunction, renal impairment, and renal failure. These terms are not consistently defined and used in the epidemiological literature and might lead to heterogeneous results. SI.Table 26 provides the prevalence of renal impairment from multiple studies in patients with AF.

SI.Table 26 The prevalence of renal impairment in patients with AF

	Country	Design	Year	Population	Prevalence of Renal Impairment
R12-0729	Italy	Pro-spective cohort	Pub-lished 2011	AF patients at ≥80 years of age, who started VKA treatment after 80 years of age (N=3015)	**Prevalence of renal failure** (defined as a serum creatinine ≥1.5 mg/dL): 13.1%
P05-12151	35 ESC member countries	Pro-spective survey	2003-2004	Patients participating in Euro Heart Survey on Atrial Fibrillation	**Prevalence of renal failure:** 6%
R11-4339	Sweden	Cross-sectional study (subgroup analysis of registry data)	2007-2008	AF patients on anticoagulation treatment (n=2603)	**Prevalence of severe renal impairment** (defined as eGFR <30 mL/min/1.73 m^2 using the MDRD formula)**:** 4%
R14-0464	UK	Population-base cohort study	2005-2010	Patients with AF from a study using CPRD data	**Prevalence of renal impairment:** 15.2%
R10-4269	Germany	Pro-spective cohort	2004-2006	Patients participating in the German Competence Network on Atrial Fibrillation study (AFNET)	**Prevalence of renal failure** First detected AF: 9.2% Permanent AF: 14.5%
R11-4343	Denmark	Pro-spective cohort	1997-2006	Patients with AF discharged from hospital (n=118 606)	**Prevalence of renal failure:** 2.4%
R10-4267	21 countries across Europe, America, and Asia	Pro-spective survey	2007-2008	Patients with AF enrolled in the registry on cardiac rhythm disorders assessing the control of AF (RECORD AF)	**Prevalence of renal disease:** 6%
R12-0729	Italy	Pro-spective cohort	Pub-lished 2011	Patients enrolled in the EPICA study with AF at ≥80 years of age who started VKA treatment after 80 years of age (n=3015)	**Prevalence of renal disease**(defined as a serum creatinine ≥1.5 mg/dL**:** 13.1%
R17-1280	US	Population-based Pro-spective cohort	2000-2010	Incident AF patients in Olmsted County, Minnesota	**Prevalence of renal disease** Incident AF 2008-2010: 7.1% Incident AF 2000-2003: did not significantly change
R17-1273	Sweden	Case-control with pro-spective follow-up	1995-2008	Hospitalised AF patients (n=272 818) and controls (n=239 818) identified through the Swedish National Patient Registry	**Prevalence of chronic renal failure** AF patients: 1.6% Controls: 0.3% AF men: 2.0% AF women: 1.2%

SI.Table 26 (cont'd) The prevalence of renal impairment in patients with AF

	Country	Design	Year	Population	Prevalence of Renal Impairment
P17-04025	Japan	Cross-sectional	2011-2012	AF patients in the community from the Fushimi AF Registry representing a typical urban community (n=3183)	**Prevalence of chronic kidney disease** (defined as persistent proteinuria or eGFR<60 mL/min/1.73 m^2 for more than 3 months): 26.4% **Prevalence of hemodialysis**: 2.9%.

Mortality of renal impairment

No data on the mortality of renal failure in the target population were found. However, in the US between 1994 and 1998 among persons with AF aged 45 years or older, 9% to 16% of deaths depending on race and gender were reported to have diseases of the genitourinary system as underlying cause of death [R10-0675].

Co-medication

No data on the co-medication due to renal failure in the target population were found.

SI.4 aVTEt

SI.4.1 Incidence and prevalence

Incidence

Venous thromboembolism includes DVT and PE. The incidence rate of VTE varies by country and the age distribution of the studied population (SI.Table 27). Other study characteristics, including definition and procedures to ascertain VTE cases influenced the magnitude of the incidence rates observed in each study.

SI.Table 27 Estimates of VTE incidence in several countries

Study size, age	**Study period**	**Incidence of DVT**	**Incidence of PE**	**Incidence of total VTE**	**References**
France, Germany, Italy, Spain, Sweden, UK (estimated incidence rates)[&]					
310.4 M All ages	2004	148 per 100 000 PY[&]	95 per 100 000 PY[&]	245 per 100 000 PY[&]	[R09-0200; R12-5099]
Denmark					
18 954 ≥ 20 years	1976 - 2007	NA	NA	269 per 100 000 PY[~] (95% CI, 252 - 286)	[R11-4531]
France					
342 017 All ages	April 1998 - March 1999	124 per 100 000 population per year[§] (95% CI, 112 - 136)	60 per 100 000 population per year[§] (95% CI, 52 - 69)	183 per 100 000 population per year[§] (95% CI, 169 - 198)	[R04-2879]
UK					
1 814 669 10 - 79 years	1994 - 2000	40.3 per 100 000 PY	34.2 per 100 000 PY	74.5 per 100 000 PY	[P07-06581]
Tromso, Norway					
26 755 25 - 97 years	1994 - 2007	NR	NR	160 per 100 000 PY [~] (95% CI, 146 - 175)	[R12-5106]
Sweden					
11, 8 M 0 - 75 years	1987 - 2007	NR	NR	34.3 per 100 000 PY[x]	[R12-5100]
US					
151 349 (all ages)	July 1985 - December 1986	48 per 100 000 population per year (95% CI: 43 - 54)	23 per 100 000 population per year (95% CI: 19 - 27)	71 per 100 000 population per year	[R05-0417]
106 470 (all ages)	1966 – 1990	48 per 100 000 population per year^ (95% CI: 45 - 51)	69 per 100 000 population per year^ (95% CI: 65 - 73)	117 per 100 000 population per year^ (95% CI: 112 - 122)	[R08-5647]

SI.Table 27 (cont'd) Estimates of VTE incidence in several countries

Study size, age	Study period	Incidence of DVT	Incidence of PE	Incidence of total VTE	References
US					
19 293 ≥ 45 years	1987 – 1998	NA	NA	145 per 100 000 PY (95% CI: 127 - 166)~	[R09-4890]
21 680 ≥ 45 years	7.6 years	117 per 100 000 PY#	45 per 100 000 PY#	192 per 100 000 PY*	[R05-0358]
477 800 All ages	1999, 2001, 2003	95 per 100 000 population per year* (95% CI: 90 - 101)	34 per 100 000 population per year* (95% CI: 31 - 37)	114 per 100 000 population per year* (95% CI: 108 - 120)	[R11-4370]
Japan (estimated incidence rates)					
NA 20 - 89 years	August - September 1996	NA	2.8 per 100 000 population per year (95% CI: 2.61 - 2.94)	NA	[R11-4369]
NA all-ages	August - September 2000	NA	3.2 per 100 000 population per year (95% CI: 2.92 - 3.39)	NA	[P11-11038]
Australia					
151 923 All ages	October 2003 - October 2004	35 per 100 000 population per year+ (95% CI: 26 - 44)	21 per 100 000 population per year+ (95% CI: 14 - 28)	57 per 100 000 population per year+ (95% CI: 47 - 67)	[R09-4372]
China					
650 000 All-ages	1997 – 2000	NA	NA	16.6 per 100 000 population per year	[R11-4361]

& Incidence of first lifetime and recurrent DVT.
~ Crude incidence rate.
§ Incidence rate for all events including recurrences.
^ Age- and sex-adjusted incidence to the 1980 US white population.
# Unadjusted incidence rate.
* Age-adjusted incidence rate.
+ Incidence adjusted to the WHO World Standard Population.
X Calculated from information provided.

The annual incidence of VTE rises sharply with age in both sexes [R05-0417, R08-5647, R04-2879, R05-0358, R11-4371].

There are racial differences in VTE incidence, with African-Americans having the highest incidence and Asian populations having the lowest incidence [R12-5099]. Genetic predisposition to thrombosis in European populations and African-Americans may play a role in racial differences in VTE. Differences in risk factors for VTE across populations might account for some of the racial differences. However, other aspects related to surveillance for VTE and access to medical care might influence racial differences in VTE incidence.

The annual incidence rates by age category for DVT and PE per 100 000 population in US during a time period of 18 months (1985 to 1986) are shown in SI.Table 28 below [R05-0417].

SI.Table 28 Annual age-specific incidence rates for DVT and PE per 100 000 population

Age group [years]	Incidence rates of DVT	Incidence rates of PE
0 – 9	0	0
10 – 19	3	2
20 – 29	14	6
30 – 39	25	7
40 – 49	17	12
50 – 59	43	19
60 – 69	119	73
70 – 79	232	84
>80	291	159
Overall rate	48 (95% CI: 43 - 54)	23 (95% CI: 19 - 27)

The incidence rates by sex and age category for overall VTE per 100 000 in Sweden from 1987 to 2007 are shown in SI.Table 29. The outcome definition was broad due to the evaluation of the known familial aggregation of thromboembolic risk and included venous thrombosis or embolism other than DVT and PE [R12-5100]. The overall analysis supported the familial background of the different manifestations of VTE. For men, the incidence rates per 100 000 PY were 10.5 (95% CI: 10.3 - 10.8) for DVT and 12.0 (95% CI: 11.7 - 12.3) for PE [R12-5101]. For women, incidence rates per 100 000 PY were 10.9 (95% CI: 10.7 - 11.2) for DVT and 12.5 (95% CI: 12.2 - 12.8) for PE.

SI.Table 29 Sex and age-specific incidence rates for VTE per 100 000 PY in Sweden over 20 years of follow-up (1987 to 2007)

Age group [years]	**Males** **Incidence rate (95% CI)**	**Females** **Incidence rate (95% CI)**
0 – 9	0.6 (0.5-0.8)	0.5 (0.3-0.6)
10 – 19	2.7 (2.4-3.0)	6.8 (6.3-7.3)
20 – 29	11.0 (10.4-11.6)	29.2 (28.1-30.2)
30 – 39	21.5 (20.6-22.3)	33.9 (32.8-35.0)
40 – 49	44.7 (43.5-46.0)	44.5 (43.2-45.8)
50 – 59	85.2 (83.2-87.1)	76.1 (74.2-78.0)
60 – 69	150.4 (146.3-154.5)	122.6 (118.9-126.3)
≥70	235.2 (218.5-251.8)	213.6 (198.3-228.8)
Overall rate (95% CI)	32.5 (32.1-33.0)	36.2 (36.2-35.7)

The estimates of VTE, DVT, and PE incidence by sex in several countries are shown in SI.Table 30, SI.Table 31, and SI.Table 32.

SI.Table 30 Estimates of VTE incidence by sex in several countries

Country	**Study Size Age**	**Study Period**	**Men**	**Women**	**Reference**
France	342 017 All-ages	April 1998 - March 1999	152 per 100 000 population per year # (95% CI: 134 - 172)	203 per 100 000 population per year # (95% CI: 183 - 226)	[R04-2879]
US	106 470 All-ages	1966 - 1990	130 per 100 000 population per year (95% CI: 122 - 138)	110 per 100 000 population per year (95% CI: 104 - 116)	[R08-5647]
US	19 293 ≥ 45 years	1987 - 1998	158 per 100 000 PY* (95% CI: 130 - 191)	114 per 100 000 PY* (95% CI: 93 - 139)	[R09-4890]
Australia	151 923 All-ages	October 2003 - October 2004	89 per 100 000 population per year (95% CI: 68 - 110)	78 per 100 000 population per year (95% CI: 59 - 97)	[R09-4372]

Sex-specific incidence rate for all events including recurrences.
* Age-adjusted incidence rate.

SI.Table 31 Estimates of DVT incidence per 100 000 population per year by sex in several countries

Country	Study size age	Study period	Men	Women	Reference
Sweden	230 835 All ages	1987	155	162	[R09-4371]
France	342 017 All ages	April 1998 - March 1999	105 # (95% CI: 90 - 122)	132 # (95% CI: 116 - 150)	[R04-2879]
US	151 349 All ages	July 1985 - December 1986	48 (95% CI: 40 - 57)	48 (95% CI: 41 - 57)	[R05-0417]
US	106 470 All ages	1966 - 1990	47 (95% CI: 42 - 52)	50 (95% CI: 46 - 54)	[R08-5647]
Australia	151 923 All ages	October 2003 - October 2004	58 (95% CI: 41 - 75)	47 (95% CI: 32 - 62)	[R09-4372]

Sex-specific incidence rates for all events including recurrences.

SI.Table 32 Estimates of PE incidence per 100 000 population per year by sex in several countries

Country	Study size age	Study period	Men	Women	Reference
France	342 017 All ages	April 1998 - March 1999	47 # (95% CI: 37 - 59)	71 # (95% CI: 59 - 85)	[R04-2879]
US	151 349 All ages	July 1985 - December 1986	25 (95% CI: 19 - 31)	21 (95% CI: 17 - 27)	[R05-0417]
US	106 470 All ages	1966 - 1990	82 (95% CI: 76 - 89)	60 (95% CI: 55 - 64)	[R08-5647]
Australia	151 923 All ages	October 2003 - October 2004	31 (95% CI: 19 - 43)	31 (95% CI: 19 - 43)	[R09-4372]

Sex-specific incidence rates for all events (including recurrences).

Prevalence

An analysis of healthcare claims data from 200 007 patients in the Thomson Reuters national MarketScan Commercial and Medicare databases (January 2002 to December 2006) reported

the overall US prevalence of VTE in 317 cases per 100 000 in 2002 and 422 cases per 100 000 in 2006, representing an increase of 33.1% during the study period [R11-4373]. In addition, the observed prevalence of VTE was higher in women than in men throughout the analysis. Moreover, the prevalence of VTE in the population increased with age, with the highest increase of prevalence in the group of >85 years.

A study based on health insurance claims data from a large privately insured US adult population (MarketScan Commercial Claims and Encounters and MarketScan Medicare Supplemental Coordination of Benefits databases, Thomson Reuters, New York) estimated the prevalence of VTE during 2005 through 2006 in 580 per 100 000 [R11-4366].

To estimate the number of people with VTE each year in the US, the CDC analysed 2007 to 2009 data from the NHDS [R12-5113]. The unit of analysis was hospitalisations and not the number of persons with the diagnosis of VTE. Therefore, multiple hospitalisations for an individual patient in a given year are counted more than once. Whether VTE was present on admission or onset occurred during the hospital stay cannot be determined, as well as if hospitalisations were for incident or recurrent events. The results of the analysis estimated that an average of 547 596 hospitalisations with VTE occurred each year among those aged 18 years or older in the US. The average annual rates of hospitalisations with each discharge diagnosis was as follows: 152 per 100 000 adults for DVT, 122 per 100 000 adults for PE, and 239 per 100 000 adults for VTE, These estimated rates were substantially higher among adults aged more than 60 years than among those aged 18 to 59 years. SI.Table 33 provides the estimated average annual rate, per 100 000 population, of hospitalisations with a diagnosis of DVT, PE, or VTE, by patient sex and age group.

In the EINSTEIN cohort study of DVT and PE in North America, out of 812 participants, 326 were treated for DVT and 486 were treated for PE. The majority of VTE patients were hospitalised for PE and the rest for DVT (84% and 16%, respectively) [R17-1278].

In Japan from January 1987 through December 1999, 0.11% (95% CI: 0.09 - 0.13) of the 131 060 hospitalised patients at a single medical centre had a confirmed diagnosis of VTE [R11-4367].

SI.Table 33 Estimated average annual rate (per 100 000 population) of hospitalisations with diagnosis of DVT, PE or VTE, by patient sex and age groups. NHDS, US 2007-2009*

Age group [year]	DVT hospitalisation rate (95% CI)			PE hospitalisation rate (95% CI)			VTE hospitalisation rate (95% CI)		
	Total	Men	Women	Total	Men	Women	Total	Men	Women
18 - 39	34 (26-42)	32 (23-40)	36 (27-45)	33 (25-40)	28 (19-36)	38 (28-48)	60 (47-72)	53 (40-65)	67 (52-81)
40 - 49	81 (63-98)	97 (72-123)	64 (47-81)	82 (63-100)	85 (61-109)	78 (58-99)	143 (114-172)	154 (117-190)	132 (103-161)
50 - 59	120 (98-143)	144 (113-175)	97 (75-119)	111 (86-135)	124 (91-156)	99 (73-124)	200 (164-237)	226 (180-272)	176 (138-213)
60 - 69	247 (194-299)	254 (197-311)	241 (181-301)	203 (160-246)	208 (159-257)	199 (150-247)	391 (315-468)	405 (321-490)	379 (293-465)
70 - 79	487 (389-584)	469 (362-576)	501 (388-614)	349 (264-434)	337 (229-445)	359 (276-446)	727 (582-872)	720 (556-884)	732 (578-885)
≥80	791 (649-934)	821 (635-1,007)	775 (629-921)	500 (392-609)	537 (368-592)	480 (368-592)	1,134 (927-1,340)	1,153 (904-1,402)	1,123 (911-1,336)
Over-all	152 (127-177)	146 (122-171)	158 (131-185)	121 (98-144)	115 (91-138)	127 (102-153)	239 (199-279)	226 (187-265)	252 (208-296)

*DVT and PE are not mutually exclusive. VTE includes patients with a diagnosis of either DVT or PE.

SI.4.2 Demographics of the population in the authorised indication –age, gender, racial and/or ethnic origin and risk factors for the disease

SI.4.2.1 Demographic profile

The percentage of females newly diagnosed as having VTE was 53% in UK during 1994 to 2000 with a median age of 63 years [P07-06581], 55% in US during 1987 to 1998 and a mean age of 59 years [R09-4890], 70.2% in Japan during 1987 to 1999 and a mean age of 64 years [R11-4367] and 54% in China during 1997 to 2000 [R11-4361].

The demographic profile of patients from the EINSTEIN DVT and PE studies in North America are provided in SI.Table 34.

SI.Table 34 Demographic profile of patients in the EINSTEIN DVT and PE studies in North America

	Total n=812
Gender (%)	425 male (52.3%) 387 female (47.7%)
Age	18-40 years old: 19.2% 40-60 years: 42.5% 60-75 years: 27.6% >75 years: 10.7%
Race	White: 86% Black: 9.2% Asian: 0.5% Native American or Alaskan: 0.5% Hispanic: 3.6% Other: 0.2%
BMI kg/m^2 (mean)	31.5
Data source: [R17-1278]	

The percentage of females among incident cases of DVT in Sweden during 1987 was 54% with a mean age of 72 years in this group [R09-4371], 57% in France during 1998/1999 with a mean age of 66 years [R04-2879], 50.7% in Denmark during 1980 to 2005 [R11-4410] and 53% in US during 1985 to 1986 with a mean age of 65 years [R05-0417].

The percentage of females with a new diagnostic of PE in France during 1998/1999 was 61% with a mean age of 71 years [R04-2879], 54.9% in Denmark during 1980 to 2005 [R11-4410] and 49% in US during 1985 to 1986 with a mean age of 66 years [R05-0417].

In a study of 4 European cohorts (2 in the UK, one in Austria, and one in the Netherlands), in a total of 2185 patients with a first venous thrombosis, 1043 were men and 1142 were women. Men had a mean age of 53 when experiencing their first venous thrombosis, while women with reproductive risk factors were on average 34 years old, and women without reproductive risk factors were on average 56 years old [R17-1323].

SI.4.2.2 Risk factors for the disease

From 15% to 25% of VTE cases occur in patients with cancer, and another 20% occur in patients who had surgery within the last 3 months [R09-4866]. In the PIOPED II trial, of the patients with PE, 94% had one or more of the following risk factors: bed rest of 3 days or more within the last month, travel of 4 hours or more within the last month, surgery within 3 months, cancer, past history of DVT or PE, trauma of lower extremities or pelvis, central

venous instrumentation within 3 months, stroke, paresis or paralysis, heart failure or COPD [R12-5534].

Obesity seems to be a risk factor for both PE and DVT but the risk is more apparent among young people [P07-06581, R12-5534, R12-5531]. In the Copenhagen City Heart Study both obesity and smoking were important risk factors for VTE [R11-4531]. On the other hand, in a meta-analysis, smoking did not significantly increase the risk of VTE (OR, 1.15; 95% CI: 0.92 - 1.44) but hypertension (OR, 1.51; 95% CI: 1.23 - 1.85) and diabetes (OR, 1.41; 95% CI: 1.12 - 1.77) did [R12-5531]. Hypertension (diastolic blood pressure ≥100 mmHg) was also a risk factor in the Copenhagen City Heart Study (OR, 1.34; 95% CI: 1.08 - 1.66) [R11-4531]. Height seems to be a risk factor for VTE, especially among men [R12-5536, R12-5534]. Pregnancy is a risk factor for VTE, and the rate of pregnancy-associated VTE is higher in older women (aged 35 to 44 years) than in younger women. [P07-06581, R12-5534].

Among women, oral contraceptives are a well-known risk factor for VTE, although the absolute risk seems to be low. Estrogen content is positively associated with the magnitude of the risk. Reports regarding the effect of duration of use are inconsistent, and the effect of oral contraceptives is synergistic with the effect of obesity [R12-5534, P07-06581]. Hormone replacement therapy increases the risk of VTE by 2- to 3-fold, although the risk seems higher when estrogens are combined with progesterone [P07-06581, R12-5534]. On the other hand, the increase in risk seems confined to oral formulations, and transdermal treatments appear to be risk free [R12-5532]. Tamoxifen, a selective estrogen-receptor modulator used to prevent and treat breast cancer, has also been associated with an increase incidence of VTE [R12-5534]. Other drugs that increase the risk of VTE, in decreasing order of magnitude, are oral corticosteroids, NSAIDs, and aspirin [P07-06581]. A non-interventional study conducted in France on 4 945 088 women found that a total of 1800 PE occurred, resulting in an absolute risk rate of 33 per 100 000 women years of oral contraceptive use [R17-1330].

Inherited and acquired thrombophilias, although rare, increase the risk of VTE. Much more common, heart failure, COPD, stroke, and cancer increase also the risk of VTE [R12-5534]. In a case-control study, the odds ratio of VTE was 2.08 (95% CI: 1.76 - 2.48) for heart failure, 1.54 (95% CI: 1.32 - 1.79) for COPD, 1.32 (95% CI: 1.13 - 1.54) for cerebrovascular disease, and 3.24 (95% CI: 2.84 - 3.69) for cancer [P07-06581]. Other conditions that increase the risk of VTE by nearly 2-fold are ulcerative colitis, rheumatoid arthritis, and nephrotic syndrome [R12-5534, P07-06581].

Although data on the risk of varicose veins is not conclusive [R12-5534], one study found an odds ratio of VTE for varicose veins of 1.78 (95% CI: 1.48 - 2.15) [P07-06581].

SI.4.3 The main existing treatment options

All clinical guidelines agree that the treatments of choice for low risk PE are intravenous LMWH or subcutaneous UFH with monitoring, weight-based subcutaneous UFH without monitoring, or subcutaneous fondaparinux at weight-adjusted doses without monitoring. For high risk PE, thrombolysis is indicated unless there is an absolute contraindication. In patients with absolute contraindications to thrombolysis and in those in whom thrombolysis

has failed to improve haemodynamic status, surgical embolectomy is the preferred therapy. If this is not immediately available, catheter embolectomy or thrombus fragmentation may be considered [P08-12590; P11-07302; P08-08095].

Current American College of Chest Physician guidelines for long-term treatment of PE and DVT recommend treatment with dabigatran, rivaroxaban, apixaban, or edoxaban over VKAs [P16-00349] for 3 months if there are no additional risk factors or if the risk factors were transient. In patients without moderate or high risk of bleeding with a second unprovoked episode, long-term treatment should be implemented. Long-term treatment is also recommended among patients with VTE and cancer, however, LMWH is recommended over VKA therapy, dabigatran, rivaroxaban, or edoxaban. In patients who receive long-term anticoagulant treatment, the risk-benefit ratio of continuing such treatment should be reassessed at regular intervals. The dose of VKA should be adjusted to maintain a target INR of 2.5 (range, 2.0 - 3.0) regardless of treatment duration [P08-12590].

Intravenous LMWH or subcutaneous UFH with monitoring, weight-based subcutaneous UFH without monitoring, or subcutaneous fondaparinux at weight-adjusted doses without monitoring are also the treatments of choice for confirmed DVT [P08-08095]. For both PE and DVT, the heparin treatment should be continued for 5 days, combined with initiation of VKAs on the first treatment day, and discontinued when the INR is greater than 2.0 for at least 24 hours [P08-08095].

In a recent guideline by the American College of Chest Physicians, preference is given to LMWH or fondaparinux over intravenous or subcutaneous UHF. In this guideline, anticoagulation with rivaroxaban or parenteral LMWH is recommended as initial VTE treatment. For long-term treatment, the guideline suggests dabigatran, rivaroxaban, apixaban, or edoxaban over VKA in patients with VTE and no cancer. VKA is recommended over LMWH for the same indication [P16-00349]. In patients with VTE and cancer, LMWH rather than VKA therapy or other OAC is recommended. Finally, in patients with VTE and cancer who are not treated with LMWH, VKA is recommended over dabigatran or rivaroxaban for long-term therapy [P12-02755].

Treatment options and optimal use are provided in SI.Table 35.

SI.Table 35 Treatment options for the prevention of VTE in patients with acute DVT and/or PE and prevention of related death

Treatment options		**Optimal use of treatment**
Anti-coagulants	Dabigatran	Recommended for use in VTE patients with no cancer as anticoagulant therapy (for 3 months)
	Rivaroxaban	
	Apixaban	
	Edoxaban	
	VKAs	Recommended as an alternative to NOACs in patients with no cancer, or as an alternative to LMWH in patients with cancer
	LMWH	Recommended for use in VTE patients with cancer as anticoagulant therapy (for 3 months)

SI.4.4 Natural history of the indicated condition in the population, including mortality and morbidity

SI.4.4.1 Mortality

The 1-month fatality rate in UK during 1994 to 2000 was 1.4% after an episode of DVT and 22.6% after PE [P07-06581].

The overall mortality in UK from 1994 to 2000, was 14.2% (49.50 per 1000 PY) in a VTE cohort and 4.7% (14.50 per 1000 PY) in the control group, and the adjusted RR for death was 2.4 (95% CI: 2.2 - 2.6) for VTE patients compared to patients without VTE [R11-4409].

12% of the total number of deaths per annum occurring in France, Germany, Italy, Spain, Sweden, and the UK are due to VTE with the proportion varying from 10% in the UK to 14% in Italy [R09-0200].

The prospective SWIVTER enrolled 1247 consecutive patients aged 18 years or older with acute DVT or PE from 4 academic and 14 non-academic acute care hospitals from January 2009 through May 2010 [R12-5097]. Prior history of VTE was present in 23% of patients. The overall in-hospital mortality rate was 5.3%, and the rate of non-fatal recurrent VTE was 2.3%. Age was an important determinant of mortality rate; 3.2% among those aged less than 65 years and 6.6% among those aged 65 years or older. The median duration of hospital stay was 11 days.

The case-fatality rates for DVT and PE in the US from1985 to 1986 were 5% and 23%, respectively [R05-0417].

The mortality within a month and 6 months for PE diagnosis in Japan during 2000 was 16% and 20%, respectively [P11-11038].

SI.4.4.2 Morbidity

The profile of potential health risks following VTE includes PTS and PH. PTS symptoms include chronic leg pain, swelling, redness, and ulcers (sores) [R11-4365].

In UK, the prevalence of mild and moderate PTS among women with a single previous episode of DVT at age ≤50 years (n = 43) was 67% and 7%, respectively [R11-4362].

In Italy, during a median follow-up of 94.3 months, the cumulative incidence of CTPH in patients with an acute episode of PE but without prior venous thromboembolism (n = 223), was 1% (95% CI: 0.0 - 2.4) at 6 months, 3.1% (95% CI: 0.7 - 5.5) at 1 year, and 3.8% (95% CI: 1.1 - 6.5) at 2 years [R11-4363].

Another Italian study evaluated 239 patients with acute PE without prior VTE history [R11-4599]. Median age of patients was 59 years (range, 16 - 89 years). Overall mortality was 1.3% during a median time of 36 months. The incidence of CTPH was 0.4 per 100 PY. Cumulative recurrence of VTE was 1.5% (95% CI: 0.2% - 3.2%) at 3 months, 4.4% (95% CI: 1.4% - 7.4%) at 6 months, 7.1% (95% CI: 3.5% - 10.5%) at 1 year, 9.4% (95% CI: 5.4% - 13.4%) at 1.5 years, 15.7% (95% CI: 10.4% - 21.1%) at 2 years and 43% (95% CI: 33.3% - 52.7%) at 5 years.

The estimated total number of associated complications per annum within 6 European countries in 2004, was 395 673 for PTS and 4135 for PH [R09-0200].

A non-interventional study on the incidence of postoperative DVT in the US found that out of 2 669 772 patients (43% males and 57% females) undergoing surgery from 2005 to 2010, 0.69 % developed DVT within 30 days after surgery. In general patients were older and had higher incidence of COPD, history of CHF, perioperative sepsis and longer lengths of hospital stay. The incidence of postoperative DVT was 0.66% after general surgery, 0.99% after vascular surgery and 2.07% after cardiac surgery [R17-1274].

An Italian non-interventional study of 84 253 patients found that current use of antipsychotic drugs more than doubled the risk of PE (OR 2.31, 95% CI: 1.16-4.59). The use of both first and second generation antipsychotics were associated with an increased risk by four times (OR 4.21, 95% CI: 1.59-11.59) [R17-1328].

SI.4.5 Important comorbidities

See Section SI.5.5.

SI.5 sVTEp

For general incidence, prevalence, demographic profile, risk factors, treatment options, and natural history including mortality and morbidity of patients with VTE, DVT, and/or PE, please refer to Section SI.4.

SI.5.1 Incidence and prevalence

SI.Table 36 shows the recurrence rates of venous thromboembolisms reported in published studies from several countries.

In a multinational, multicenter registry-based study (RIETE) performed in several European countries and Brazil, which included over 16 000 patients diagnosed with VTE, the cumulative recurrence of VTE at 3 months was 1.9% [R12-5288].

In an Italian multicenter registry, the overall VTE recurrence rate during a follow-up of 24 months was 3.6 per 100 PY [R12-4147]. Another Italian study evaluated 239 patients with acute PE without prior VTE history who were referred in a thrombosis center [R11-4599]. Median age of patients was 59 years (range, 16 to 89 years). Cumulative recurrence of VTE (95% CI) was 1.5% (0.2% - 3.2%) at 3 months, 4.4% (1.4% - 7.4%) at 6 months, 7.1% (3.5% - 10.5%) at 1 year, 9.4% (5.4% - 13.4%) at 1.5 years, 15.7% (10.4% - 21.1%) at 2 years, and 43% (33.3% - 52.7%) at 5 years.

In the Netherlands, between November 2002 and September 2004, 3% (95% CI: 1.8% - 4.6%) of the patients with PE had an objectively confirmed recurrent VTE event during the 3-month follow-up period. Of patients with a recurrent VTE, 70% had a recurrent PE (2.1% overall), and 30% (6 of 20 patients) had DVT (0.9% overall). Recurrent thrombotic events occurred predominantly within the first 3 weeks after the diagnosis [R09-4887]. In the same country, a multicenter registry found a cumulative recurrence rate at 3 months to be 0.34% for DVT and 1.7% for VTE [R12-5102].

A large case-control study using the GPRD (UK) identified 20 090 patients aged 18 years and older with VTE on or after 01 January 1995, through 30 October 2009 [R12-2550]. The incidence of VTE recurrence with hospitalisation was 97 per 1000 PY. The largest risk of recurrence occurred within the first 3 months after the first VTE.

In a study of 4 European cohorts (2 in the UK, 1 in Austria, and 1 in the Netherlands), the incidence rate of recurring venous thrombosis for men was 6.0 (95% CI: 5.3 - 8.6) per 100 person-years, the average time between the first and recurring events was 2.3 years. Women with reproductive risk factors had a recurring venous thrombosis incidence rate of 1.1 (95% CI: 0.7 - 1.5) per 100 person-years, with on average 4.5 years between the first and recurrent events. Women without reproductive risk factors had a recurring venous thrombosis incidence rate of 2.4 (95% CI: 1.7 - 3.2) per 100 person-years, with an average of 2.3 between the first and recurrent events [R17-1323].

In a large cohort study using the RAMQ database in Canada, the recurrence rate of VTE was 2.4 per 100 PY (95% CI: 2.3 - 2.5 per 100 PY) during a follow-up of 3.9 years [R12-5535].

The mean (SD) age of patients included in this cohort was 62 (18) years. In this study, the risk of recurrent VTE was higher among men than among women (RR, 1.13; 95% CI: 1.07 - 1.19).

In a population-based cohort of patients with incident VTE among all residents of Olmstead County (Minnesota, US) the highest recurrence of VTE occurred during the first 14-days (55.4 per 100 PY) [R12-5285; R12-5284]. The corresponding recurrence rates were 30.0 per 100 PY at 90 days and 17.7 per 100 PY at 180 days.

The rates of recurrent PE (with or without DVT) among patients with VTE in a population-based data study conducted in the US during 1999, 2001, and 2003, was 1.6% within 30 days of follow-up, 4.1 % within 1 year, and 5.0% within 3 years for patients aged younger than 65 years and 1.0% within 30 days, 2.7% within 1 year, and 4.9% within 3 years in patients aged 65 years and older [R11-4370]. In a recent publication including additional data from 2005, the overall rate of PE was 1.5% and of DVT was 11.5% among 2488 patients with VTE [R12-5107].

SI.Table 36 VTE recurrence estimates in several countries

Study Size Age	**Follow-up**	**Recurrence of DVT**	**Recurrence of PE**	**Recurrence of VTE**	**References**
Spain, France, Italy, Israel, Germany, Switzerland, Macedonia and Brazil (RIETE registry)					
16 199 <29 to >79 years	3 months	1.2%	0.7%	1.9%	[R12-5288]
Italy (MASTER Multicenter Registry)					
1988 18 years and older	24 months	3.84 per 100 PY	3.09 per 100 PY	3.63 per 100 PY	[R12-4147]
The Netherlands (Multicenter Registry)					
297 18 years and older	3 months	0.34% (95% CI: 0.01% - 1.9%)	1.7% (95% CI: 0.55% - 3.9%)	NR	[R12-5102]
The UK (The GPRD)					
20 090 18 years and older	5 years	NR	NR	97 per 1000 PY	[R12-2550]
RAMQ Quebec, Canada					
5243 <35 to >75 years	3.9 years	NR	NR	2.4 per 100 PY 95% CI: 2.3 - 2.5 per 100 PY	[R12-5535]
Olmsted County, Minnesota, US					
1166 0 - 100 years	180 days	NR	NR	30.0 per 100 PY at 90 days 17.7 per 100 PY at 180 days	[R12-5285; R12-5284
Worcester, Massachusetts, US					
151 349 All-ages	Annual rate	NR	NR	30 per 100 000 PY	[R05-0417]
2488 18 years and older	992 days of median follow-up	11.5%	1.5 %	NR	[R12-5107]

Recurrence rates of VTE were higher in elderly patients with VTE compared to younger cases [R12-2550, R12-5284]. SI.Table 37 shows the recurrence rates by age and sex groups reported in the UK study.

SI.Table 37 VTE age-specific and sex-specific recurrence rates of VTE hospitalisation per 1000 PY

Category	Recurrence rate of VTE per 1000 PY
Age group [year]	
18 – 39	84.9
40 – 59	75.2
60 – 79	95.4
>80	139.7
Sex	
Women	97.9
Men	96.3
Overall rate	97.0

In a non-interventional study using claims data in the US across 6 payor databases (IMS, Optum, MSCommercial, MSMedicare, Humana and Medicaid) between 2010 and 2012, recurrent VTE related hospitalisations occurred in 10 to 23% of patients across the databases. Recurrent rates among PE patients (12-32%) were higher than those for DVT patients (6-16%) [R17-1295].

SI.5.2 Demographics of the population in the authorised indication –age, gender, racial and/or ethnic origin and risk factors for the disease

SI.5.2.1 Demographic profile

Among patients with VTE in the RAMQ database (Canada), the percentage of females with recurrent VTE was 8.9%, with a mean age at the time of recurrence of 64 years [R12-5535]. In the UK, 44.5% (1326 of 2978) of recurrent VTE cases occurred in females [R12-2550]. In the MASTER Italian Registry, 50.6% of VTE recurrences occurred in females, and 54.6% occurred in patients aged 61 years or older [R12-4147].

SI.5.2.2 Risk factors for the disease

Independent predictors of VTE recurrence include male sex, increasing age and BMI, neurological disease with extremity paresis, and active malignancy [R12-5619, R12-5284]. Other factors found to be independent predictors of VTE recurrence are idiopathic VTE, lupus anticoagulant or antiphospholipid antibody, antithrombin, and protein C or protein S deficiency. In the MASTER registry, in-hospital management was independently associated with the recurrence of VTE [R12-4147]. Early recurrence seems to be highest during the heparin transition to warfarin treatment. Active cancer is an important predictor of early recurrence [R12-5284]. In the Worcester VTE study, the occurrence of a major bleeding event following a diagnosis of VTE was the only predictor of recurrence of VTE during a 3-year follow-up period [R11-4370].

In a study of 4 European cohorts (2 in the UK, 1 in Austria, and 1 in the Netherlands), men had a 2.8-fold (95% CI: 2.2 - 3.4) higher risk of recurrent venous thrombosis than women, this risk was 5.2-fold increased (95% CI: 3.5 - 7.7) compared with women with a reproduction-related first venous thrombosis and 2.3-fold (95% CI: 1.7 - 3.2) compared with women without reproductive risk factors [R17-1323].

SI.5.3 The main existing treatment options

In a population-based cohort study, low-intensity heparin and standard-intensity warfarin anticoagulation were effective in preventing VTE recurrence [R12-5285]. In the most recent guideline on VTE [P12-02755], treatment duration and treatment intensity guide the prevention of recurrent VTE, depending on the baseline risk of having a recurrent VTE. Once a second unprovoked VTE has occurred, the guideline recommends extended anticoagulant therapy (for more than 12 months), instead of only 3 months of therapy, in those who have a low haemorrhage risk and extended anticoagulant therapy in those with a moderate haemorrhage risk. For those patients with high haemorrhage risk, the guideline suggests 3 months of anticoagulant therapy over extended therapy. In all patients who receive extended anticoagulant therapy, the continuing use of treatment should be reassessed at periodic intervals (e.g. annually). Regarding the mode of treatment, for those patients who are candidates for extended therapy because of a second VTE, the guideline suggests treatment with the same anticoagulant chosen for the first 3 months.

SI.5.4 Natural history of the indicated condition in the population, including mortality and morbidity

SI.5.4.1 Mortality

In the Netherlands, between November 2002 and September 2004, recurrent PE was fatal in 79% (95% CI: 49% - 95%) of the patients with recurrent PE. The resulting case-fatality rate was 55% [R09-4887].

In the multinational (several European countries and Brazil), multicenter RIETE-based study, 5.9% of patients with VTE died during the 3-months of follow-up [R12-5288]. Among patients with recurrent PE, 28% died of the PE event. Age was a determinant factor of mortality, the mean (SD) age of fatal cases was 71 (16) years. In addition, 29% of patients presenting with major bleeding during follow-up died.

Among VTE cases identified in a CPRD study (UK), the mortality rate due to VTE during the follow-up was 37.4 per 1000 PY [R12-2550]. The mortality was higher during the first year after the VTE event than thereafter.

In the Italian MASTER registry, the death rate of patients with recurrent VTE was 16.5 per 100 PY [R12-4147].

In the study performed in Olmstead County, Minnesota (US), the 2-week case-fatality rate was 2% for recurrent DVT alone and 11% for recurrent PE with or without DVT [R12-5285].

SI.5.5 Important comorbidities

In a case-control study with 8368 cases of VTE in Denmark during 1999 to 2006, the use of co-medications during the 60 days before the index date was 4.4% for antipsychotics, 5.8% for hormone replacement therapy, 9.9% for oral glucocorticoids, and 2.6% for VKA. For NSAIDs, the use ranged from 8.2% for ibuprofen to 0.4% for naproxen [P11-10351].

In a case-control study with 6550 cases of VTE done in the UK in GPRD during the period 1994 to 2000, the prevalence of current use, defined as when the supply of the most recent prescription lasted until the index date or ended in the 30 days before the index date, was 13.8% for NSAIDs, 10.3% for aspirin, 7.9% for oral corticosteroids, and 2.1% for statins [P07-06581]. Among women, the prevalence of current use of oral contraceptives was 23.1% and of hormone replacement therapy was 15.2%.

Active cancer

Incidence and prevalence of active cancer

SI.Table 38 provides the incidence of cancer in patients with VTE. The incidence ranges from 1% up to 6% in patients with DVT and the risk of cancer is greater in patients with DVT or PE.

SI.Table 38 The incidence of active cancer in patients with VTE

	Country	Design	Year	Population	Incidence of Active Cancer
R11-4364	Denmark	Population-based study based on existing data	1997-1999	Patients with cancer	**RR of a second cancer diagnosis in patients with vs. without VTE (95% CI):** 1.3 (1.1 -1.4)
R12-5096	Denmark	Population based study	2004-2009	Patients with an inpatient or outpatient diagnosis of superficial or deep leg venous thrombosis or PE (n=77 247)	**Risk of cancer at 1-year follow-up** DVT patients: 2.7% PE patients: 2.9% **Standardised incidence ratio (95%CI) at 1-year follow up comparing observed vs expected incidence of cancer in the Danish population** DVT patients: 2.7 (2.6 -2.9) PE patients 3.3 (3.0 -3.5) **Incidence of cancer during years 2-15 of follow up** DVT patients: 5.8% PE patients: 4.7% **Standardised incidence ratio (95%CI) for years 2-15 of follow up comparing observed vs expected incidence of cancer in the Danish population** DVT patients: 1.1 (1.1 -1.2) PE patients: 1.2 (1.1 -1.2)
R12-4147	Italy	Non-interventional study based on existing data		Patients in the MASTER Italian registry with VTE	**Cumulative incidence of cancer during 24 months of follow-up:** 1.3%
R12-5528	Canada	Prospective		Patients with incident VTE (n=1852)	**Rate per 100 PY of new cancers (95% CI)**: 1.32 (1.09 -1.60)

SI.Table 39 provides the prevalence of active cancer in patients with VTE. Prevalence of active cancer generally ranged from 13% to 25% with some lower estimates in selected studies.

SI.Table 39 The prevalence of active cancer in patients with VTE

	Country	Design	Year	Population	Prevalence of Active Cancer
R09-4371	Sweden	Pro-spective	1987	Patients with incident VT(n=366)	**Malignancy**: 20%
R12-5110	Denmark	Population based non-interventional study based on existing data	1999-2009	Patients with hospital-diagnosed VTE defined as lower limb DVT or PE from Northern Denmark representing 30% of Danish population (n=15 009)	**Pre-existing cancer or cancer diagnosed within 3 months before the VTE:** 22%
R12-5106	Norway	Population based	1994-2007	Patients >24 years old with a hospital diagnosis of VTE from the Tromso study	**Cancer**: 22.9%
R12-5104	UK	Case-control	Pub-lished 2011	Patients aged 18 or older with first-time DVT (n=11 557) or PE (n=5162) from a general practice database of approximately 3.5 million patients	**Cancer during previous 1 year before VTE diagnosis** DVT: 9.2% PE: 11.3%
R12-5286	Netherlands	Case-control	1994-2004	Patients with VTE in anti-coagulation clinics (n-4947)	**Cancer**: 13%
P07-06581	UK	Non-inter-ventional	1994-2000	Patients with VTE (n=6550)	**Cancer**: 16%
R12-5288	Multinational: Spain, France, Italy, Israel, Germany, Switzerland, Republic of Macedonia, and Brazil	Pro-spective	2003-2010	Patients with symptomatic acute lower limb DVT (n=16 199)	**Cancer at the time of DVT diagnosis** (defined as newly diagnosed cancer or cancer that was being treated) Overall: 20% ≤ 29 years old: 2.5% 60-69 years old: 26%
R12-4147	Italy	Non-inter-ventional study based on existing data	Pub-lished 2012	Patients with VTE from the MASTER registry	**Cancer** Overall: 18% Recurrent VTE: 19.5%
R12-5102	Netherlands	Pro-spective	Pub-lished 2011	Hospitalised patients diagnosed with DVT or PE	**Cancer**: 9.4%
R12-5097	Switzerland	Pro-spective	Pub-lished 2012	Hospitalised patients diagnosed with DVT or PE	**Cancer**: 25%
R05-0358	US	Population based	Pub-lished 2004	Patients with DVT and PE from 2 cohorts: the CHS and ARIC study	**Cancer 1 year before diagnosis of DVT or PE** CHS: 51% ARIC: 39%

SI.Table 39 (cont'd) The prevalence of active cancer in patients with VTE

	Country	Design	Year	Population	Prevalence of Active Cancer
R12-5098, R12-5109	US	Non-interventional study based on existing data	Published 2011	Inpatients with a diagnosis of PE from the NIS and Kids Inpatient database	**Cancer** Overall: 16% Aged < 18 years: 16%
R12-5107	US	Non-interventional study	Published 2012	Patients with a confirmed/validated diagnosis of VTE from the Worcester Venous Thromboembolism Study	**Active cancer or history of cancer:** 26%
R12-5285	US	Prospective	Published 2011	Patients with VTE in Olmstead County Minnesota	**Active cancer**: 23%
P11-11038	Japan		2000	Patients with PE	**Malignancy**: 13%
R12-5287	Taiwan	Non-interventional study based on existing data	2002	Patients aged 18 years or older from the NHI database with a hospital discharge diagnosis of VTE (n=2774)	**Malignant neoplasm:** 22%
R17-1295	US	Non-interventional study based on existing data	2009-2012	Patients with primary diagnosis of DVT or PE associated with an inpatient and/or ER claim. Two years data evaluated from IMS, Optum, Humana, MSCommercial, MSMedicare, and Medicaid.	**Cancer:** 40%

Additionally, a US claims-database analysis including 12.7 million patients between 2002 and 2006 estimated the US prevalence of VTE, and compared the co-morbid condition between VTE patients (n=200 007) and non-VTE patients [R11-4373]. The prevalence of active cancer in VTE patients was 2.7% whereas in non-VTE patients it was 0.9% resulting in an adjusted odds ratio (with vs. without VTE) of 1.93 (95% CI: 1.84 – 2.02).

Mortality of active cancer

The percentage of deaths with the underlying cause of cancer was 56.0% among patients with VTE (N = 500) in UK during 1994 to 2000 [R11-4409]. In another UK study, among 46 355 VTE cases, the mortality rate due to neoplasms (ICD 10 codes C00-D48) was 85.4 per 1000 PY [R12-2550].

During the 3-month follow-up period of a study conducted in the Netherlands between November 2002 and September 2004, 35% of the deceased patients with PE (55 out of 673) died due to malignancy [R09-4887].

In the SWIVTER cited previously, among adult patients with a hospital-diagnosed DVT or PE, cancer was an independent predictor of in-hospital death (HR = 5.2; 95% CI: 2.7 - 9.8) [R12-5097].

The analysis of a Cancer Registry in US during 1993 to 1995 showed that venous thromboembolism was associated with an increased risk of death for all stages and cancer types, significant for all but regional and metastatic renal cancer, with a median overall RR of 3.7 (range of HRs, 1.3 - 14.4) [R11-4358]. In a more recent study, by after 8 years of follow-up, 55% of the patients with cancer had died [R12-5286].

Co-medication

The prescribed medicines vary by cancer type. No data are available on concomitant use of anticancer treatments in the studies cited above.

Hypertension

Incidence and prevalence of hypertension

Hypertension is a common and chronic co-morbidity and therefore is better described by its prevalence, see below.

The percentage of hypertension among patients with VTE (n = 6550) in UK during 1994 to 2000 was 23.33% [P07-06581]. In a case-control study with about 16 000 cases of VTE in the UK during 1991 to 2006, the prevalence of hypertension was 26% [R12-5104].

In a cohort study conducted in Denmark during 1977 to 2007, 10% of the patients with VTE (n = 97 558) presented hypertension [R11-4532].

The percentage of hypertension among patients with VTE (n = 1897) in US during 1999, 2001 and 2003 was 52.76% [R11-4370]. In a reanalysis of the same study but including 2005 data, the prevalence of hypertension was 54.2% [R12-5107].

A non-interventional study conducted in the US including 4557 patients across 6 payor databases (IMS, Optum, MSCommercial, MSMedicare, Humana, Medicaid) from 2010 to 2012 found that more than 50% of patients with DVT and PE had hypertension [R17-1295].

In the NHI database study, among patients aged 18 years or older with a hospital discharge diagnosis of VTE (N = 2774) from 01 January through 31 December 2002, the prevalence of systemic hypertension was 51.2% [R12-5287].

Mortality of hypertension

There were no data on mortality of hypertension found in the target population.

Co-medication

There were no data on co-medication for hypertension found in the target population.

Coronary artery disease

Incidence and prevalence of coronary artery disease

There were no data on incidence of coronary artery disease found in the target population. In a case-control study with around 20 000 cases of VTE in the UK during 1991 to 2006, prior myocardial infarction was present in 3.7 % of cases [R12-5104]. In addition, 9.9% of cases had a diagnosis code of angina, and almost 10% of the cases presented with prior familial history of coronary heart disease.

In the case-control study in the Netherlands, the prevalence of myocardial infarction among 5000 cases of VTE was 2.8% [R12-5286].

Among patients with VTE in the Worcester Venous Thromboembolism Study (USA), the overall prevalence of ischaemic heart disease was 13% [R12-5107].

In another publication from the same study, cases of incident VTE identified in 1999, 2001, and 2003 (n = 473) were classified with or without concomitant symptomatic atherosclerosis (n=1345). Symptomatic atherosclerosis was defined as the presence of prior history of ischaemic heart disease, coronary revascularisation procedure, or peripheral arterial disease [R12-5114]. Patients with concomitant symptomatic atherosclerosis (26% of the VTE patients) were older; more frequently men; and more frequently had hypertension, diabetes, heart failure, peripheral arterial disease, myocardial infarction, or ischaemic heart disease manifestations and developed VTE during hospitalisation for another condition more often than patients without symptomatic atherosclerosis. Among patients with and without atherosclerosis, cumulative rates of the following conditions were similar: recurrent DVT (13.3% and 16.1%, respectively), PE (4.6% and 5.5%, respectively), in-hospital death (5.5% and 4.1%, respectively), death within 30 days of diagnosis (9.5% and 7.5%, respectively) were similar. In-hospital major bleeding was higher among patients with symptomatic atherosclerosis, 7.6%, than without it, 3.8%.

In a study using data from the NHI database from 01 January through 31 December 2002, the prevalence of coronary heart disease was 31.7% among patients aged 18 years or older with a hospital discharge diagnosis of VTE (n=2774) [R12-5287].

A US claims-database analysis including 12.7 million patients between January 2002 and December 2006 estimated the US prevalence of VTE, and compared the co-morbid condition between VTE patients (n=200 007) and non-VTE patients [R11-4373]. The prevalence of

coronary heart disease in VTE patients was 18.3% whereas in non-VTE patients it was 5.3% resulting in an adjusted odds ratio (with vs. without VTE) of 1.77 (95% CI: 1.74–1.81).

Mortality of coronary artery disease

The percentage of deaths caused by coronary heart disease was 9.8% among patients with VTE (n = 500) in UK during 1994 to 2000 [R11-4409].

During the 3-month follow-up period in a study conducted in the Netherlands between November 2002 and September 2004, 16% of the deceased PE patients (55 out of 673) died due to a cardiovascular disease [R09-4887].

Co-medication

There were no data on co-medication for coronary artery disease found in the target population.

Diabetes mellitus

Incidence and prevalence of diabetes mellitus

Diabetes is a common and chronic co-morbidity and therefore is better described by its prevalence, see below.

The percentage of diabetes among patients with VTE (n = 6550) in UK during 1994 to 2000 was 5.8% [P07-06581]. In a case-control study with about 16 000 cases of VTE in the UK during 1991 to 2006, the prevalence of diabetes was 7.5% [R12-5014].

In Sweden during 1997 to 1999, about 19% of the patients with VTE (n = 302) presented with diabetes [R11-4529]. However, a study using data from a Swedish registry including 1247 patients with VTE during the period 2009 to 2010 found a lower prevalence of diabetes, 9.1% [R12-5097].

In a cohort study conducted in Denmark during 1977 to 2007, 6.7% of the patients with VTE (n = 97 558) had diabetes [R11-4532]. In another Danish study, among 15 009 patients diagnosed with VTE during 1999 to 2009, the prevalence of diabetes was 7.8% [P11-10351].

The prevalence of diabetes in a cohort study of patients with VTE in the Netherlands was 3.7% [R12-5286].

In a recent publication of the Worcester Venous Thromboembolism Study, the prevalence of diabetes among patients with VTE was 19.1% [R12-5107]. In a study of inpatient data during the 1998 to 2008 time period, using the US NIS, the prevalence of diabetes among patients admitted for PE was 14.7% [R12-5098].

In the NHI database study among patients aged 18 years or older with a hospital discharge diagnosis of VTE (n=2774) from 01 Jan through 31 Dec 2002, the prevalence of diabetes was 26.4% [R12-5287].

A US claims-database analysis including 12.7 million patients between January 2002 and December 2006 estimated the US prevalence of VTE, and compared the co-morbid condition between VTE patients (n=200 007) and non-VTE patients [R11-4373]. The prevalence of coronary heart disease in VTE patients was 16.5% whereas in non-VTE patients it was 4.4% resulting in an adjusted odds ratio (with vs. without VTE) of 2.57 (95% CI: 2.52 – 2.63).

A non-interventional study conducted in the US including 4557 patients across 6 payor databases (IMS, Optum, MSCommercial, MSMedicare, Humana, Medicaid) from 2010 to 2012 found that between 11-36% patients with DVT and PE had diabetes.

Mortality of diabetes mellitus

Among patients with diabetes in the Worcester Venous Thromboembolism Study (US), the mortality within 30 days of diagnosis was 9.9%. In-hospital death occurred in 6.3% of the patients with diabetes [R12-5107].

Co-medication

Among patients with VTE (n = 6550) in the UK during 1994 to 2000, 1.3% were treated with insulin and 3.1% were treated with oral antidiabetic drugs [P07-06581]. In the Worcester Venous Thromboembolism Study in the US during 1999 to 2005, the same percentages were 6.3% and 8.7%, respectively [R12-5107].

In Sweden during 1997 to 1999, 43% of the diabetic patients with VTE were being treated with insulin, either alone or in combination with oral medication, 25% with oral hypoglycemic agents, and 32% with non-pharmacological treatment [R11-4529].

Heart failure

Incidence and prevalence of heart failure

A study conducted in US by combining 2 population-based cohorts from the CHS and ARIC study reported that 8% of the patients with DVT and 10% of the patients with PE presented with heart failure within 90 days of thrombosis [R05-0358].

In an international multicenter registry of patients with acute VTE (n = 10 114), 5.6% of them presented chronic heart failure as an underlying disease [R11-4582].

The percentage of heart failure in patients with VTE (n = 6550) in UK during 1994 to 2000 was 7.25% [P07-06581].

A Danish, nationwide, population-based, case-control study including 109 752 patients with a first-recorded hospitalisation for PE and/or DVT were identified between 1980 and 2007 [R12-5103]. Among these 3 groups of cases, the prevalence of heart failure within the 3 months prior to hospitalisation for VTE was 7.3% of those with PE only, 4.2% of those with PE and DVT, and 2.2% of those with only DVT. The corresponding figures for history of heart failure more than 3 months before the index VTE hospitalisation were 7.9% (PE only), 3.6% (PE and DVT), and 3.8% (only DVT).

In a cohort study in the Netherlands of patients with VTE, the prevalence of heart failure was 1.2% [R12-5286].

In the multinational, multicenter RIETE-based study, based on data from 16 199 consecutively enrolled patients with confirmed diagnoses of acute lower limb DVT, the prevalence of chronic heart failure was 4%, ranging from 0.1% in patients aged 29 years or younger to 10% in patients aged 70 to 79 years [R12-5288].

Among patients with VTE in the Worcester Venous Thromboembolism Study (US), the prevalence of heart failure was 17.3% [R12-5107]. Similarly, in the study performed in Olmsted County, Minnesota, the prevalence of congestive heart failure among incident VTE cases was 18% [R12-5285].

The prevalence of heart failure in patients with VTE in Japan during 1987 to 1999 was 10% [R11-4367].

In the NHI database study, among patients aged 18 years or older with a hospital discharge diagnosis of VTE (N = 2774) from 01 January through 31 December 2002, the prevalence of congestive heart failure was 18.6% [R12-5287].

A US claims-database analysis including 12.7 million patients between January 2002 and December 2006 estimated the US prevalence of VTE, and compared the co-morbid condition between VTE patients (n=200 007) and non-VTE patients [R11-4373]. The prevalence of heart failure in VTE patients was 14.9% whereas in non-VTE patients it was 2.1% resulting in an adjusted odds ratio (with vs. without VTE) of 3.23 (95% CI: 3.15 – 3.32).

Mortality of heart failure

In an international multicenter registry of patients with acute VTE (n = 10 114), 0.1% had heart failure as underlying cause of death [R11-4582].

Co-medication

There were no data on co-medication for heart failure found in the target population.

Pulmonary disease/infection

Incidence and prevalence of pulmonary disease/infection

There were no data on incidence of pulmonary disease/infection found in the target population.

SI.Table 40 provides the prevalence of pulmonary disease/infection in patients with VTE. Multiple pulmonary outcomes were identified. The prevalence of COPD in patients with DVT or PE was between 4% and 25%, chronic lung disease in 1% to 14%, respiratory tract infection in 1% to 4%, and a combination of pulmonary disease or infection in 37% of patients with DVT.

SI.Table 40 The prevalence of pulmonary disease/infection in patients with VTE

	Country	Design	Year	Population	Prevalence of Pulmonary Disease/Infection
R11-4408	International	Pro-spective	2001-2009	Patients with VTE (n=28 920)	**COPD:** 10.3%
R11-4582	International		Pub-lished 2008	Patients with acute VTE (n=10 114)	**Chronic lung disease:** 5.6%
P07-06581	UK	Non-inter-ventional	1994-2000	Patients with VTE (n=6550)	**COPD:** 8.4%
R11-4532	Denmark	Pro-spective	1977-2007	Patients with VTE (n=97 558)	**COPD:** 9.2%
R12-5110	Denmark	Non-inter-ventional study based on existing data	1999-2009	Patients with hospital-diagnosed VTE (n = 15 009)	**COPD:** 25% **Hospital-diagnosed respiratory tract infection and/or filled a community antibiotic prescription within 3 months before the VTE:** 3.7%
R12-5097	Switzerland	Non-inter-ventional study based on existing data	2009-2010	Patients diagnosed with acute DVT or PE at acute care hospitals (SWIVTER)	**Chronic lung disease** Overall: 14% ≥ 65 years old: 14% <65 years old: 8.1%
R12-5288	International	Non-inter-ventional study based on existing data	Pub-lished 2011	Patients with confirmed diagnoses of acute lower limb DVT (n=16 199)	**Chronic lung disease:** Overall: 8.1% ≤ 29 years old: 1.1% 70-79 years old: 12%

SI.Table 40 (cont'd) The prevalence of pulmonary disease/infection in patients with VTE

	Country	Design	Year	Population	Prevalence of Pulmonary Disease/Infection
R12-5104	UK	Case-control	Published 2011	Patients aged more than 18 years with a first-time diagnosis of DVT or PE identified using the READ code system	**COPD** DVT patients: 4.0% PE patients: 5.0% **Respiratory infection in patients with DVT** Last year: 4.0% Last month: 0.6%
R12-5286	Netherlands	Case-control	1994-2004	Patients with VTE	**Chronic bronchitis or emphysema:** 6.4%
R12-5107	US	Non-interventional study	1999-2005	Patients with a confirmed diagnosis of VTE (n=2488)	**COPD:** 19.5%
R12-5098	US	Non-interventional study based on existing data	1998-2008	Hospitalised patients with a primary diagnosis of PE (n=223 766)	**COPD:** 24%
R11-4373	US	Non-interventional study based on existing data	2002-2006	Patients with and without VTE (N=12 700 000)	**Pulmonary disease/infections** VTE patients: 38.7% Non-VTE patients: 6.2% **Adjusted odds ratio (95%CI) for pulmonary disease/infections in patients with vs without VTE** 6.40 (6.29, 6.50)

Mortality of pulmonary disease/infection

An international multicenter registry of patients with acute VTE performed between March 2001 and December 2009, reported that at day 7, the overall mortality was significantly higher in COPD patients (2.6%) than in non-COPD patients (1.7%). PE was the cause of death in the vast majority of COPD patients (66%). At 3 months, the cumulative incidence of mortality was significantly higher in VTE patients with COPD (10.8%) than in VTE patients without COPD (7.6%). The main cause of death in VTE patients with COPD was PE with 21% [R11-4408].

In the SWITVTER registry study, chronic lung disease was a predictor of hospital death (HR=2.9; 95% CI: 1.4 - 5.9) [R12-5097].

Co-medication

There were no data on co-medication for pulmonary disease/infection found in the target population.

Cerebrovascular disease

Incidence and prevalence of cerebrovascular disease

In Denmark during 1977 to 2007, in a cohort study the RRs of subarachnoid haemorrhage in the first year after the thrombotic event compared with population controls was 1.91 (95% CI: 1.13 - 3.22) for patients with DVT and 2.69 (95% CI: 1.32 - 5.48) for patients with PE [R11-4532].

The percentage of cerebrovascular disease among patients with VTE (n = 6550) in UK during 1994 to 2000 was 7.2% [P07-06581]. In a case-control study with about 20 000 cases of VTE in the UK during 1991 to 2006, the prevalence of stroke was 2.6% [R12-5104].

A study of data from SWIVTER including 1247 patients with VTE during the period 2009 to 2010 found the prevalence of stroke/transient ischaemic accident to be 5.4% [R12-5097].

Of 5000 cases with VTE in the Netherlands, 3% of patients had stroke or haemorrhage of the brain [R12-5286]. In a large case-control study in the Netherlands on 4311 patients with venous thrombosis, there was a 4.9-fold increased risk for hemorrhagic stroke found [R17-1305].

In a recent publication in the same population, the prevalence of cerebrovascular disease among patients with VTE was 11.4% [R12-5107]. In a study of inpatient data during 1998 to 2008 using the US NIS, the prevalence of cerebrovascular disease among patients admitted for PE was 14.7% [R12-5098]. In a later study from the same group the prevalence of cerebral haemorrhage among patients with PE treated with thrombolytic therapy was 0.9% [R12-5533].

A study conducted in US who combined population-based cohorts from 2 studies: the CHS and ARIC study reported that 8% and 2% of the patients with DVT and PE presented cancer within 90 days of thrombosis, respectively [R05-0358].

A US claims-database analysis including 12.7 million patients between January 2002 and December 2006 estimated the US prevalence of VTE, and compared the co-morbid condition between VTE patients (n=200 007) and non-VTE patients [R11-4373]. The prevalence of stroke in VTE patients was 3.9% whereas in non-VTE patients it was 0.5% resulting in an adjusted odds ratio (with vs. without VTE) of 4.37 (95% CI: 4.14 – 4.63).

Mortality of cerebrovascular disease

There were no data on mortality of cerebrovascular disease found in the target population.

Co-medication

There were no data on co-medication for cerebrovascular disease found in the target population.

Obesity

Incidence and prevalence of obesity

Obesity is a common and chronic co-morbidity and therefore is better described by its prevalence, see below.

In an international multicenter registry of patients with acute VTE (n = 10 114), 27% were obese [R11-4582].

The percentage of cases with obesity among patients with VTE (n = 6550) in UK during 1994 to 2000 was about 20% [P07-06581].

In a cohort study conducted in Denmark during 1977 to 2007, 6.7% of the patients with VTE (n = 97 558) presented obesity [R11-4532]. The prevalence of obesity among patients with a hospital-diagnosed VTE (n=15 009) diagnosed from 01 Jan 1999, through 31 Dec 2009, in Northern Denmark was 8% [R12-5110]. Data from the Million Women Study (mean age, 56.1 years at recruitment) conducted in the UK from 1996 through 2001 were analysed to evaluate the risk of VTE in relation to BMI [R12-5108]. During an average of 6 years of follow-up per woman, in the absence of surgery, 4585 women had a hospital admission for or died from VTE. Of these women, 31% were obese - BMI of 30 kg/m2 or greater. Increasing BMI was associated with an increased risk of hospital admission with or death from VTE; the risk of VTE in women with a BMI of 35 kg/m2 or greater was 3 to 4 times higher than among women with a BMI of 22.5 to 24.9 kg/m2 (RR = 3.5; 95% CI: 3.1 - 3.9). The trend for an increased risk of VTE with increasing BMI was also apparent among women who underwent outpatient or inpatient surgery (outpatient surgery: RR = 1.7; 95% CI: 1.2 - 2.5; inpatient surgery: RR = 1.6; 95% CI: 1.4 - 1.8).

The percentage of cases with obesity among patients with VTE (n = 405) in the US during 1985 to 1986 was 19% [R05-0417].

A study that analysed data from the NIS on short-stay hospitals throughout the US from 1998 to 2008 indicated that among 2 237 660 patients hospitalised with a primary diagnosis of PE; the prevalence of obesity was 9.1%. The RR for PE was higher among obese patients than among non-obese patients (RR = 2.03; 95% CI: 2.02 - 2.03). The RR for PE among obese patients compared with non-obese patients was highest among teenagers and young adults (RR = 5.8; 95% CI: 5.6 - 6.1 for ages 11 to 20 years; RR = 4.5; 95% CI: 4.7 - 4.9 for ages 21 to 30 years; and RR = 3.3; 95% CI: 3.3 - 3.4 for ages 31 to 40 years) [R12-5098].

Mortality of obesity

An international multicenter registry of patients with acute VTE, reported that the RR for death was 0.5 (95% CI: 0.4 - 0.6) for patients with BMI >30 [R11-4582].

Based on data from the NIS in the US, all-cause in-hospital mortality in patients admitted to the hospital with a diagnosis of PE was 4.3% for obese patients [R12-5098]. Among obese patients whose condition was stable, all-cause in-hospital mortality was 3.8% among those who did not receive thrombolytic therapy and 10% among those who received thrombolytic therapy [R12-5098].

Co-medication

There were no data on co-medication for obesity found in the target population.

SI.6 PAEDIATRIC VTE - ACUTE VENOUS THROMBOEMBOLISM IN PAEDIATRIC POPULATION

SI.6.1 Incidence

Venous thromboembolism includes deep vein thrombosis and pulmonary embolism. Population-based estimates of the incidence rate of paediatric VTE vary by country; literature estimates range from 0.14-0.49 per 10 000 persons per year. The incidence rates of VTE are available, both by country (SI.Table 41) and by the age distribution (SI.Table 42) of the populations studied. Study characteristics, including case definitions and procedures to ascertain VTE cases influenced the magnitude of the incidence rates reported in each study. For example, paediatric VTE occurs primarily in very sick children, many of whom are actively monitored for the development of VTE as a consequence of their illness.

SI.Table 41 Estimates of paediatric VTE incidence rates per 10 000 person year by Country

Country	Study Design	Study Period	Age Range (years)	Source Population	Study Size	DVT	PE	VTE
Denmark[1] [P11-14206]	Retrospective	1994-2006	0-18	Population-based	~5.5 million	NA*	0.04	0.21
The Netherlands[2] [R06-2301]	Prospective	1997-1999	0-18	Population-based	3 626 343	NA*	NA*	0.14
USA[3] [R11-4524]	Retrospective	1979-2001	0-17	Population-based	75 000	0.04	0.09	0.49
Canada [R17-1457]	Retrospective	1994-2004	1-17	Population-based	1 610 234	NA*	NA*	0.29[4]
Canada [P94-81556]	Prospective	1990-1992	0-18	Multi-centre	137	0.07	NA*	NA*

[1]Incidence rates calculated using population age- and sex-distribution data from Statistics Denmark

[2]Incidence rates calculated using population age-distribution data from Statistics Netherlands

[3]Incidence rates calculated using 2003 USA Census data

[4]Incidence rates calculated using Quebec census data for years 1991, 1996, 2001, and 2006

Incidence rates for paediatric VTE demonstrate a bimodal age distribution: incidence rates are high in infancy, low during childhood, and increase again during later adolescence [R19-2555]. Annual incidence rates by age category for VTE from two retrospective population-based cohort studies from Denmark and Canada are shown in SI.Table 42 below [R17-1457; P11-14206]. This bimodal peak was similarly reported in other paediatric studies in Canada, USA and Netherlands, respectively [P94-81556; R11-4524; R06-2301].

SI.Table 42 Age-specific incidence rates per 10 000 person-year for paediatric VTE for Denmark [P11-14206] and Canada [R17-1457]

	Denmark: Study period: 1994-2006		Canada: Study period: 1994-2004	
	Age Range (years)	VTE Incidence Rate (95% CI)	Age Range (years)	VTE Incidence Rate (95% CI)
Neonatal	0-28 days	0.24 (0.16, 0.38)	NA*	NA*
Childhood	<1	0.38 (0.27, 0.54)	NA*	NA*
	1-4	0.02 (0.01, 0.04)	1-5	0.04 (0.03, 0.05)
	5-9	0.02 (0.01, 0.04)	6-10	0.03 (0.02, 0.04)
	10-14	0.05 (0.03, 0.08)	11-14	0.06 (0.05, 0.07)
Late adolescence	15-18	0.85 (0.75, 0.96)	15-17	0.16 (0.14, 0.18)

Note: Incidence rates are rounded to the nearest hundredth

SI.6.2 Prevalence

No information on prevalence of paediatric VTE, DVT, or PE was identified in this non-systematic review of the literature.

SI.6.3 Demographics of the population in the acute venous thromboembolism indication in the paediatric population and risk factors for the disease

SI.6.3.1 Demographic profile of acute venous thromboembolism in paediatric population

The demographic profile of participants in a retrospective population-based cohort study from Quebec, Canada [R17-1457] is provided in SI.Table 43 below. Of those with incident VTE between 1994 and 2004, 67% were female and the median age at first VTE hospital admission was 15 years. Stratified by VTE type, 40% of females were newly diagnosed with DVT, 12% were newly diagnosed with PE, and 5% were newly diagnosed with both DVT and PE (see SI.Table 43 below) [R17-1457].

SI.Table 43 Demographic profile of participants in the Quebec (Canada) population-based cohort from 1994-2004 [R17-1457]

Canada: Study period: 1994-2004	
Total children	**N=487**
Sex	305 female (67%) 182 male (37%)
Age category	1-5 years old: 14% 6-10 years old: 10% 11-14 years old: 20% 15-17 ears old: 56%

The incidence rates by sex and age category for overall VTE per 10 000 people aged 18 years and younger in a retrospective population-based cohort study in Denmark from 1994 to 2006 are shown in SI.Table 44 below [P11-14206]. This analysis included data on the neonatal period (defined as the first 28 days of life). The incidence rates of paediatric VTE were higher in males compared to females in infancy, whereas the opposite pattern was seen in later adolescence. In Denmark, adolescent females in the 15-18 year age group were 3.1 times more likely to experience a VTE compared to adolescent males [P11-14206]. This increased risk among females in later adolescence is supported by other paediatric studies [R17-1457; R11-4524; R12-5100; R08-5647].

SI.Table 44 Sex and age-specific incidence rates per 10 000 person-years for paediatric VTE for Denmark [P11-14206]

		Denmark **Study period: 1994-2006**	
Childhood Stage	**Age Range (years)**	**Male VTE** **Incidence rate (95% CI)**	**Female VTE** **Incidence Rate (95% CI)**
Neonate	0-28 days	0.41 (0.26, 0.65)	0.07 (0.02, 0.22)
	<1	0.59 (0.40, 0.86)	0.17 (0.08, 0.35)
Childhood	1-4	0.01 (0.003, 0.045)	0.03 (0.01, 0.07)
	5-9	0.02 (0.01, 0.05)	0.02 (0.007, 0.05)
	10-14	0.05 (0.03, 0.10)	0.05 (0.02, 0.09)
Late Adolescence	15-18	0.41 (0.33, 0.53)	1.30 (1.13, 1.49)
	Overall	0.13 (0.11, 0.16)	0.29 (0.25, 0.33)

Note: Incidence rates calculated using population age- and sex-distribution data from Statistics Denmark. Incidence rates rounded to the nearest hundredth.

There are also racial differences in VTE incidence. In a retrospective population-based study that used data from the United States National Hospital Discharge Survey, African-American

children had a VTE incidence rate that was 1.84 times that of White children (95% CI 1.80, 1.87) [R11-4524].

SI.6.3.2 Risk factors for acute paediatric venous thromboembolism in paediatric populations

Approximately 70% to 90% of children display at least one recognised VTE risk factor [P94-81556; R06-2301; P10-02627] including, but not limited to, the use of central venous lines, perinatal disease, congenital disease, surgery, limited or altered mobility, renal disease, various malignancies, rheumatic diseases, metabolic diseases, use of oral contraceptive pills or other hormonal supplements, and use of other medications such as prednisone or heparins [R17-1457; P10-02627; P19-06500; R15-1904; P19-06504; R19-2556; R19-2560].

Paediatric VTE risk factors can be categorised according to whether the thrombophilia is acquired or inherited and can vary depending on age. The most significant risk factor for development of VTE among children is the use of central venous catheters [R19-2555; R17-1457; R06-2301; P10-02627; P19-06500; R15-1904; P19-06504; R19-2556; R19-2560; P19-06496]. Although present across all paediatric age groups the incidence of central venous lines is highest in neonates and young infants [P10-02627]. Among children who developed a VTE, a central venous catheter was thought to trigger more than 90% of the neonatal venous thromboses and more than 50% of all cases of VTE in other age groups [R19-2555; P19-00949]. Other acquired VTE risk factors in children related to perinatal disease includes birth asphyxia, respiratory distress syndrome, infants of diabetic mothers, neonatal infections, necrotising enterocolitis, dehydration, congenital nephrotic syndrome, and polycythaemia [P10-02627; P19-06500; R19-2556; R19-2560; P19-06496].

Risk factors for paediatric VTE may also be related to medical intervention including surgery, renal transplantation, immobilisation or altered mobility (defined as bedridden for 3 or more days), plaster casts, and extracorporeal membrane oxygenation [R17-1457; P11-14206; R06-2301; P19-06500; R19-2556; R19-2560; R19-2559].

Other acquired risk factors are related to acute or chronic diseases. Between 9% and 22.6% of children with VTE have some underlying malignancy [R19-2555]. The most common malignancy associated with VTE is acute lymphoblastic leukaemia [R19-2555]. In addition to malignancy, other acute or chronic disease-related VTE risk factors include trauma, sepsis, dehydration, acute rheumatic disease, nephrotic syndrome, renal disease, cardiac malformation, chronic rheumatic disease, and metabolic disease [R17-1457; P10-02627; P19-06500; P19-06504; R19-2556; R19-2560; P19-06496].

Among adolescent females, OCP use is the most important risk factor for VTE [P11-14206; P19-06500; R19-2560; R19-2559]. The highest level of risk occurs in the first 3 months of use, and the risk gradually plateaus after one year of regular use. The relative risk overall is 3 to 5-fold higher compared to non-OCP users [R19-2559] and the risk increases with concomitant inherited thrombophilia. Other medication-related risk factors include the use of prednisone, coagulation factor concentrates, heparins, and antifibrinolytic agents, and L-asparaginase [P10-02627; P19-06500; R19-2556].

Another possible risk factor for paediatric VTE is being overweight or obese, defined as body mass indices of 85th-94th and ≥ 95th percentiles, respectively [P19-06500; P19-06504; R19-2560; R19-2559; R19-2561]. While this is well-characterised in adults, there are minimal paediatric-specific data. Being overweight or obese generally is thought to increase VTE risk through a chronic low-grade inflammatory state, platelet activation, and endothelial dysfunction [R19-2559].

Given that VTE is a multifactorial disease in which there are multiple inheritable and environmental risk factors that can affect the overall risk of VTE, risk factors to consider include deficiencies of antithrombin, protein C and protein S, and gene mutations of factor V Leiden (G1691A), prothrombin (factor II G20210A), and methylenetetrahydrofolate reductase (MTHFR), hyperhomocysteinemia, elevated lipoprotein(a), congenital heart disease, and sickle cell disease [R19-2555; R06-2301; P10-02627; P19-06500; P19-06504; R19-2560; P19-06496].

SI.6.4 The main existing treatment options

The goals of therapy for VTE are to prevent progression or embolisation of the clot and to prevent recurrence of VTE in susceptible individuals or those in high risk clinical situations [P19-00956]. Prevention of post-thrombotic syndrome is another important goal of treatment [P19-06499].

Factors to consider when making treatment decisions include the clinical urgency, bleeding risk, the likelihood of long-term adverse events such as PTS as well as the expertise and proficiency of the medical team conducting the treatment modalities [P17-00563].

Only 1 anticoagulant, dalteparin (a low molecular weight heparin) is approved in the United States for treatment of paediatric VTE and prevention of recurrence; it is approved for use in children aged 1 month or older (FDA approval May 2019) [R19-2627]. Current practice includes off-label treatment with unfractionated heparin, LMWH, fondaparinux or vitamin K antagonists [P19-00949]. Injectable direct thrombin inhibitors such as argatroban and bivalirudin are used for second line therapy in the setting of heparin induced thrombocytopenia [P19-00956]. Thrombolytic therapy and thrombectomy are also used in the paediatric population.

Among 92 paediatric VTE episodes included in a study from the Italian Registry of Thrombosis in Children, treatment included admission to a paediatric intensive care unit in 25 (27%) and supportive care only in 4 (4%). Therapeutic interventions among the 96% of patients who were treated included (not mutually exclusive): LMWH (72%), OAC (22%), UFH (17%), thrombolytic therapy (9%), aspirin (5%). Adverse events among the treated patients included a major bleed among 3 of 8 (38%) of patients who received thrombolytics, and heparin induced thrombocytopenia among 1 of 15 (7%) and 1 of 63 (2%) of patients who received UHF and LMWH, respectively [P19-06503].

Treatment Guidelines
The most recent treatment guidelines for paediatric VTE are from the American Society of Haematology [P19-00949]. Their guidelines for management of paediatric VTE discuss

whether to treat and what type of treatment, rather than specific recommended treatments, dosage, and durations. These guidelines recommend (1) anticoagulation for symptomatic and asymptomatic VTE compared to no anticoagulation, and (2) in catheter-related events, to remove the central venous catheter, if feasible. All other therapeutic interventions for PE and DVT are suggestions only (e.g. thrombolysis is suggested in cases of massive PE only) [P19-00949].

Clinical practice guidelines from the American College of Chest Physicians for the management of VTE in neonates and children include recommendations derived or extrapolated from adult data due to the relative lack of data in children. The guidelines are all based on low-level evidence (case reports, case series and expert opinion) and also predated the availability of newer direct acting oral anticoagulants [P19-00949]. In neonates, therapy with LMWH or UFH for 6 weeks to 3 months (with continued prophylaxis if a catheter is still in place at the end of therapy) is recommended. Other therapeutic options include supportive care only, thrombolytic therapy, and surgical intervention to remove the thrombus; however, thrombolytic therapy is not recommended in neonates unless the thrombus is critically compromising organs or limbs [P12-03887]. In children with first VTE, anticoagulation with either UFH or LMWH is recommended for initial treatment as well as ongoing therapy (6 to 12 months of treatment are recommended for idiopathic VTE and 3 months of treatment are recommended for risk factor-related VTE if the risk is resolved; recommendations for other scenarios are described in the guidelines). For those with catheter-related VTE for which the catheter cannot be removed, anticoagulation should continue while the catheter is in place. For children prescribed a VKA, the suggestion was that the drug be monitored to a target INR range of 2.5 (range 2.0-3.0) except in the setting of prosthetic cardiac valves, where adherence to the adult recommendations was suggested [P12-03887]. Children with recurrent idiopathic VTE should be treated indefinitely with vitamin K antagonists [P12-03887]. Thrombolysis is recommended only in limb preserving scenarios. Surgical embolectomy for life-threatening thrombi is supported by case reports only [P12-03887].

Draft guidelines from the British Society for Haematology include initiation of therapy with LMWHs and following with either warfarin (goal INR 2.5 [range 2.0-3.0]) or continued LMWH (particularly in children 1 year of age or younger). Use of UFH in situations where rapid reversal may be required is also recommended. Therapy should continue for up to 3 months in secondary VTE and 6 months in idiopathic VTE. Long term anticoagulation is recommended for recurrent idiopathic VTE [P11-13187].

SI.6.5 Natural history of the acute venous thromboembolism in the untreated population, including mortality and morbidity

SI.6.5.1 Mortality

Mortality rates directly attributed to VTE are low in paediatric patients and range from 1.5-2.2%. Additionally, mortality risk associated with PE is lower in paediatric populations compared to adult populations [R19-2559].

In a retrospective population-based study in Denmark, between 1994 and 2006, among 372 children between the ages of 0 to 18 years of age, there were 25 deaths resulting in an all-

cause mortality risk over a median follow-up time of 8.6 years (IQR 5.1-12.1 years) of 6.7%. The mortality rate of VTE was 0.004 per 10 000 person-years (95% CI 0.01, 0.08). The all-cause 30-day case fatality rate was 4% (95% CI 2.3, 6.7) and the thromboembolism-related 30-day case fatality rate was 1.6% (95% CI 0.6%, 3.5%). Among neonates, all-cause and thromboembolism-related 30-day case fatality rates were 17.1% (95% CI 6.3%, 36.3%) and 8.6% (95% CI 1.8%, 25.1%), respectively. Of 6 thromboembolism-related deaths, half were due to PE [P11-14206].

In another prospective population-based study performed in the Netherlands, among 99 children aged between 0 to 18 years, the overall all-cause mortality was 15% in the neonatal group and 17% in the children younger than 18 years of age [R06-2301].

In a retrospective population-based cohort study in Canada, between 1994 and 2004, among 518 children aged between 0 and 17 years of age, there were 33 deaths resulting in an overall all-cause mortality risk of 6.4%. The mortality rate after incident VTE was 11.4 deaths per 1000 child-years (95% CI 8.1, 16.1). 21% of deaths occurred in the 30 days after the initial VTE diagnosis. Mortality varied by age category, with the highest mortality observed among the youngest age group (<1 year olds (33.6 per 1000 children-years [95% CI 12.6, 89.5]) and 1 to 5 year olds (34.2 per 1000 children-years [95% CI 18.4, 63.5]). Mortality also varied by sex; males were 1.32 times more likely to die after the initial VTE diagnosis compared to females [R17-1457].

In a retrospective study conducted in Thailand between 1998 and 2015, among 28 neonatal hospital admissions with thromboembolism (VTE not specified), there were 3 deaths resulting in an overall all-cause mortality risk of 14.3% [P19-06505].

SI.6.5.2 Morbidity

Recurrence
Data regarding recurrent VTE in paediatric populations are sparse. Recurrence of VTE occurs in 7% to 10% of children [P19-06500; R19-2559; P12-03887]. Recurrence occurs in 3% of neonates [R19-2559] and in 22% of adolescents [P19-06504]. See Section SI.2 for further information on recurrent VTE in paediatric population.

Post-thrombotic syndrome
Post-thrombotic syndrome is a syndrome of chronic venous insufficiency that can occur from 6 months to 5 years after a DVT [P19-06502]. Physiologically, the symptoms derive from venous hypertension and include oedema, pain, dilated collateral veins, stasis dermatitis and can include ulceration of the affected limb. Post-thrombotic syndrome occurs in 12% to 65% of children following DVT. Risk factors for the development of PTS include delayed initial treatment, the presence of lupus anticoagulant and recurrent thrombosis [P12-03887; P19-06502; R16-1710; P17-01686].

Among 35 paediatric patients with proximal DVT who were prospectively followed at 2 children's hospitals in the USA for the development of PTS, 8 (22%) developed clinically significant PTS over a median follow-up period of 33 months (range 13-65). Investigators sought to determine risk factors for the development of PTS; the presence of lupus

anticoagulant was the only factor among the clinical and laboratory parameters explored that was associated with the development of PTS [P17-01686].

Thrombectomy and thrombolysis were used to treat a series of 16 patients aged 11 to 19 years (median, 16 years) with proximal DVT who were at high risk for PTS due to acutely increased plasma levels of factor VIII and D-dimer at a hospital in the US. During the 1- to 2-year follow-up, 8 (50%) experienced PTS between 0.5 and 12 months after the DVT; 2 (13%) did not experience PTS and follow-up data were not available for 6 patients (37%) [P11-03999].

SI.6.6 Important co-morbidities

Common co-morbidities identified in paediatric VTE populations include (not in order of prevalence) [P19-06504; R19-2560; R19-2559].

- Anatomical abnormalities
- Antithrombin deficiencies
- Asparaginase therapy
- Asphyxia
- Autoimmune disease
- Cancer
- Cardiovascular disease
- Central venous catheter
- Congenital heart disease
- Contraception/hormone use
- Sedentary lifestyle (e.g. continuous video/computer gaming)
- Diabetes mellitus
- End stage renal disease with low protein
- Hypovolemia
- Inherited thrombophilia
- Infection
- Inflammatory bowel disease
- Iron deficiency anaemia
- Metabolic disease
- Nephrotic syndrome
- Neurovascular disorders
- Obesity
- Pregnancy
- Prothrombin gene mutations
- Sickle cell disease
- Trauma

SI.7 PAEDIATRIC VTE - SECONDARY PREVENTION OF VENOUS THROMBOEMBOLISM IN THE PAEDIATRIC POPULATION

SI.7.1 Incidence

Recurrent VTE occurs in 2% to 22% of patients. Reports of recurrent VTE in children are limited by their retrospective design and inconsistent intensity and duration of documented follow-up [P19-06503; P19-06504].

Among 92 paediatric VTE episodes included in a study from the Italian Registry of Thrombosis in Children, 2% experienced documented recurrence. However, follow-up data for the 92 VTE episodes was only available for 33 patients (follow-up duration 3 to 50 months), suggesting that this may be an underestimate [P19-06503].

In a retrospective study of 64 adolescents (12 to 21 years of age) with VTE who were treated at a US children's hospital between 2004 and 2014, 14 (22%) experienced recurrent VTE. The mean time to recurrence was 4.8 years and 25% of the population had recurrence by 3.2 years [P19-06504].

In a retrospective study from a children's hospital in Canada between 2000 and 2014, among 339 children with lower extremity DVT, recurrent DVT was 5.4 times more frequent in the 56 patients with non-line-related DVT (10.7%) than in the 188 non-neonatal patients with line-related DVT (2.0%) (median follow-up durations were 2.0 and 3.5 years, respectively). No recurrence was observed among 95 neonates with line-related DVT over a median of 4.3 years of follow-up [P19-06498].

Between 1998 and 2011, 569 paediatric patients were diagnosed with VTE at a paediatric haematology department in Turkey. A retrospective analysis indicated that 32 (5.6%) had a documented recurrence. Of these, 29 (90.6%) had an underlying chronic disorder. The median time to recurrence was 6.5 months (range 1-180) [P12-11672].

SI.7.2 Prevalence

No information on the prevalence of recurrent paediatric VTE, DVT, or PE was identified in the non-systematic review of the literature.

SI.7.3 Demographics of the paediatric population with recurrent venous thromboembolism and risk factors for the disease

SI.7.3.1 Demographics

No demographic data related specifically to recurrent paediatric VTE, DVT, or PE were identified in the non-systematic review of the literature.

SI.7.3.2 Risk factors

Recurrence is associated with underlying conditions such as cardiovascular disease, malignancy, and neurovascular disorders, as well as thrombophilias [R19-2559]. Potential

risk factors for VTE recurrence include intrinsic coagulation deficiencies, homozygous factor V Leiden, prothrombin gene mutation, antiphospholipid antibody, and elevated D-dimer and factor VIII (both at the time of VTE diagnosis and after anticoagulant therapy) [P12-03887].

As noted above, non-line-related lower extremity DVT was associated with a higher frequency of recurrence (10.7%) than line-related lower extremity DVT (2.0%) in a retrospective study from a children's hospital in Canada [P19-06498].

SI.7.4 The main existing treatment options

Draft guidelines for the investigation, management and prevention of VTE in children from the British Society for Haematology recommend that children with recurrent idiopathic DVT (not secondary to identifiable risk factors such as central venous access line) receive lifelong anticoagulation [P11-13187].

In a systematic review, with the objective of identifying optimal therapeutic or prophylactic dosing of LMWH in paediatric patients, a total of 49 English language studies published between 1980 and 2017 were identified [R19-2558]. Among the 986 children from 19 studies that reported on recurrent thromboembolism while receiving therapeutic doses of LMWH, 32 (3.2%) developed a recurrent VTE. Additionally, among 962 children in 12 studies of prophylactic treatment with LMWH, 21 (2.2%) experienced a new VTE [R19-2558].

Between 1998 and 2011, 569 paediatric patients were diagnosed with VTE at a paediatric haematology department in Turkey; the treatment for primary and secondary VTE among the patients who had recurrence included the therapies listed in SI.Table 45 [P12-11672].

SI.Table 45 Treatment of first and second VTE among 32 patients with recurrent VTE at a paediatric haematology department in Turkey [P12-11672]

Treatment	First Event, % Treated	Second Event, % Treated
LMWH	62.5	46.9
UFH	31.3	59.4
Thrombolytic	15.6	28.1
Thrombectomy	12.5	0.0
Oral Anticoagulant	12.5	31.3
Aspirin	9.4	3.1

SI.7.5 Natural history of recurrent venous thromboembolism in the paediatric population, including mortality and morbidity

SI.7.5.1 Mortality

No mortality data related specifically to recurrent paediatric VTE, DVT, or PE were identified in the non-systematic review of the literature.

SI.7.5.2 Morbidity

No morbidity data related specifically to recurrent paediatric VTE, DVT, or PE were identified in the non-systematic review of the literature.

SI.7.6 Important co-morbidities

Co-morbidities among patients with recurrent VTE are similar to those with acute VTE and are often related to underlying disease processes. Some specific co-morbidities include [P12-11672; R19-2557; P19-06497; R19-2562]:

- Cancer
- Congenital heart disease
- Inherited thrombophilia
- Infection
- Obesity
- Prothrombin gene mutations

SI.8 REFERENCES

SI.8.1 Published references

P05-12151 Nieuwlaat R, Capucci A, Camm AJ, Olsson SB, Andresen D, Davies DW, Cobbe S, Breithardt G, Heuzey JY le, Prins MH, Levy S, Crijns HJGM, Euro Heart Survey Investigators Atrial fibrillation management: a prospective survey in ESC Member Countries: the Euro Heart Survey on atrial fibrillation. Eur Heart J 26 (22), 2422 - 2434 (2005).

P07-06581 Huerta C, Johansson S, Wallander MA, Garcia Rodriguez LA. Risk factors and short-term mortality of venous thromboembolism diagnosed in the primary care setting in the United Kingdom. Arch Intern Med 167 (9), 935 - 943 (2007).

P07-12708 Friberg L, Hammar N, Pettersson H, Rosenqvist M. Increased mortality in paroxysmal atrial fibrillation: report from the Stockholm Cohort-Study of Atrial Fibrillation (SCAF). Eur Heart J 28 (19), 2346 - 2353 (2007).

P08-08095 Kearon C, Kahn SR, Agnelli G, Goldhaber S, Raskob GE, Comerota AJ. Antithrombotic therapy for venous thromboembolic disease: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). Chest 133 (6) (Suppl), 454S - 545S (2008).

P08-12590 Torbicki A, Perrier A, Konstantinides S, Agnelli G, Galie N, Pruszczyk P, Bengel F, Brady AJB, Ferreira D, Janssens U, Klepetko W, Mayer E, Remy-Jardin M, Bassand JP. Guidelines on the diagnosis and management of acute pulmonary embolism: the Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC). Eur Heart J 29 (18), 2276 - 2315 (2008).

P09-13748 Benyoucef S, Hughes M, Mehta N. Atrial fibrillation (December 2008). (Cardium Study; no 3) Waltham: Decision Resources (2008).

P10-02627 Parker RI. Thrombosis in the pediatric population. Critical Care Medicine. 2010;38(2):S71-S5.

P11-03999 Goldenberg NA, Branchford B, Wang M, Ray C, Jr., Durham JD, Manco-Johnson MJ. Percutaneous mechanical and pharmacomechanical thrombolysis for occlusive deep vein thrombosis of the proximal limb in adolescent subjects: findings from an institution-based prospective inception cohort study of pediatric venous thromboembolism. Journal of vascular and interventional radiology : JVIR. 2011;22(2):121-32.

P11-07302 Jaff MR, McMurtry MS, Archer SL, Cushman M, Goldenberg N, Goldhaber SZ, Jenkins JS, Kline JA, Michaels AD, Thistlethwaite P, Vedantham S, White RJ, Zierler BK, American Heart Association Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation, Council on Peripheral Vascular Disease, and Council on Arteriosclerosis, Thrombosis and Vascular Biology. Management of massive and submassive pulmonary embolism, iliofemoral deep vein thrombosis, and chronic thromboembolic pulmonary hypertension: a scientific statement from the American Heart Association. Circulation 123 (16), 1788 - 1830 (2011).

P11-09430 National Institute for Health and Clinical Excellence. Venous thromboembolism: reducing the risk: reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in patients admitted to hospital (issue date: January 2010, this guideline updates NICE clinical guideline 46 and replaces it, last updated: June 2015). Website: nice.org.uk/nicemedia/pdf/CG92NICEGuidance.pdf (access date:4 March 2017) ; (NICE clinical guideline; 92) (2015).

P11-10351 Schmidt M, Christiansen CF, Horvath-Puho E, Glynn RJ, Rothman KJ, Sorensen HT. Non-steroidal anti-inflammatory drug use and risk of venous thromboembolism. J Thromb Haemost 9 (7), 1326 - 1333 (2011).

P11-11038 Kitamukai O, Sakuma M, Takahashi T, Kagaya Y, Watanabe J, Shirato K. Incidence and characteristics of pulmonary thromboembolism in Japan 2000. Intern Med (Tokyo) 42 (11), 1090 - 1094 (2003).

P11-13187 Chalmers E, Ganesen V, Liesner R, Maroo S, Nokes T, Saunders D, et al. Guideline on the investigation, management and prevention of venous thrombosis in children. British journal of haematology. 2011;154(2):196-207.

P11-14206 Tuckuviene R, Christensen AL, Helgestad J, Johnsen SP, Kristensen SR. Pediatric venous and arterial noncerebral thromboembolism in Denmark: a nationwide population-based study. The Journal of pediatrics. 2011;159(4):663-9.

P12-02755 Kearon C, Akl EA, Comerota AJ, Prandoni P, Bounameaux H, Goldhaber SZ, Nelson ME, Wells PS, Gould MK, Dentali F, Crowther M, Kahn SR. Antithrombotic therapy for VTE disease: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 141 (2) (Suppl), e419S - e494S (2012).

P12-02756 Falck-Ytter Y, Francis CW, Johanson NA, Curley C, Dahl OE, Schulman S, Ortel TL, Pauker SG, Colwell CW. Prevention of VTE in orthopedic surgery patients: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 141 (2) (Suppl), e278S - e325S (2012).

P12-03887 Monagle P, Chan AKC, Goldenberg NA, Ichord RN, Journeycake JM, Nowak-Gottl U, et al. Antithrombotic therapy in neonates and children: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 Suppl):e737S-e801S.

P12-11672 Gokce M, Altan I, Unal S, Kuskonmaz B, Aytac S, Cetin M, et al. Recurrent pediatric thrombosis: the effect of underlying and/or coexisting factors. Blood coagulation & fibrinolysis : an international journal in haemostasis and thrombosis. 2012;23(5):434-9.

P16-00349 Kearon C, Akl EA, Ornelas J, Blaivas A, Jimenez D, Bounameaux H, et al. Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report. Chest. 2016 Feb;149(2):315-52. PubMed PMID: 26867832. Epub 2016/02/13. eng.

P17-00563 Radulescu VC, D'Orazio JA. Venous Thromboembolic Disease in Children and Adolescents. Advances in experimental medicine and biology. 2017;906:149-65.

P17-01686 Gillespie MA, Lyle CA, Goldenberg NA. Updates in pediatric venous thromboembolism. Current opinion in hematology. 2015;22(5):413-9.

P17-04025 Akao M, Chun YH, Wada H, Esato M, Hashimoto T, Abe M, et al. Current status of clinical background of patients with atrial fibrillation in a

community-based survey: the Fushimi AF Registry. Journal of cardiology. 2013 Apr;61(4):260-6. PubMed PMID: 23403369. Epub 2013/02/14. eng.

P17-04830 Kirchhof P. 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC), developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC, endorsed by the European Stroke Organisation (ESO). Eur J Cardiothorac Surg 50 (5), e1 (2016).

P19-00949 Monagle P, Cuello CA, Augustine C, Bonduel M, Brandão LR, Capman T, et al. American Society of Hematology 2018 Guidelines for management of venous thromboembolism: treatment of pediatric venous thromboembolism. Blood advances. 2018;2(22):3292-316.

P19-00956 Malec L, Young G. Treatment of Venous Thromboembolism in Pediatric Patients. Frontiers in pediatrics. 2017;5:26-26.

P19-06496 Zaidi AU, Hutchins KK, Rajpurkar M. Pulmonary embolism in Children. Frontiers in Pediatrics. 2017;5.

P19-06497 Avila ML, Amiri N, Stanojevic S, Vu TT, Barron K, Krol P, et al. Can thrombophilia predict recurrent catheter-related deep vein thrombosis in children? Blood. 2018;131(24):2712-9.

P19-06498 Avila ML, Pullenayegum E, Williams S, Yue N, Krol P, Brandao LR. Postthrombotic syndrome and other outcomes of lower extremity deep vein thrombosis in children. Blood. 2016;128(14):1862-9.

P19-06499 Betensky M, Bittles MA, Colombani P, Goldenberg NA. How We Manage Pediatric Deep Venous Thrombosis. Seminars in Interventional Radiology. 2017;34(1):35-49.

P19-06500 Biss TT. Venous Thromboembolism in Children: Is It Preventable? Seminars in thrombosis and hemostasis. 2016;42(6):603-11.

P19-06502 Dandoy CE, Kukreja KU, Gruppo RA, Patel MN, Tarango C. Outcomes in children with deep vein thrombosis managed with percutaneous endovascular thrombolysis. Pediatric radiology. 2015;45(5):719-26.

P19-06503 Giordano P, Grassi M, Saracco P, Molinari AC, Gentilomo C, Suppiej A, et al. Paediatric venous thromboembolism: a report from the Italian Registry of Thrombosis in Children (RITI). Blood transfusion = Trasfusione del sangue. 2018;16(4):363-70.

P19-06504 Ishola T, Kirk SE, Guffey D, Voigt K, Shah MD, Srivaths L. Risk factors and co-morbidities in adolescent thromboembolism are different than those in younger children. Thrombosis research. 2016;141:178-82.

P19-06505 Sirachainan N, Limrungsikul A, Chuansumrit A, Nuntnarumit P, Thampratankul L, Wangruangsathit S, et al. Incidences, risk factors and outcomes of neonatal thromboembolism. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet. 2018;31(3):347-51.

P94-81556 Andrew M, David M, Adams M, Ali K, Anderson R, Barnard D, et al. Venous thromboembolic complications (VTE) in children: first analyses of the Canadian Registry of VTE. Blood. 1994;83(5):1251-7.

R03-1228 Benjamin EJ, Levy D, Vaziri SM, D'Agostino RB, Belanger AJ, Wolf PA. Independent risk factors for atrial fibrillation in a population-based cohort: the Framingham Heart Study. JAMA 271 (11), 840 - 844 (1994).

R03-1233 Go AS, Hylek EM, Phillips KA, Chang Y, Henault LE, Selby JV, Singer DE. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) study. JAMA 285 (18), 2370 - 2375 (2001).

R04-2879 Oger E, EPI-GETBO Study Group. Incidence of venous thromboembolism: a community-based study in Western France. Thromb Haemost 83, 657 - 660 (2000).

R05-0358 Cushman M, Tsai AW, White RH, Heckbert SR, Rosamond WD, Enright P, Folsom AR. Deep vein thrombosis and pulmonary embolism in two cohorts: the longitudinal investigation of thromboembolism etiology. Am J Med 117, 19 - 25 (2004).

R05-0417 Anderson FA, Wheeler HB, Goldberg RJ, Hosmer DW, Patwardhan NA, Jovanovic B, Forcier A, Dalen JE. A population-based perspective of the hospital incidence and case-fatality rates of deep vein thrombosis and pulmonary embolism: the Worcester DVT study. Arch Intern Med 151, 933 - 938 (1991).

R06-2145 Lakshminarayan K, Solid CA, Collins AJ, Anderson DC, Herzog CA. Atrial fibrillation and stroke in the general Medicare population: a 10-year perspective (1992 to 2002). Stroke 37 (8), 1969 - 1974 (2006).

R06-2301 van Ommen CH, Heijboer H, Buller HR, Hirasing RA, Heijmans HS, Peters M. Venous thromboembolism in childhood: a prospective two-year registry in The Netherlands. The Journal of pediatrics. 2001;139(5):676-81.

R06-2834 Wang TJ, Massaro JM, Levy D, Vasan RS, Wolf PA, D'Agostino RB, Larson MG, Kannel WB, Benjamin EJ. A risk score for predicting stroke or death in individuals with new-onset atrial fibrillation in the community: the Framingham Heart Study. JAMA 290 (8), 1049 - 1056 (2003).

R08-2897 Geerts WH, Bergqvist D, Pineo GF, Heit JA, Samama CM, Lassen MR, Colwell CW. Prevention of venous thromboembolism: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). Chest 133 (6) (Suppl), 381S - 453S (2008).

R08-4650 Liu SS, Gonzalez Della Valle A, Besculides M, Gaber LK, Memtsoudis SG. Trends in mortality, complications, and demographics for primary hip arthroplasty in the United States. Int Orthop, (2008).

R08-4651 Mantilla CB, Horlocker TT, Schroeder DR, Berry DJ, Brown DL. Frequency of myocardial infarction, pulmonary embolism, deep venous thrombosis, and death following primary hip or knee arthroplasty. Anesthesiology 96 (5), 1140 - 1146 (2002).

R08-4652 Rahme E, Dasgupta K, Burman M, Yin H, Bernatsky S, Berry G, Nedjar H, Kahn SR. Postdischarge thromboprophylaxis and mortality risk after hip- or knee-replacement surgery. Can Med Assoc J 178 (12), 1545 - 1554 (2008).

R08-4737 Zhan C, Kaczmarek R, Loyo-Berrios N, Sangl J, Bright RA. Incidence and short-term outcomes of primary and revision hip replacement in the United States. J Bone Joint Surg (Am) 89 (3), 526 - 533 (2007).

R08-4738 Bjornara BT, Gundmundsen TE, Dahl OE. Frequency and timing of clinical venous throboembolism after major joint surgery. J Bone Joint Surg (Br) 88 (3), 386 - 391 (2006).

R08-4740 Howie C, Hughes H, Watts AC, Scottish Arthoplasty Project. Venous thromboembolism associated with hip and knee replacement over a ten-year period: a population-based study. J Bone Joint Surg (Br) 87 (12), 1675 - 1680 (2005).

R08-4873 Kannel WB, Wolf PA, Benjamin EJ, Levy D. Prevalence, incidence, prognosis, and predisposing conditions for atrial fibrillation: population-based estimates. Am J Cardiol 82 (Suppl 8A), 2N - 9N (1998).

R08-5647 Silverstein MD, Heit JA, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ. Trends in the incidence of deep vein thrombosis and pulmonary embolism: a 25-year population-based study. Arch Intern Med 158, 585 - 593 (1998).

R09-0200 Cohen AT, Agnelli G, Anderson FA, Arcelus JI, Bergqvist D, Brecht JG, Greer IA, Heit JA, Hutchinson JL, Kakkar AK, Mottier D, Oger E, Samama MM, Spannagl M, VTE Impact Assessment Group In Europe (VITAE). Venous thromboembolism (VTE) in Europe: the number of VTE events and associated morbidity and mortality. Thromb Haemost 98, 756 - 764 (2007).

R09-2455 Stewart S, Hart CL, Hole DJ, McMurray JJV. A population-based study of the long-term risks associated with atrial fibrillation: 20-year follow-up of the Renfrew/Paisley study. Am J Med 113 (5), 359 - 364 (2002).

R09-2457 Frost L, Vestergaard P, Mosekilde L, Mortensen LS. Trends in incidence and mortality in the hospital diagnosis of atrial fibrillation or flutter in Denmark, 1980 - 1999. Int J Cardiol 103 (1), 78 - 84 (2005).

R09-2458 Friberg J, Scharling H, Gadsboll N, Jensen GB. Sex-specific increase in the prevalence of atrial fibrillation (The Copenhagen City Heart Study). Am J Cardiol 92 (12), 1419 - 1423 (2003).

R09-2459 DeWilde S, Carey IM, Emmas C, Richards N, Cook DG. Trends in the prevalence of diagnosed atrial fibrillation, its treatment with anticoagulation and predictors of such treatment in UK primary care. Heart (Lond) 92 (8), 1064 - 1070 (2006).

R09-4371 Nordstrom M, Lindblad B, Bergqvist D, Kjellstrom T. A prospective study of the incidence of deep-veil thrombosis within a defined urban population. J Intern Med 232, 155 - 160 (1992).

R09-4372 Ho WK, Hankey GJ, Eikelboom JW. The incidence of venous thromboembolism: a prospective, community-based study in Perth, Western Australia. Med J Aust 189 (3), 144 - 147 (2008).

R09-4866 White RH. The epidemiology of venous thromboembolism. Circulation 107, I4 - I8 (2003).

R09-4870 Zhou Z, Hu D. An epidemiological study on the prevalence of atrial fibrillation in the Chinese population of mainland China. J Epidemiol 18 (5), 209 - 216 (2008).

R09-4872 Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. Circulation 98 (10), 946 - 952 (1998).

R09-4875 Heeringa J, Kuip DAM van der, Hofman A, Kors JA, Herpen G van, Stricker BHC, Stijnen T, Lip GYH, Witteman JCM. Prevalence, incidence and lifetime risk of atrial fibrillation: the Rotterdam study. Eur Heart J 27, 949 - 953 (2006).

R09-4884 Lloyd-Jones DM, Wang TJ, Leip EP, Larson MG, Levy D, Vasan RS, D'Agostino RB, Massaro JM, Beiser A, Wolf PA, Benjamin EJ. Lifetime risk for development of atrial fibrillation: the Framingham Heart Study. Circulation 110, 1042 - 1046 (2004).

R09-4887 Nijkeuter M, Soehne M, Tick LW, Kamphuisen PW, Kramer MHH, Laterveer L, Houten AA van, Kruip MJHA, Leebeek FWG, Bueller HR,

Huisman MV. The natural course of hemodynamically stable pulmonary embolism: clinical outcome and risk factors in a large prospective cohort study. Chest 131 (2), 517 - 523 (2007).

R09-4890 Tsai AW, Cushman M, Rosamond WD, Heckbert SR, Polak JF, Folsom AR. Cardiovascular risk factors and venous thromboembolism incidence: the longitudinal investigation of thromboembolism etiology. Arch Intern Med 162, 1182 - 1189 (2002).

R09-4891 Sawin CT, Geller A, Wolf PA, Belanger AJ, Baker E, Bacharach P, Wilson PWF, Benjamin EJ, D'Agostino RB. Low serum thyrotropin concentrations as a risk factor for atrial fibrillation in older persons. N Engl J Med 331 (19), 1249 - 1252 (1994).

R09-5182 O'Reilly RF, Burgess IA, Zicat B. The prevalence of venous thromboembolism after hip and knee replacement surgery. Med J Aust 182 (4), 154 - 159 (2005).

R10-0421 Ruigomez A, Johansson S, Wallander MA, Garcia Rodriguez LA. Incidence of chronic atrial fibrillation in general practice and its treatment pattern. J Clin Epidemiol 55, 358 - 363 (2002).

R10-0598 Go AS, Hylek EM, Chang Y, Phillips KA, Henault LE, Capra AM, Jensvold NG, Selby JV, Singer DE. Anticoagulation therapy for stroke prevention in atrial fibrillation: how well do randomized trials translate into clinical practice? JAMA 290 (20), 2685 - 2692 (2003).

R10-0649 Inoue H, Fujiki A, Origasa H, Ogawa S, Okumura K, Kubota I, Aizawa Y, Yamashita T, Atarashi H, Horie M, Ohe T, Doi Y, Shimizu A, Chishaki A, Saikawa T, Yano K, Kitabatake A, Mitamura H, Kodama I, Kamakura S. Prevalence of atrial fibrillation in the general population of Japan: an analysis based on periodic heFalth examination. Int J Cardiol 137, 102 - 107 (2009).

R10-0675 Wattigney WA, Mensah GA, Croft JB. Increased atrial fibrillation mortality: United States, 1980 - 1998. Am J Epidemiol 155 (9), 819 - 826 (2002).

R10-4267 Heuzey JY le, Breithardt G, Camm J, Crijns H, Dorian P, Kowey PR, Merioua I, Prystowsky EN, Schwartz PJ, Torp-Pedersen C, Weintraub W. The RecordAF study: design, baseline data, and profile of patients according to chosen treatment strategy for atrial fibrillation. Am J Cardiol 105, 687 - 693 (2010).

R10-4268 Nieuwlaat R, Prins MH, Heuzey JY le, Vardas PE, Aliot E, Santini M, Cobbe SM, Widdershoven JWMG, Baur LH, Levy S, Crijns HJGM. Prognosis, disease progression, and treatment of atrial fibrillation patients

during 1 year: follow-up of the Euro Heart Survey on Atrial Fibrillation. Eur Heart J 29 (9), 1181 - 1189 (2008).

R10-4269 Nabauer M, Gerth A, Limbourg T, Schneider S, Oeff M, Kirchhof P, Goette A, Lewalter T, Ravens U, Meinertz T, Breithardt G, Steinbeck G. The registry of the German Competence NETwork on Atrial Fibrillation: patient characteristics and initial management. Europace 11, 423 - 434 (2009).

R10-4270 Murphy NF, Simpson CR, Jhund PS, Stewart S, Kirkpatrick M, Chalmers J, MacIntyre K, McMurray JJV. A national survey of the prevalence, incidence, primary care burden and treatment of atrial fibrillation in Scotland. Heart (Lond) 93 (5), 606 - 612 (2007).

R10-4273 Friberg L, Hammar N, Rosenqvist M. Stroke in paroxysmal atrial fibrillation: report from the Stockholm Cohort of Atrial Fibrillation. Eur Heart J 31, 967 - 975 (2010).

R10-4274 Alonso A, Agarwal SK, Soliman EZ, Ambrose M, Chamberlain AM, Prineas RJ, Folsom AR. Incidence of atrial fibrillation in whites and African-Americans: the Atherosclerosis Risk In Communities (ARIC) study. Am Heart J 158 (1), 111 - 117 (2009).

R10-4276 Frost L, Andersen LV, Vestergaard P, Husted S, Mortensen LS. Trends in risk of stroke in patients with a hospital diagnosis of nonvalvular atrial fibrillation: national cohort study in Denmark, 1980 - 2002. Neuroepidemiology 26, 212 - 219 (2006).

R10-4632 Humphries KH, Kerr CR, Connolly SJ, Klein G, Boone JA, Green M, Sheldon R, Talajic M, Dorian P, Newman D. New-onset atrial fibrillation: sex differences in presentation, treatment, and outcome. Circulation 103 (19), 2365 - 2370 (2001).

R10-5127 Australian Orthopaedic Association National Joint Replacement Registry. Annual report 2009: hip and knee arthroplasty, September 1999 to December 2008.Website:.aoa.org.au ; Adelaide: Australian Orthopaedic Association (AOA) (2009).

R10-5128 Canadian Institute for Health Information. Hip and knee replacements in Canada: Canadian Joint Replacement Registry (CJRR) 2008 - 2009 annual report. Ottawa: Canadian Institute for Health Information (CIHI) (2009).

R10-5129 Veit C, Bauer J, Doebler K, Fischer B, editors. Qualitaet sichtbar machen: BQS-Qualitaetsreport 2008. Website: bqs-qualitaetsreport.de ; Duesseldorf: Bundesgeschaeftsstelle Qualitaetssicherung (2009).

R10-5298 Pedersen AB, Mehnert F, Johnsen SP, Sorensen HT. Risk of revision of a total hip replacement in patients with diabetes mellitus: a population-based follow up study. J Bone Joint Surg (Br) 92 (7), 929 - 934 (2010).

R10-5299 Roach JA, George CJ, John L, Plocki R. Assessing the safe resumption of antihypertensive medications following total hip or knee arthroplasty surgery. Orthop Nurs 28 (4), 176 - 182 (2009).

R10-5300 Robertsson O, Stefansdottir A, Lidgren L, Ranstam J. Increased long-term mortality in patients less than 55 years old who have undergone knee replacement for osteoarthritis: results from the Swedish Knee Arthroplasly Register. J Bone Joint Surg (Br) 89 (5), 599 - 603 (2007).

R10-5302 Baser O, Supina D, Sengupta N, Wang L, Kwong L. Impact of postoperative venous thromboembolism on Medicare recipients undergoing total hip replacement or total knee replacement surgery. Am J Health Syst Pharm 67, 1438 - 1445 (2010).

R10-5304 Paavolainen P, Pukkala E, Pulkkinen P, Visuri T. Causes of death after total hip arthroplasty: a nationwide cohort study with 24,638 patients. J Arthroplasty 17 (3), 274 - 281 (2002).

R10-5335 National Institute for Health and Welfare. (EU) total hip replacements per 100 000 inhabitants (id: 10051). Website: uusi.sotkanet.fi/taulukko/AF/105,106,107,108/3/3A/0/10051/ (access date 23.09.10) ; SOTKAnet Statistics and Indicator Bank (2010).

R10-5336 OECD health data 2010 - version: June 2010.. Website: ecosante.org (2010).

R10-5337 Statistisches Bundesamt Deutschland: Bevoelkerungsstand. Website: destatis.de/jetspeed/portal/cms/Sites/destatis/Internet/DE/Navigation /Statistiken/Bevoelkerung/Bevoelkerungsstand/Bevoelkerungsstand.psml (access date 23.09.10) (2010).

R10-5338 Hospital Episode Statistics (HES): main procedures and interventions: 4 character 2008 - 09. Website: hesonline.nhs.uk/Ease/servlet/ContentServer?siteID=1937&categoryID=215 (access date 23.09.10) (2009).

R10-5339 Mid-2009 population estimates: England; estimated resident population by single year of age and sex (table 4). Website: statistics.gov.uk (2009).

R11-1463 Langenberg M, Hellemons BSP, Ree JW van, Vermeer F, Lodder J, Schouten HJA, Knottnerus JA. Atrial fibrillation in elderly patients: prevalence and comorbidity in general practice. Br Med J 313 (7071), 1534 (1996).

R11-1465 Krahn AD, Manfreda J, Tate RB, Mathewson FAL, Cuddy TE. The natural history of atrial fibrillation: incidence, risk factors, and prognosis in the Manitoba Follow-Up Study. Am J Med 98 (5), 476 - 484 (1995).

R11-2945 Camm AJ, Breithardt G, Crijns H, Dorian P, Kowey P, Heuzey JY le, Merioua I, Pedrazzini L, Prystowsky EN, Schwartz PJ, Torp-Pedersen C, Weintraub W. Real-life observations of clinical outcomes with rhythm- and rate-control therapies for atrial fibrillation: RECORDAF (Registry on Cardiac Rhythm Disorders Assessing the Control of Atrial Fibrillation). J Am Coll Cardiol 58 (5), 493 - 501 (2011).

R11-4338 Lanes S, Fraeman K, Meyers A, Ives JW, Huang HY. Incidence rates for thromboembolic, bleeding and hepatic outcomes in patients undergoing hip or knee replacement surgery. J Thromb Haemost 9, 325 - 332 (2011).

R11-4339 Jonsson KM, Wieloch M, Sterner G, Nyman U, Elmstahl S, Engstrom G, Svensson PJ. Glomerular filtration rate in patients with atrial fibrillation on warfarin treatment: a subgroup analysis from the AURICULA registry in Sweden. Thromb Res, (2011).

R11-4340 Conen D, Chae CU, Glynn RJ, Tedrow UB, Everett BM, Burning JE, Albert CM. Risk of death and cardiovascular events in initially healthy women with new-onset atrial fibrillation. JAMA 305 (20), 2080 - 2087 (2011).

R11-4343 Hansen ML, Sorensen R, Clausen MT, Fog-Petersen ML, Raunso J, Gadsboll N, Gislason GH, Folke F, Andersen SS, Schramm TK, Abildstrom SZ, Poulsen HE, Kober L, Torp-Pedersen C. Risk of bleeding with single, dual, or triple therapy with warfarin, aspirin, and clopidogrel in patients with atrial fibrillation. Arch Intern Med 170 (16), 1433 - 1441 (2010).

R11-4358 Chew HK, Wun T, Harvey D, Zhou H, White RH. Incidence of venous thromboembolism and its effect on survival among patients with common cancers. Arch Intern Med 2006;166:458-464.

R11-4361 Liu HSY, Kho BCS, Chan JCW, Cheung FMF, Lau KY, Choi FPT, Wu WC, Yau TK. Venous thromboembolism in the Chinese population - experience in a regional hospital in Hong Kong. Hong Kong Med J 8 (6), 400 - 405 (2002).

R11-4362 McColl MD, Ellison J, Greer IA, Tait RC, Walker ID. Prevalence of the post-thrombotic syndrome in young women with previous venous thromboembolism. Br J Haematol 108, 272 - 274 (2000).

R11-4363 Pengo V, Lensing AWA, Prins MH, Marchiori A, Davidson BL, Tiozzo F, Albanese P, Biasiolo A, Pegoraro C, Iliceto S, Prandoni P, Thromboembolic Pulmonary Hypertension Study Group. Incidence of chronic thromboembolic pulmonary hypertension after pulmonary embolism. N Engl J Med 350 (22), 2257 - 2264 (2004).

R11-4364 Sorensen HT, Pedersen L, Mellemkjar L, Johnsen SP, Skriver MV, Olsen JH, Baron JA. The risk of a second cancer after hospitalisation for venous thromboembolism. Br J Cancer 93 (7), 838 - 841 (2005).

R11-4365 Vazquez SR, Kahn SR. Postthrombotic syndrome. Circulation 121 (8), e217 - e219 (2010).

R11-4366 Boulet SL, Grosse SD, hooper WC, Beckman MG, Atrash HK. Prevalence of venous thromboembolism among privately insured US adults. Arch Intern Med 170 (19), 1774 - 1775 (2010).

R11-4367 Kishimoto M, Lim HY, Tokuda Y, Narita M, Kitazono H, Ito H, Seto TB, Sumida KN, Gelber RP. Prevalence of venous thromboembolism at a teaching hospital in Okinawa, Japan. Thromb Haemost 93, 876 - 879 (2005).

R11-4369 Kumasaka N, Sakuma M, Shirato K. Incidence of pulmonary thromboembolism in Japan. Jpn Circ J 63, 439 - 441 (1999).

R11-4370 Spencer FA, Gore JM, Lessard D, Emery C, Pacifico L, Reed G, Gurwitz JH, Goldberg RJ. Venous thromboembolism in the elderly: a community-based perspective. Thromb Haemost 100 (5), 780 - 788 (2008).

R11-4371 Stein PD, Hull RD, Kayali F, Ghali WA, Alshab AK, Olson RE. Venous thromboembolism according to age: the impact of an aging population. Arch Intern Med 164, 2260 - 2265 (2004).

R11-4373 Deitelzweig SB, Johnson BH, Lin J, Schulman KL. Prevalence of clinical venous thromboembolism in the USA: current trends and future projections. Am J Hematol 86 (2), 217 - 220 (2011).

R11-4408 Bertoletti L, Quenet S, Mismetti P, Hernandez L, Martin-Villasclaras JJ, Tolosa C, Valdes M, Barron M, Todoli JA, Monreal M, RIETE Investigators. Clinical presentation and outcome of venous thromboembolism in chronic obstructive pulmonary disease. Eur Respir J, (2011).

R11-4409 Huerta C, Johansson S, Wallander MA, Garcia Rodriguez LA. Risk of myocardial infarction and overall mortality in survivors of venous thromboembolism. Thromb J 6, 10 (2008).

R11-4410 Sorensen HT, Horvath-Puho E, Pedersen L, Baron JA, Prandoni P. Venous thromboembolism and subsequent hospitalisation due to acute arterial cardiovascular events: a 20-year cohort study. Lancet 370, 1773 - 1779 (2007).

R11-4524 Stein PD, Kayali F, Olson RE. Incidence of venous thromboembolism in infants and children: data from the National Hospital Discharge Survey. The Journal of pediatrics. 2004;145(4):563-5.

R11-4529 Petrauskiene V, Falk M, Waernbaum I, Norberg M, Eriksson JW. The risk of venous thromboembolism is markedly elevated in patients with diabetes. Diabetologia 48, 1017 - 1021 (2005).

R11-4531 Holst AG, Jensen G, Prescott E. Risk factors for venous thromboembolism: results from the Copenhagen City Heart Study. Circulation 121, 1896 - 1903 (2010).

R11-4532 Sorensen HT, Horvath-Puho E, Christensen S, Pedersen L, Prandoni P, Baron JA. Venous thromboembolism and subsequent diagnosis of subarachnoid hemorrhage: a 20-year cohort study. J Thromb Haemost 8, 1710 - 1715 (2010).

R11-4582 Barba R, Zapatero A, Losa JE, Valdes V, Todoli JA, Micco P di, Monreal M, RIETE Investigators. Body mass index and mortality in patients with acute venous thromboembolism: findings from the RIETE registry. J Thromb Haemost 6, 595 - 600 (2008).

R11-4599 Poli D, Grifoni E, Antonucci E, Arcangeli C, Prisco D, Abbate R, Miniati M. Incidence of recurrent venous thromboembolism and of chronic thromboembolic pulmonary hypertension in patients after a first episode of pulmonary embolism. J Thromb Thrombol 30, 294 - 299 (2010).

R11-4743 Robertsson O, Bizjajeva S, Fenstad AM, Furnes O, Lidgren L, Mehnert F, Odgaard A, Pedersen AB, Havelin LI. Knee arthroplasty in Denmark, Norway and Sweden: a pilot study from the Nordic Arthroplasty Register Association. Acta Orthop 81 (1), 82 - 89 (2010).

R12-0729 Poli D, Antonucci E, Testa S, Tosetto A, Ageno W, Palareti G, Italian Federation of Anticoagulation Clinics (FCSA). Bleeding risk in very old patients on vitamin K antagonist treatment : results of a prospective collaborative study on elderly patients followed by Italian Centres for Anticoagulation. Circulation 124 (7), 824 - 829 (2011).

R12-2026 Schnabel RB, Wilde S, Wild PS, Munzel T, Blankenberg S. Atrial fibrillation: its prevalence and risk factor profile in the German general population. Vorhofflimmern: Praevalenz und Risikofaktorenprofil in der Allgemeinbevoelkerung. Dtsch Aerztebl Int 109 (16), 293 - 299 (2012).

R12-2550 Gallagher AM, Vries F de, Plumb JM, Hass B, Clemens A, Staa TP van. Quality of INR control and outcomes following venous thromboembolism. Clin Appl Thromb Hemost, (2012).

R12-4147 Verso M, Agnelli G, Ageno W, Imberti D, Moia M, Palareti G, Pistelli R, Cantone V, MASTER Investigators. Long-term death and recurrence in patients with acute venous thromboembolism: the MASTER registry. Thromb Res 130, 369 - 373 (2012).

R12-5014 Tennekes H, Kaufmann W, Dammann M, Ravenzwaay B van. The stability of historical control data for common neoplasms in laboratory rats and the implications for carcinogenic risk assessment. Regul Toxicol Pharmacol 40, 293 - 304 (2004).

R12-5096 Sorensen HT, Svorke C, Farkas DK, Christiansen CF, Pedersen L, Lash TL, Prandoni P, Baron JA. Superficial and deep venous thrombosis, pulmonary embolism and subsequent risk of cancer. Eur J Cancer 48, 586 - 593 (2012).

R12-5097 Spirk D, Husmann M, Hayoz D, Baldi T, Frauchiger B, Engelberger R, Amann-Vesti B, Baumgartner I, Kucher N. Predictors of in-hospital mortality in elderly patients with acute venous thrombo-embolism: the SWIss Venous ThromboEmbolism Registry (SWIVTER). Eur Heart J 33, 921 - 926 (2012).

R12-5098 Stein PD, Matta F, Goldman J. Obesity and pulmonary embolism: the mounting evidence of risk and the mortality paradox. Thromb Res 128, 518 - 523 (2011).

R12-5099 Zakai NA, McClure LA. Racial differences in venous thromboembolism. J Thromb Haemost 9, 1877 - 1882 (2011).

R12-5100 Zoller B, Li X, Sundquist J, Sundquist K. Age- and gender-specific familial risks for venous thromboembolism: a nationwide epidemiological study based on hospitalizations in Sweden. Circulation 124, 1012 - 1020 (2011).

R12-5101 Zoller B, Li X, Sundquist J, Sundquist K. Determination of age-specific and sex-specific familial risks for the different manifestations of venous thromboembolism: a nationwide family study in Sweden. Thromb Haemost 106 (1), 102 - 112 (2011).

R12-5102 Zondag W, Mos ICM, Creemers-Schild D, Hoogerbrugge ADM, Dekkers OM, Dolsma J, Eijsvogel M, Faber LM, Hofstee HMA, Hovens MMC, Jonkers GJPM, Kralingen KW van, Kruip MJHA, Vlasveld T, Vreede MJM de, Huismann MV, Hestia Study Investigators. Outpatient treatment in patients with acute pulmonary embolism: the Hestia study. J Thromb Haemost 9, 1500 - 1507 (2011).

R12-5103 Sorensen HT, Horvath-Puho E, Lash TL, Christiansen CF, Pesavento R, Pedersen L, Baron JA, Prandoni P. Heart disease may be a risk factor for pulmonary embolism without peripheral deep venous thrombosis. Circulation 124, 1435 - 1441 (2011).

R12-5104 Clayton TC, Gaskin M, Meade TW. Recent respiratory infection and risk of venous thromboembolism: case-control study through a general practice database. Int J Epidemiol 40, 819 - 827 (2011).

R12-5106 Enga KF, Brakkan SK, Hansen-Krone IJ, Wilsgaard T, Hansen JB. Coffee consumption and the risk of venous thromboembolism: the Tromso study. J Thromb Haemost 9, 1334 - 1339 (2011).

R12-5107 Piazza G, Goldhaber SZ, Kroll A, Goldberg RJ, Emery C, Spencer FA. Venous thromboembolism in patients with diabetes mellitus. Am J Med 125 (7), 709 - 716 (2012).

R12-5108 Parkin L, Sweetland S, Balkwill A, Green J, Reeves G, Beral V, Million Women Study Collaborators. Body mass index, surgery, and risk of venous thromboembolism in middle-aged women: a cohort study. Circulation 125, 1897 - 1904 (2012).

R12-5109 Settty BA, O'Brien SH, Kerlin BA. Pediatric venous thromboembolism in the United States: a tertiary care complication of chronic diseases. Pediatr Blood Cancer 59, 258 - 264 (2012).

R12-5110 Schmidt M, Horvath-Puho E, Thomsen RW, Smeeth L, Sorensen HT. Acute infections and venous thromboembolism. J Intern Med 271, 608 - 618 (2012).

R12-5113 Centers for Disease Control and Prevention (CDC). Venous thromboembolism in adult hospitalizations - United States, 2007 - 2009. MMWR 61 (22), 401 - 404 (2012).

R12-5114 Piazza G, Goldhaber SZ, Lessard DM, Goldberg RJ, Emery C, Spencer FA. Venous thromboembolism in patients with symptomatic atherosclerosis. Thromb Haemost 106 (6), 1095 - 1102 (2011).

R12-5284 Heit JA. Predicting the risk of venous thromboembolism recurrence. Am J Hematol 87, S63 - S67 (2012).

R12-5285 Heit JA, Lahr BD, Petterson MT, Bailey KR, Ashrani AA, Melton LJ. Heparin and warfarin anticoagulation intensity as predictors of recurrence after deep vein thrombosis or pulmonary embolism: a population-based cohort study. Blood 118 (18), 4992 - 4999 (2011).

R12-5286 Flinterman LE, Hylckama Vlieg A van, Cannegieter SC, Rosendaal FR. Long-term survival in a large cohort of patients with venous thrombosis: incidence and predictors. Plos Med 9 (1), e1001155 (2012).

R12-5287 Lee CH, Cheng CL, Lin LJ, Tsai LM, Yang YHK. Epidemiology and predictors of short-term mortality in symptomatic venous thromboembolism - a nationwide population based study. Circ J 75, 1998 - 2004 (2011).

R12-5288 Sanchez D, Miguel J de, Sam A, Wagner C, Zamarro C, Nieto R, Garcia L, Aujesky D, Yusen RD, Jimenez D. The effects of cause of death classification on prognostic assessment of patients with pulmonary embolism. J Thromb Haemost 9, 2201 - 2207 (2011).

R12-5528 Douketis JD, Gu C, Piccioli A, Ghirarduzzi A, Pengo V, Prandoni P. The long-term risk of cancer in patients with a first episode of venous thromboembolism. J Thromb Haemost 7 (4), 546 - 551 (2009).

R12-5531 Ageno W, Becattini C, Brighton T, Selby R, Kamphuisen PW. Cardiovascular risk factors and venous thromboembolism: a meta-analysis. Circulation 117 (1), 93 - 102 (2008).

R12-5532 Renoux C, Dell'Aniello S, Suissa S. Hormone replacement therapy and the risk of venous thromboembolism: a population-based study. J Thromb Haemost 8, 979 - 986 (2010).

R12-5533 Stein PD, Matta F, Steinberger DS, Keyes DC. Intracerebral hemorrhage with thrombolytic therapy for acute pulmonary embolism. Am J Med 125 (1), 50 - 56 (2012).

R12-5534 Stein PD, Matta F. Epidemiology and incidence: the scope of the problem and risk factors for development of venous thromboembolism. Clin Chest Med 31, 611 - 628 (2010).

R12-5535 Tagalakis V, Kondal D, Ji Y, Boivin JF, Moride Y, Ciampi A, Kahn SR. Men had a higher risk of recurrent venous thromboembolism than women: a large population study. Gend Med 9 (1), 33 - 43 (2012).

R12-5536 Severinsen MT, Johnsen SP, Tjonneland A, Overvad K, Dethlefsen C, Kristensen SR. Body height and sex-related differences in incidence of venous thromboembolism: a Danish follow-up study. Eur J Intern Med 21, 268 - 272 (2010).

R12-5619 Heit JA. Venous thromboembolism: disease burden, outcomes and risk factors. J Thromb Haemost 3, 1611 - 1617 (2005).

R13-0090 Watanabe H, Tanabe N, Watanabe T, Darbar D, Roden DM, Sasaki S, Aizawa Y. Metabolic syndrome and risk of development of atrial fibrillation: the Niigata preventive medicine study. Circulation 117 (10), 1255 - 1260 (2008).

R13-0091 Frost L, Vestergaard P. Alcohol and risk of atrial fibrillation or flutter: a cohort study. Arch Intern Med 164, 1993 - 1998 (2004).

R13-0094 Kannel WB, Abbott RD, Savage DD, McNamara PM. Epidemiologic features of chronic atrial fibrillation: the Framingham Study. N Engl J Med 306 (17), 1018 - 1022 (1982).

R13-0096 Aviles RJ, Martin DO, Apperson-Hansen C, Houghtaling PL, Rautaharju P, Kronmal RA, Tracy RP, Wagoner DR van, Psaty BM, Lauer MS, Chung MK. Inflammation as a risk factor for atrial fibrillation. Circulation 108 (24), 3006 - 3010 (2003).

R13-0111 LaMori JC, Mody SH, Gross HJ, daCosta DiBonaventura M, Patel AA, Schein JR, et al. Burden of comorbidities among patients with atrial fibrillation. Therapeutic advances in cardiovascular disease. 2013 Apr;7(2):53-62. PubMed PMID: 23090783. Epub 2012/10/24. eng.

R13-0175 Fox CS, Parise H, D'Agostino RB, Lloyd-Jones DM, Vasan RS, Wang TJ, Levy D, Wolf PA, Benjamin EJ. Parental atrial fibrillation as a risk factor for atrial fibrillation in offspring. JAMA 291 (23), 2851 - 2855 (2004).

R13-0176 Wang TJ, Parise H, Levy D, D'Agostino RB, Wolf PA, Vasan RS, Benjamin EJ. Obesity and the risk of new-onset atrial fibrillation. JAMA 292 (20), 2471 - 2477 (2004).

R13-3833 Stewart S, Hart CL, Hole DJ, McMurray JJV. Population prevalence, incidence, and predictors of atrial fibrillation in the Renfrew/Paisley study. Heart (Lond) 86 (5), 516 - 521 (2001).

R13-3858 Bjorck S, Palaszewski B, Friberg L, Bergfeldt L. Atrial fibrillation, stroke risk, and warfarin therapy revisited: a population-based study. Stroke. 2013 Nov;44(11):3103-8. PubMed PMID: 23982711. Epub 2013/08/29. eng.

R13-4723 Senoo K, Suzuki S, Sagara K, Otsuka T, Matsuno S, Uejima T, et al. Coronary artery diseases in Japanese patients with nonvalvular atrial fibrillation. Journal of cardiology. 2014 Feb;63(2):123-7. PubMed PMID: 24070790. Epub 2013/09/28. eng.

R14-0464 Gallagher AM, van Staa TP, Murray-Thomas T, Schoof N, Clemens A, Ackermann D, et al. Population-based cohort study of warfarin-treated patients with atrial fibrillation: incidence of cardiovascular and bleeding outcomes. BMJ open. 2014 Jan 27;4(1):e003839. PubMed PMID: 24468720. Pubmed Central PMCID: PMC3913087. Epub 2014/01/29. eng.

R14-3859 Gomez-Doblas JJ, Muniz J, Martin JJ, Rodriguez-Roca G, Lobos JM, Awamleh P, et al. Prevalence of atrial fibrillation in Spain. OFRECE study results. Revista espanola de cardiologia (English ed). 2014 Apr;67(4):259-69. PubMed PMID: 24774588. Epub 2014/04/30. eng.

R15-1904 Gray BW, Gonzalez R, Warrier KS, Stephens LA, Drongowski RA, Pipe SW, et al. Characterization of central venous catheter-associated deep venous thrombosis in infants. Journal of pediatric surgery. 2012;47(6):1159-66.

R16-1710 Creary S, Heiny M, Croop J, Fallon R, Vik T, Hulbert M, et al. Clinical course of postthrombotic syndrome in children with history of venous thromboembolism. Blood coagulation & fibrinolysis : an international journal in haemostasis and thrombosis. 2012;23(1):39-44.

R17-1273 Andersson T, Magnuson A, Bryngelsson IL, Frobert O, Henriksson KM, Edvardsson N, et al. All-cause mortality in 272,186 patients hospitalized with incident atrial fibrillation 1995-2008: a Swedish nationwide long-term case-control study. European heart journal. 2013 Apr;34(14):1061-7. PubMed PMID: 23321349. Pubmed Central PMCID: PMC3618889. Epub 2013/01/17. eng.

R17-1274 Aziz F, Patel M, Ortenzi G, Reed AB. Incidence of Postoperative Deep Venous Thrombosis Is Higher among Cardiac and Vascular Surgery Patients as Compared with General Surgery Patients. Annals of vascular surgery. 2015;29(4):661-9. PubMed PMID: 25733224. Epub 2015/03/04. eng.

R17-1275 Bayley E, Brown S, Bhamber NS, Howard PW. Fatal pulmonary embolism following elective total hip arthroplasty: a 12-year study. The bone & joint journal. 2016 May;98-B(5):585-8. PubMed PMID: 27143726. Epub 2016/05/05. eng.

R17-1276 Belmont PJ, Jr., Goodman GP, Hamilton W, Waterman BR, Bader JO, Schoenfeld AJ. Morbidity and mortality in the thirty-day period following total hip arthroplasty: risk factors and incidence. The Journal of arthroplasty. 2014 Oct;29(10):2025-30. PubMed PMID: 24973000. Epub 2014/06/29. eng.

R17-1277 Bernstein J, Derman P Dramatic increase in total knee replacement utilization rates cannot be fully explained by a disproportionate increase among younger patients. Orthopedics 2014. 37(7):e656-e659.

R17-1278 Bookhart BK, Haskell L, Bamber L, Wang M, Schein J, Mody SH. Length of stay and economic consequences with rivaroxaban vs enoxaparin/vitamin K antagonist in patients with DVT and PE: findings from the North American EINSTEIN clinical trial program. Journal of medical economics. 2014 Oct;17(10):691-5. PubMed PMID: 25065536. Epub 2014/07/30. eng.

R17-1280 Chamberlain AM, Gersh BJ, Alonso A, Chen LY, Berardi C, Manemann SM, et al. Decade-long trends in atrial fibrillation incidence and survival: a community study. The American journal of medicine. 2015 Mar;128(3):260-7 e1. PubMed PMID: 25446299. Pubmed Central PMCID: PMC4340721. Epub 2014/12/03. eng.

R17-1281 Cho SE, Delate T, Witt DM, Clark NP. Thromboembolic and bleeding outcomes of extended duration low-intensity warfarin following elective

total knee arthroplasty. Thrombosis research. 2015 Feb;135(2):267-71. PubMed PMID: 25555318. Epub 2015/01/04. eng.

R17-1282 Clark NP, Cho SE, Delate T, Witt DM. Thromboembolic and bleeding outcomes of low-intensity warfarin thromboprophylaxis following elective total hip arthroplasty. Thrombosis research. 2013 May;131(5):390-5. PubMed PMID: 23522854. Epub 2013/03/26. eng.

R17-1283 Dua A, Desai SS, Lee CJ, Heller JA. National Trends in Deep Vein Thrombosis following Total Knee and Total Hip Replacement in the United States. Annals of vascular surgery. 2017 Jan;38:310-4. PubMed PMID: 27531085. Epub 2016/08/18. eng.

R17-1284 Duncan ME, Pitcher A, Goldacre MJ. Atrial fibrillation as a cause of death increased steeply in England between 1995 and 2010. Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology. 2014 Jun;16(6):797-802. PubMed PMID: 24381330. Epub 2014/01/02. eng.

R17-1285 Colilla S, Crow A, Petkun W, Singer DE, Simon T, Liu X. Estimates of current and future incidence and prevalence of atrial fibrillation in the U.S. adult population. The American journal of cardiology. 2013 Oct 15;112(8):1142-7. PubMed PMID: 23831166. Epub 2013/07/09. eng.

R17-1287 Cotte FE, Chaize G, Kachaner I, Gaudin AF, Vainchtock A, Durand-Zaleski I. Incidence and cost of stroke and hemorrhage in patients diagnosed with atrial fibrillation in France. Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association. 2014 Feb;23(2):e73-83. PubMed PMID: 24119623. Epub 2013/10/15. eng.

R17-1288 Garland A, Rolfson O, Garellick G, Karrholm J, Hailer NP. Early postoperative mortality after simultaneous or staged bilateral primary total hip arthroplasty: an observational register study from the Swedish Hip Arthroplasty Register. BMC musculoskeletal disorders. 2015 Apr 08;16:77. PubMed PMID: 25887667. Pubmed Central PMCID: PMC4393879. Epub 2015/04/19. eng.

R17-1289 Huxley RR, Misialek JR, Agarwal SK, Loehr LR, Soliman EZ, Chen LY, et al. Physical activity, obesity, weight change, and risk of atrial fibrillation: the Atherosclerosis Risk in Communities study. Circulation Arrhythmia and electrophysiology. 2014 Aug;7(4):620-5. PubMed PMID: 24907285. Pubmed Central PMCID: PMC4230341. Epub 2014/06/08. eng.

R17-1290 Illingworth KD, El Bitar YF, Banerjee D, Scaife SL, Saleh KJ. Inpatient mortality after primary total hip arthroplasty: analysis from the National

Inpatient Sample database. The Journal of arthroplasty. 2015 Mar;30(3):369-73. PubMed PMID: 25529285. Epub 2014/12/23. eng.

R17-1291 Karasoy D, Gislason GH, Hansen J, Olesen JB, Torp-Pedersen C, Johannessen A, et al. Temporal changes in patient characteristics and prior pharmacotherapy in patients undergoing radiofrequency ablation of atrial fibrillation: a Danish nationwide cohort study. Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology. 2013 May;15(5):669-75. PubMed PMID: 23284140. Epub 2013/01/04. eng.

R17-1292 Kodani E, Atarashi H, Inoue H, Okumura K, Yamashita T, Origasa H. Use of warfarin in elderly patients with non-valvular atrial fibrillation -- subanalysis of the J-RHYTHM Registry. Circulation journal : official journal of the Japanese Circulation Society. 2015;79(11):2345-52. PubMed PMID: 26329097. Epub 2015/09/04. eng.

R17-1293 Krijthe BP, Kunst A, Benjamin EJ, Lip GY, Franco OH, Hofman A, et al. Projections on the number of individuals with atrial fibrillation in the European Union, from 2000 to 2060. European heart journal. 2013 Sep;34(35):2746-51. PubMed PMID: 23900699. Pubmed Central PMCID: PMC3858024. Epub 2013/08/01. eng.

R17-1295 Lang K, Patel AA, Munsell M, Bookhart BK, Mody SH, Schein JR, et al. Recurrent hospitalization and healthcare resource use among patients with deep vein thrombosis and pulmonary embolism: findings from a multi-payer analysis. Journal of thrombosis and thrombolysis. 2015 May;39(4):434-42. PubMed PMID: 25079971. Pubmed Central PMCID: PMC4379443. Epub 2014/08/01. eng.

R17-1296 Larsson SC, Drca N, Wolk A. Alcohol consumption and risk of atrial fibrillation: a prospective study and dose-response meta-analysis. Journal of the American College of Cardiology. 2014 Jul 22;64(3):281-9. PubMed PMID: 25034065. Epub 2014/07/19. eng.

R17-1297 Laukkanen JA, Zaccardi F, Karppi J, Ronkainen K, Kurl S. Reduced kidney function is a risk factor for atrial fibrillation. Nephrology (Carlton, Vic). 2016 Aug;21(8):717-20. PubMed PMID: 26780558. Epub 2016/01/19. eng.

R17-1298 Lozano LM, Tio M, Rios J, Sanchez-Etayo G, Popescu D, Sastre S, et al. Severe and morbid obesity (BMI >/= 35 kg/m(2)) does not increase surgical time and length of hospital stay in total knee arthroplasty surgery. Knee surgery, sports traumatology, arthroscopy : official journal of the ESSKA. 2015 Jun;23(6):1713-9. PubMed PMID: 24770349. Epub 2014/04/29. eng.

R17-1299 Paxton EW, Inacio MC, Singh JA, Love R, Bini SA, Namba RS. Are There Modifiable Risk Factors for Hospital Readmission After Total Hip

Arthroplasty in a US Healthcare System? Clinical orthopaedics and related research. 2015 Nov;473(11):3446-55. PubMed PMID: 25845947. Pubmed Central PMCID: PMC4586234. Epub 2015/04/08. eng.

R17-1301 Proietti M, Marra AM, Tassone EJ, De Vuono S, Corrao S, Gobbi P, et al. Frequency of Left Ventricular Hypertrophy in Non-Valvular Atrial Fibrillation. The American journal of cardiology. 2015 Sep 15;116(6):877-82. PubMed PMID: 26183791. Epub 2015/07/18. eng.

R17-1302 Pugely AJ, Martin CT, Gao Y, Belatti DA, Callaghan JJ. Comorbidities in patients undergoing total knee arthroplasty: do they influence hospital costs and length of stay? Clinical orthopaedics and related research. 2014 Dec;472(12):3943-50. PubMed PMID: 25190193. Pubmed Central PMCID: PMC4397785. Epub 2014/09/06. eng.

R17-1303 Martinez C, Katholing A, Wallenhorst C, Granziera S, Cohen AT, Freedman SB. Increasing incidence of non-valvular atrial fibrillation in the UK from 2001 to 2013. Heart (British Cardiac Society). 2015 Nov;101(21):1748-54. PubMed PMID: 26307057. Epub 2015/08/27. eng.

R17-1305 Ocak G, Vossen CY, Verduijn M, Dekker FW, Rosendaal FR, Cannegieter SC, et al. Risk of venous thrombosis in patients with major illnesses: results from the MEGA study. Journal of thrombosis and haemostasis : JTH. 2013 Jan;11(1):116-23. PubMed PMID: 23106832. Epub 2012/10/31. eng.

R17-1306 Odum SM, Springer BD, Dennos AC, Fehring TK. National obesity trends in total knee arthroplasty. The Journal of arthroplasty. 2013 Sep;28(8 Suppl):148-51. PubMed PMID: 23953395. Epub 2013/08/21. eng.

R17-1307 Ohlmeier C, Mikolajczyk R, Haverkamp W, Garbe E. Incidence, prevalence, and antithrombotic management of atrial fibrillation in elderly Germans. Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology. 2013 Oct;15(10):1436-44. PubMed PMID: 23487542. Epub 2013/03/15. eng.

R17-1308 Ohyama Y, Imai M, Kurabayashi M. Estimated glomerular filtration rate and proteinuria are separately and independently associated with the prevalence of atrial fibrillation in general population. PloS one. 2013;8(11):e79717. PubMed PMID: 24223186. Pubmed Central PMCID: PMC3819254. Epub 2013/11/14. eng.

R17-1315 Belmont PJ, Jr., Goodman GP, Waterman BR, Bader JO, Schoenfeld AJ. Thirty-day postoperative complications and mortality following total knee arthroplasty: incidence and risk factors among a national sample of 15,321 patients. The Journal of bone and joint surgery American volume. 2014 Jan 01;96(1):20-6. PubMed PMID: 24382720. Epub 2014/01/03. eng.

R17-1316 Wilke T, Groth A, Mueller S, Pfannkuche M, Verheyen F, Linder R, et al. Incidence and prevalence of atrial fibrillation: an analysis based on 8.3 million patients. Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology. 2013 Apr;15(4):486-93. PubMed PMID: 23220354. Epub 2012/12/12. eng.

R17-1317 Xu D, Murakoshi N, Sairenchi T, Irie F, Igarashi M, Nogami A, et al. Anemia and reduced kidney function as risk factors for new onset of atrial fibrillation (from the Ibaraki prefectural health study). The American journal of cardiology. 2015 Feb 01;115(3):328-33. PubMed PMID: 25579885. Epub 2015/01/13. eng.

R17-1322 Renoux C, Patenaude V, Suissa S. Incidence, mortality, and sex differences of non-valvular atrial fibrillation: a population-based study. Journal of the American Heart Association. 2014 Nov 03;3(6):e001402. PubMed PMID: 25366150. Pubmed Central PMCID: PMC4338735. Epub 2014/11/05. eng.

R17-1323 Roach RE, Lijfering WM, Tait RC, Baglin T, Kyrle PA, Cannegieter SC, et al. Sex difference in the risk of recurrent venous thrombosis: a detailed analysis in four European cohorts. Journal of thrombosis and haemostasis : JTH. 2015 Oct;13(10):1815-22. PubMed PMID: 26270772. Epub 2015/08/14. eng.

R17-1324 Roldan V, Marin F, Fernandez H, Manzano-Fernandez S, Gallego P, Valdes M, et al. Renal impairment in a "real-life" cohort of anticoagulated patients with atrial fibrillation (implications for thromboembolism and bleeding). The American journal of cardiology. 2013 Apr 15;111(8):1159-64. PubMed PMID: 23337836. Epub 2013/01/23. eng.

R17-1325 Sano F, Ohira T, Kitamura A, Imano H, Cui R, Kiyama M, et al. Heavy alcohol consumption and risk of atrial fibrillation. The Circulatory Risk in Communities Study (CIRCS). Circulation journal : official journal of the Japanese Circulation Society. 2014;78(4):955-61. PubMed PMID: 24553265. Epub 2014/02/21. eng.

R17-1326 Schnabel RB, Yin X, Gona P, Larson MG, Beiser AS, McManus DD, et al. 50 year trends in atrial fibrillation prevalence, incidence, risk factors, and mortality in the Framingham Heart Study: a cohort study. Lancet (London, England). 2015 Jul 11;386(9989):154-62. PubMed PMID: 25960110. Pubmed Central PMCID: PMC4553037. Epub 2015/05/12. eng.

R17-1328 Tournier M. Current antipsychotic drug treatment may increase the risk of pulmonary embolism. Evidence-based mental health. 2015 Nov;18(4):115. PubMed PMID: 26449538. Epub 2015/10/10. eng.

R17-1330 Weill A, Dalichampt M, Raguideau F, Ricordeau P, Blotiere PO, Rudant J, et al. Low dose oestrogen combined oral contraception and risk of pulmonary embolism, stroke, and myocardial infarction in five million French women: cohort study. BMJ (Clinical research ed). 2016 May 10;353:i2002. PubMed PMID: 27164970. Pubmed Central PMCID: PMC4862376. Epub 2016/05/12. eng.

R17-1361 Canadian Institute for Health Information (CIHI). Hip and knee replacements in Canada, 2014 - 2015: Canadian Joint Replacement Registry annual report. Website: secure.cihi.ca/free_products/cjrr-annual-report-2016-en.pdf (access date: 11 April 2017) ; Ottawa: Canadian Institute for Health Information (CIHI) (2017).

R17-1362 Canadian Institute for Health Information (CIHI). Hipand knee replacements in Canada: Canadian Joint Replacement Registry 2015 annual report. Website: secure.cihi.ca/free_products/CJRR_2015_Annual_Report_EN.pdf (access date: 11 April 2017) ; Ottawa: Canadian Institute for Health Information (CIHI) (2015).

R17-1363 OECD. Health at a glance 2011: OECD indicators. Website: dx.doi.org/10.1787/health_glance-2011-en (access date: 11 April 2017) ; Paris: OECD Publishing (2011).

R17-1364 Health at a glance: Europe 2014 (chart set). Website: oecd.org/els/health-systems/Health-at-a-Glance-Europe-2014-CHARTSET. pdf (access date: 11 April 2017) ; OECD (2014).

R17-1457 Sabapathy CA, Djouonang TN, Kahn SR, Platt RW, Tagalakis V. Incidence Trends and Mortality from Childhood Venous Thromboembolism: A Population-Based Cohort Study. The Journal of pediatrics. 2016;172:175-80.e1.

R17-1466 Hospital episode statistics: admitted patient care, England - 2014 - 15. Website: content.digital.nhs.uk/catalogue/PUB19124/hosp-epis-stat-admi-summ-rep-20 14-15-rep.pdf (access date: 24 April 2017) ; Hospital Episode Statistics Analysis, Health and Social Care Information Centre (hscic) (2015).

R17-1484 Office of National Statistics [Internet]. 2016 [cited 2017Mar21]. Available from: Website: ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates.

R19-2555 Kelleher D, Shalhoub J, Davies AH. Venous thromboembolism in the paediatric patient. Phlebology. 2012;27:81-5.

R19-2556 Kenet G, Limperger V, Shneyder M, Nowak-Gottl U. Risk factors for symptomatic venous and arterial thromboembolism in newborns, children and adolescents - What did we learn within the last 20years? Blood cells, molecules & diseases. 2017;67:18-22.

R19-2557 Klaassen ILM, van Els AL, van de Wetering MD, van Ommen CH. Increasing Incidence and Recurrence Rate of Venous Thromboembolism in Paediatric Oncology Patients in One Single Centre Over 25 Years. Thromb Haemost. 2017;117(11):2156-62.

R19-2558 Klaassen ILM, Sol JJ, Suijker MH, Fijnvandraat K, van de Wetering MD, Heleen van Ommen C. Are low-molecular-weight heparins safe and effective in children? A systematic review. Blood reviews. 2019;33:33-42.

R19-2559 Mahajerin A, Croteau SE. Epidemiology and Risk Assessment of Pediatric Venous Thromboembolism. Frontiers in pediatrics. 2017;5:68.

R19-2560 Srivaths L, Dietrich JE. Prothrombotic Risk Factors and Preventive Strategies in Adolescent Venous Thromboembolism. Clinical and applied thrombosis/hemostasis : official journal of the International Academy of Clinical and Applied Thrombosis/Hemostasis. 2016;22(6):512-9.

R19-2561 Stokes S, Breheny P, Radulescu A, Radulescu VC. Impact of Obesity on the Risk of Venous Thromboembolism in an Inpatient Pediatric Population. Pediatric Hematology and Oncology. 2014;31(5):475-80.

R19-2562 Timp JF, Cannegieter SC, Tichelaar V, Braekkan SK, Rosendaal FR, le Cessie S, et al. Antibiotic use as a marker of acute infection and risk of first and recurrent venous thrombosis. British journal of haematology. 2017;176(6):961-70.

R19-2627 FDA approves first anticoagulant (blood thinner) for pediatric patients to treat potentially life-threatening blood clots (FDA news release, for immediate release: May 16, 2019). Website: fda.gov/news-events/press-announcements/fda-approves-first-anticoagulant-blood-thinner-pediatric-patients-treat-potentially-life-threatening (access date: 29 Jul 2019) (2019).

SI.8.2 Unpublished references

U10-1959-02 Cardiovascular and other outcomes in patients with atrial fibrillation. 22 Dec 2010.

ABBREVIATIONS

ACE	Angiotensin converting enzyme
AF	Atrial fibrillation
AFNET	Central Registry of the German Competence NETwork on Atrial Fibrillation
ARAPACIS	Anklebrachial Index Prevalence Assessment: Collaborative Italian Study
ARB	Angiotensin receptor blocker
ARIC	Atherosclerosis Risk in Communities
ATRIA	Anticoagulation and Risk Factors in Atrial Fibrillation (Study)
AV	Atrioventricular (node)
aVTEt/sVTEp	Treatment of DVT and PE, and prevention of recurrent DVT and PE in adults
BMI	Body mass index
CABG	Coronary artery bypass grafting
CDC	Centers for Disease Control and Prevention
CHA_2DS_2-VASc	Congestive heart failure or left ventricular dysfunction, Hypertension, Age ≥75, Diabetes, Stroke (doubled)-Vascular disease, Age 65-74, Sex category (score)
CHS	Cardiovascular Health Study
CI	Confidence interval
CM	Clinical modification
COPD	Chronic obstructive pulmonary disease
CPRD	Clinical Practice Research Datalink
CTPH	Chronic thromboembolic pulmonary hypertension
DLP	Data lock point
DVT	Deep vein thrombosis
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
EPICA	Elder Patients followed by Italian Centers of Anticoagulation
ESC	European Society of Cardiology
FDA	Federal Drug Administration
GePaRD	German Pharmacoepidemiological Research Database

GPRD	General Practice Research Database
HAS-BLED	Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly, Drugs/alcohol concomitantly (score)
HR	Hazard ratio
ICD	International Classification of Disease
INR	International normalised ratio
IQR	Interquartile range
LMWH	Low molecular weight heparin
LVH	Left ventricular hypertrophy
MAH	Marketing Authorisation Holder
MDRD	Modification of diet in renal disease
NA	Not applicable / not available
NHDS	National Hospital Discharge Survey
NHI	Taiwanese Health Insurance
NICE	National Institute for Health and Care Excellence
NIS	Nationwide Inpatient Sample
NOAC	New oral anticoagulant
NR	Not reported
NSAID	Nonsteroidal anti-inflammatory drug
NSQIP	National Surgical Quality Improvement Program
NVAF	Non-valvular atrial fibrillation
NYHA	New York Heart Association
OAC	Oral anticoagulants
OCP	Oral contraceptives
OR	Odds ratio
PATAF	Primary Prevention of Arterial Thromboembolism in Nonrheumatic Atrial Fibrillation
PCI	Percutaneous coronary intervention
PE	Pulmonary embolism
PH	Pulmonary hypertension
PTS	Post-thrombotic syndrome
pVTEp	Primary prevention of VTEs in adult patients who have undergone

	elective THR surgery or TKR surgery
PY	Patient years
RAMQ	Régie de l'assurance maladie du Québec
RECORD AF	Registry On Cardiac Rhythm Disorders Assessing the Control of Atrial Fibrillation
RIETE	The Computerized Registry of Patients with Venous Thromboembolism
RR	Relative risk
SD	Standard deviation
SHAR	The Swedish Hip Arthroplasty Register
SPAF	Prevention of stroke and systemic embolism in adult patients with NVAF, with one or more risk factors, such as prior stroke or TIA; age ≥ 75 years; heart failure (NYHA Class ≥ II); diabetes mellitus; hypertension
sVTEp	See aVTEt/sVTEp above
SWIVTER	SWIss Venous Thromboembolism Registry
THR	Total hip replacement
TIA	Transient ischaemic attack
TKR	Total knee replacement
UFH	Unfractionated heparin
UK	United Kingdom
US(A)	United States (of America)
VKA	Vitamin K antagonist
VTE	Venous thromboembolic event
WPW	Wolff-Parkinson-White-Syndrome

MODULE SII NON-CLINICAL PART OF THE SAFETY SPECIFICATION

SII.1 KEY SAFETY FINDINGS FROM NON-CLINICAL STUDIES AND RELEVANCE TO HUMAN USAGE

SII.1.1 Non-clinical pharmacology

Dabigatran is a potent and specific inhibitor of thrombin, regardless of whether it is free in solution or bound to fibrin [U00-1351, U07-1984]. Prolongation of aPTT, ecarin clotting time, and PT is concentration dependent, with concentrations of 0.23, 0.184, and 0.825 µM required to double each test *in vitro*, respectively [U00-1351]. In addition, antithrombotic effectiveness was achieved with 0.1 mg/kg i.v. dabigatran in a rat venous stasis model [U00-1229]. In comparison, prolongation of the bleeding time in rats was first detected at doses 5-fold higher (0.5 mg/kg i.v.) [U00-1588]. Oral administration of the pro-drug, dabigatran etexilate, also resulted in a dose-dependent prolongation of the *ex vivo* aPTT and doses between 5 and 30 mg/kg dabigatran etexilate resulted in a significant antithrombotic effect with a rapid onset of action in a rat venous thrombosis model [U00-1785]. In a rat tail model of bleeding, either recombinant Factor VIIa (Novoseven) or activated prothrombin complex (Feiba) together with a high dose of dabigatran etexilate resulted in significantly less bleeding than high dose dabigatran etexilate alone [P08-08706], suggesting that these agents may be able to at least partially counteract the anticoagulant effects of dabigatran.

No major adverse effects, except bleeding at high doses, were observed in general pharmacological investigations with i.v. doses of dabigatran up to 30 mg/kg or oral doses of dabigatran etexilate up to 300 mg/kg in any species tested. This includes renal function [U98-2501, U99-1273], respiratory function [U99-1211], general behaviour [U98-2503, U98-2502, U98-2534, U98-2397, U98-2408], and gastrointestinal effects [U99-1220, U99-1371, U99-1380, U97-2804, U99-1658, U99-1382]. Gastric emptying was decreased in a dose-dependent manner by a single oral administration of 30 to 300 mg/kg dabigatran etexilate in rats, which was only significant at the highest dose [U98-2030]. A comprehensive cardiovascular profiling showed no effect on human ether-a-go-go related gene-mediated potassium current in concentrations up to 30 µM [U04-1606], no effect on action potential configuration in guinea pig papillary muscle up to 10 µM [U99-1732], and no effect in in vivo studies, including electrocardiogram [U98-2414, U99-1211, U99-1344, U99-1732]. This indicates a very low risk for proarrhythmic events.

Pharmacokinetic studies of radio-labelled and non-labelled dabigatran etexilate mesilate (BIBR 1048 MS) and dabigatran (BIBR 953 ZW) were performed in Naval Medical Research Institute mouse [U04-1254], Wistar rat [U98-2257, U98-2709, U00-1096, U02-1372], Himalayan rabbit [U05-2451], and Rhesus monkey [U99-1092, U01-1761]. The absorption after oral administration was 10% for the mouse. The absolute bioavailability was 16% for the rat, 5% for the rabbit, and 8% for the Rhesus monkey (sum of free and glucuronidated dabigatran). After oral administration of pro-drug BIBR 1048 BS conversion to the active moiety BIBR 953 ZW was fast and nearly complete. Whole body autoradiography in rats demonstrated a homogeneous distribution of radioactivity into all

organs except the central nervous system. Beside the gastrointestinal tract, the highest concentrations of radioactivity were found in the liver and in the urinary tract. The radioactivity in tissues decreased rapidly with time. In pregnant rats, only trace amounts of radioactivity were detected, suggesting a limited extent of passage across the placenta. In pigmented rats no affinity of radioactivity was detectable in the melanin containing parts of eye and skin [U00-1096, U02-1372]. The extent of plasma protein binding of BIBR 953 ZW was low in all species investigated (mouse, rat, rabbit, Rhesus monkey, and human), ranging between 22% and 39% [U00-1294, U06-1211]. In rat plasma, the predominant compound was dabigatran, while in Rhesus monkey plasma, the predominant compound were acyl-glucuronides of dabigatran. *In vivo* drug metabolism was studied in plasma, urine, faeces, and (partly) bile of mouse [U04-1913], rat [U04-1627], rabbit [U04-2115], and Rhesus monkey [U04-2009]. Excretion was studied in mouse [U04-1254], rat [U98-2257, U98-2709, U06-1452 (milk)], rabbit [U05-2451], and Rhesus monkey [U99-1092, U01-1761]. The main route of elimination after oral administration of dabigatran etexilate was via faecal excretion in all species.

SII.1.2 Toxicity

The toxic potential of dabigatran etexilate has been investigated in an extensive programme of non-clinical studies including single-dose toxicity studies in rodents, local tolerance studies in rabbits, safety pharmacology studies in rats, dose range finding studies in rats, dogs, and Rhesus monkeys, repeat-dose toxicity studies in rats (4-week, 13-week and 26-week), mice (13-week), and Rhesus monkeys (4-week, 26-week and 52-week), carcinogenicity studies in rats and mice as well as reproductive and developmental toxicity studies in rats and rabbits. In all toxicity studies performed with dabigatran etexilate, the potential toxicity of the test article was fully explored at the used dose levels evaluated.

Both in rats and Rhesus monkeys, toxicokinetic analyses showed significant plasma levels of the analyte dabigatran, indicating substantial exposure to the pharmacodynamically active moiety of dabigatran etexilate. This included a 26-week toxicity study in Chbb: THOM rats using dose levels of 10, 40, and 200 mg/kg [U03-1310], a 26-week toxicity study in Rhesus monkeys using dose levels of 12, 36, and 200 mg/kg [U03-1208], and a 52-week toxicity study in Rhesus monkeys using dose levels of 12, 36, and 200 mg/kg [U05-1557]. At high dose levels, C_{max} and AUC values increased slightly less than dose-proportional. A slight decrease in C_{max} and AUC_{0-24h} for both genders was generally observed after repeated dosing at the end of the studies in the rodent species. There was no consistent gender effect. Maximum plasma levels were reached approximately 2 hours post administration [U99-1092]. Due to the pharmacodynamic activity of dabigatran, increases in coagulation parameters (i.e. aPTT, PT and thrombin time) were observed. They were most prominent in the first 6 to 8 hours post administration and at high dose levels observable even 24 hours post administration [U98-2723].

Despite the significantly increased coagulation parameters, dabigatran etexilate was very well tolerated. The acute oral toxicity of dabigatran etexilate was low (approximate lethal dose >2000 mg/kg in both mice and rats). In repeat-dose toxicity studies up to 26 weeks in rats and up to 52 weeks in Rhesus monkeys, no adverse effects except for pharmacodynamically

mediated bruising and haemorrhages induced by administration of high doses of dabigatran etexilate were noted.

In bleeding-prone rats exposed to high doses of dabigatran etexilate resulting in extremely prolonged bleeding times, recurrent haemorrhages accompanied by deposition of fibrin and fibroses were induced by the mechanic forces exerted during gavage [U98-2720, U98-2729, U05-1378, U03-1310, U04-1864]. The affected organs were the thymus, the pancreas and, in a few animals, the heart. The incidence and severity of these findings were significantly reduced, when flexible plastic catheters were used instead of steel catheters.

Other side effects (e.g. increase in reticulocyte counts [U98-2729]) were generally mild and can be linked directly or indirectly to the exaggerated pharmacological activity of dabigatran etexilate at high dose levels. No other significant adverse effects related to the exposure to dabigatran etexilate and considered to be toxicologically meaningful were observed.

In Rhesus monkeys, the liability to suffer from haemorrhages was rather low despite considerable increases in PT and aPTT [U98-2722, U98-2723]. The evaluation of the 52-week toxicity study in Rhesus monkeys [U05-1557] did not reveal evidence of other adverse effects than already reported for the 26-week toxicity study [U03-1208]. In this species, no histological findings comparable to those in rats were observed. All other changes noted in Rhesus monkeys were of minor toxicological significance.

In all animal species used in the pre-clinical programme, there was especially no evidence for any adverse effects on the liver: long-term usage of ximelagatran, also a direct thrombin inhibitor, in clinical trials has been associated with acute hepatocellular toxicity (increases in liver transaminases), which was typically observed 1 to 6 months after start of treatment. Therefore, the available individual animal data (clinical chemistry, organ weights, gross and histopathology) were also analysed in accordance with Step I of the Committee for Medicinal Products for Human Use Draft “Guideline on Detection of Early Signals of Drug-Induced Hepatotoxicity in non-clinical Studies” from 28 Jun 2006. No early signals of hepatotoxicity were detected in either rats or Rhesus monkeys.

Genotoxicity

The genotoxic potential of dabigatran etexilate was assessed in bacterial and mammalian systems (Ames, mouse lymphoma, and rat bone marrow micronucleus assay) [U98-2147, U99-1063, U98-2789, U99-1023, U05-2047, U01-1161, U05-1295]. Test concentrations were selected up to bacterio-/cytotoxic or precipitating concentration levels in the *in vitro* assays and up to maximum tolerated/limit doses under in vivo conditions. In addition, the active moiety dabigatran was investigated in the Ames assay. Rat liver S9 fractions from Aroclor 1254-induced rats were used as metabolic activation in the *in vitro* models. The Ames and bone marrow micronucleus test were repeated using a mannitol formulation and higher dose levels, respectively. In the mouse lymphoma re-test, higher test concentrations were examined. Thus, it is concluded that dabigatran etexilate and its active moiety dabigatran are not genotoxic.

Carcinogenicity

There was no evidence for a carcinogenic potential of dabigatran etexilate [U07-2084, U07-2181].

Developmental and reproductive toxicity

The embryo-foetal development and fertility/early developmental toxicity studies in rats showed that maternal and (early) embryo-foetal toxicity occurred only at the high dose of 200 mg/kg dabigatran etexilate. The ability to mate and to bear live young and fertility were not affected by exposure to dabigatran etexilate [U03-1284]. In the pre- and postnatal development study (including maternal function) in rats, maternal toxicity was observed, however, already at 70 mg/kg dabigatran etexilate due to bleeding episodes into the genital tract during parturition [U05-1550]. No drug-related effect on the postnatal development of the offspring as shown by normal body weight development, normal survival after birth and normal physical postnatal development was noted. The embryo-foetal development toxicity study in rabbits also indicated maternal effects only at the high dose of 200 mg/kg [U02-1648, U01-1820], and no teratogenic potential was observed.

In non-clinical safety studies in non-juvenile mice, rats, guinea pigs, rabbits, dogs, and Rhesus monkeys few adverse effects were observed [U06-2168]. In general, these were directly or indirectly associated with an increased propensity for bleeding events or compensatory effects at high dose levels and, therefore, high plasma levels. Likewise, mortality in the juvenile toxicity study conducted in Han Wistar rats [n0251085-01] was associated with bleeding events at similar exposures, at which bleeding was seen in adult animals. In both adult and juvenile rats, mortality is considered to be related to the exaggerated pharmacological activity of dabigatran in association with the exertion of mechanical forces during dosing and handling. Data of the juvenile toxicity study did neither indicate an increased sensitivity in toxicity, nor any toxicity specific to juvenile animals.

SII.1.3 Other toxicity-related information or data

There was no evidence of dermal intolerance, acute eye irritation, and skin sensitisation.

SII.1.4 Conclusions

In summary, few adverse effects were observed in non-clinical safety studies in mice, rats, guinea pigs, rabbits, dogs, and Rhesus monkeys. In general, these were directly or indirectly associated with an increased propensity for bleeding events or compensatory effects at high dose levels and, therefore, high plasma levels. It is concluded, based on toxicological evaluation, that dabigatran etexilate is an active anticoagulant for which no non-anticoagulation related safety concerns have been identified. However, the usual risks of impaired blood coagulation apply.

SII.2 REFERENCES

SII.2.1 Published references

P08-08706 Ryn J van, Ruehl D, Priepke H, Hauel N, Wienen W. Reversibility of the anticoagulant effect of high doses of the direct thrombin inhibitor dabigatran, by recombinant factor VIIa or activated prothrombin complex concentrate. 13th Cong of the European Hematology Association, Copenhagen, 12 - 15 Jun 2008. Haematologica 93 (Suppl 1), 148, Abstr 0370 (2008)

SII.2.2 Unpublished references

n0251085-01 Neonatal toxicity study in the Han Wistar rat by oral (gavage) administration for 8 weeks followed by a 4-week recovery period. DDB0467. 09 June 2016.

U00-1096 BIBR 1048 MS and BIBR 953 ZW: Whole body autoradiography after oral administration of [14C]BIBR 1048 MS and intravenous administration of [14C]BIBR 953 ZW in male albino and male pigmented rats. B1348. 03 Feb 2000.

U00-1229 Antithrombotic and anticoagulant effects of the direct thrombin inhibitor BIBR 953 ZW in comparison to Refludan, melagatran, argatroban, napsagatran and heparin after i.v. administration in a rat venous thrombosis model. W05042000. 05 Apr 2000.

U00-1294 Protein binding of [14C]BIBR 953 ZW in human, rat and rhesus plasma. B1357. 28 Apr 2000.

U00-1351 The selectivity and specificity of BIBR 953 ZW towards purified human serine proteases in vitro. CR3-2000-01. 24 Apr 2000.

U00-1588 Effect of BIBR 953 ZW on tail bleeding time and activated partial thromboplastin time in the anaesthetized rat. W18082000. 18 Aug 2000.

U00-1785 Antithrombotic and anticoagulant effects of BIBR 1048 MS, the double prodrug of the direct thrombin inhibitor BIBR 953 ZW, after oral administration in a rat venous thrombosis model. W11102000. 11 Oct 2000.

U01-1161 Mutagenicity study in the mouse lymphoma L5178Y tk+/- assay with BIBR 1048 MS. 00B100. 25 Jan 2001.

U01-1761 The disposition of [14C]BIBR 953 ZW in the rhesus monkey following intravenous administration. B1228, IRI 164291. 06 Nov 2001 (Amendment 22 May 2006).

U01-1820	BIBR 1048 MS: Dose range finding study for effects on embryo-fetal development in rabbits by oral administration (gavage). 00B057. 13 Dec 2001.
U02-1372	BIBR 1048 MS and BIBR 953 ZW: Whole body autoradiography after oral administration of [14C]BIBR 1048 MS and subcutaneous administration of [14C]BIBR 953 ZW in pregnant albino rats. 25 Jun 2002.
U02-1648	BIBR 1048 MS: Study for effects on embryo-fetal development in rabbits by oral administration (gavage). 00B058. 07 Nov 2002.
U06-2168	2.6 Nonclinical Written and Tabulated Summary: Dabigatran etexilate, hard capsule, 75 mg and 110 mg. 19 Jan 2007
U03-1208	BIBR 1048 MS: 26-week oral (gavage) toxicity study in Rhesus monkeys with a 6-week recovery period. B1795. B1826. Covance 1647-1813-011. Covance 1813-011. 27 Mar 2003.
U03-1284	BIBR 1048 MS: Study for effects on embryo-fetal development in rats by oral administration (gavage). 00B056, 24 April 2003. Amendment 1. 13 Jan 2004.
U03-1310	BIBR 1048 MS: 26-week oral (gavage administration) toxicity study in the rat with a 6-week treatment-free period. 979/5-D6154. 24 Apr 2003.
U04-1254	Plasma level and excretion balance after oral administration of [14C] BIBR 1048 MS to the male mouse. A040/01UB,B1876. 27 Feb 2004.
U04-1606	Influence of dabigatran (BIBR 953 ZW) on hERG-mediated potassium current in HEK293 cells. GP2004/0341/PH2. 02 Aug 2004.
U04-1627	Metabolism of BIBR 1048 MS and BIBR 953 ZW in rats. A289/01BC, A344/02BC (B2314).16 Aug 2004.
U04-1864	BIBR 1048 MS: Dose range finding study by oral gavage administration to Han Wistar rats for 2 weeks. BOI 266/020214. 17 Sep 2004.
U04-1913	Metabolism of BIBR 1048 MS and BIBR 953 ZW in mice. A394/03BC,B2315. 20 Oct 2004.
U04-2009	Metabolism of BIBR 1048 MS and BIBR 953 ZW in rhesus monkeys. A392/03BC (B2316). 21 Nov 2005.
U04-2115	Metabolism of BIBR 1048 MS and BIBR 953 ZW in rabbits. A393/03BC,B2401. 13 Dec 2004.

U05-1295 BIBR 1048 MS: Mutagenicity study using micronucleus analysis in rat bone marrow after oral treatment (supplementary study). 04B068. 22 Mar 2005.

U05-1378 BIBR 1048 MS: Maximum tolerated dosage study by oral gavage administration to HanWistar rats for 13 weeks. BOI 277/032919. 09 Mar 2005.

U05-1550 BIBR 1048 MS: Study of fertility and early embryonic development to implantation in rats by oral administration, gavage. 02B025. 28 Apr 2005. Amendment 1. 11 May 2005.

U05-1557 BIBR 1048 MS: Toxicity Study by Oral Gavage Administration to Rhesus Monkey for 52 Weeks Followed by a 6 week Recovery. BOI 252/032248. 29 Apr 2005.

U05-2047 BIBR 1048 MS: Mutagenicity study using micronucleus analysis in rat bone marrow after oral treatment (retest). 04B285. 11 Aug 2005.

U05-2451 Plasma level and excretion balance after oral administration of [14C]BIBR 1048 MS in female rabbits. Plasma level after oral administration of BIBR 1048 MS and intravenous administration of BIBR 953 ZW in female rabbits. A065/04UBB2426. 23 Nov 2005.

U06-1211 Protein binding of [14C] BIBR 953 ZW in mouse and rabbit plasma. A130/06GR, B2798. A066/04UB. 29 Mar 2006.

U06-1452 Metabolism and excretion of [14C] BIBR 1048 MS in milk after oral administration to lactating rats. A150/06RB. B2962. 23 May 2006.

U06-2168 2.6 Nonclinical Written and Tabulated Summary: Dabigatran etexilate, hard capsule, 75 mg and 110 mg. 19 Jan 2007.

U07-1984 The Effect of Dabigatran on Thrombin Inhibition in the Clot-bound and Fluid Phase. 2007/LUI/Lab1/Report1. 04 Oct 2007.

U07-2084 Carcinogenicity Study by Oral Gavage Administration to Han Wistar Rats for 104 Weeks. BOI 288/042959. 05 Oct 2007.

U07-2181 Carcinogenicity study by oral gavage administration to CD-1 mice for 104 weeks. BOI 287/042668. 30 Oct 2007.

U97-2804 General pharmacology: BIBR 1048 MS - effects on gastro-intestinal transit. GP97-083-PH4. 06 Dec 1997.

U98-2030 General Pharmacology: BIBR 1048 MS – Effects on gastric emptying. GP97-084-PH4. 20 Jan 1998.

U98-2147	Mutagenicity study with BIBR 1048 MS in the S. typhimurium/mammalian-microsome assay (Ames test). 97B110. 13 Mar 1998.
U98-2257	Basic ADME of [14C]BIBR 1048 MS in the rat. B903. 06 May 1998.
U98-2397	BIBR 1048 MS / General Pharmacology: Effects of orally administered 30, 100, and 300 mg/kg BIBR 1048 MS on exploratory motility in conscious rats. GP97/081/PH5. 19 Jun 1998.
U98-2408	BIBR 1048 MS / General Pharmacology: Effects of orally administered 30, 100 and 300 mg/kg BIBR 1048 MS on hexobarbitone-induced sleeping time in rats. GP97/082/PH5. 28 May 1998.
U98-2414	Influence of BIBR 953 ZW (0.3 to 30 mg/kg IV) on cardiovascular function in anesthetized pigs. GP1998/031/PH2. 20 Jul 1998.
U98-2501	General Pharmacology: BIBR 1048 MS. Effects on renal function in conscious female dogs. GP98-036-PH4. 28 Jul 1998.
U98-2502	Effects on general behaviour in mice after oral administration of 30, 100, 300 and 1000 mg/kg BIBR 1048 MS. GP97-079-PH5. 30 Jun 1998.
U98-2503	BIBR 953 ZW General Pharmacology Effects on general behaviour in mice after intravenous administration of 3, 10, and 30 mg/kg BIBR 953 ZW. GP96-134-PH5. 10 Aug 1998.
U98-2534	BIBR 953 ZW / General Pharmacology; Effects of BIBR 953 ZW (3, 10 and 30 mg/kg, iv) on exploratory motility in conscious rats. GP96-134-PH5. 24 Aug 1998.
U98-2709	Basic ADME of [14C] BIBR 953 ZW in the rat. B984. 06 October 1998.
U98-2720	BIBR 1048 MS: Dose range finding study by oral administration (gavage) to rats over a period of 2 weeks. 97B106. 16 Dec 1998.
U98-2722	BIBR 1048 MS: Oral (Gavage) Maximum Tolerated Dose Study in Rhesus Monkeys. Inveresk Report No. 16146. 04 Nov 1998.
U98-2723	BIBR 1048 MS: 4 week oral (gavage) toxicity study in rhesus monkeys with a 4 week recovery period. Inveresk Report No. 16583. 04 Nov 1998.
U98-2729	BIBR 1048 MS: Repeated dose toxicity study in rats by oral administration (gavage) over a period of 4 weeks. 98B024. 20 Oct 1998.
U98-2789	Mutagenicity study with BIBR 953 ZW in the S. typhimurium/mammalian-microsome assay (Ames test). 98B037. 05 Oct 1998.

U99-1023	Mutagenicity study in the rat bone marrow micronucleus assay after oral treatment with BIBR 1048 MS. 98B101. 17 Dec 1998.
U99-1063	Mutagenicity study with BIBR 1048 MS/mannitol in the S. typhimurium/mammalian-microsome assay (Ames test). 98B065. 18 Dec 1998.
U99-1092	The disposition of [14C]BIBR 1048 MS in the rhesus monkey following oral administration. B1055, IRI162713, B992. 21 Jan 1999.
U99-1211	General Pharmacology: BIBR 953 ZW. Effects of 0.1, 0.3, 1.0, 3.0 and 10.0 mg/kg intravenously on cardiovascular and respiratory function in anaesthetized rabbits. GP98-019-PH4. 5 Feb 1999.
U99-1220	General pharmacology: BIBR 953 ZW, effects on gastric secretion in conscious rats. GP98-112-PH4. 26 Feb 1999.
U99-1273	General pharmacology: BIBR 953 ZW, effects on renal function in conscious female dogs. GP98-096-PH4. 04 Mar 1999.
U99-1344	Effects of BIBR 1048 MS (30, 100, or 300 mg/kg, po) on heart rate and blood pressure in conscious rats. GP-1997-080-PH5. 29 Mar 1999.
U99-1371	General pharmacology: BIBR 1048 MS, effects on gastric secretion in conscious rats. GP98-114-PH4. 26 Apr 1999.
U99-1380	General pharmacology: BIBR 953 ZW, effects on gastro-intestinal transit in rats. GP1998-106-PH4. 11 May 1999.
U99-1382	General Pharmacology: BIBR 953 ZW Effects on gastric emptying in rats. GP1998-105-PH4. 10 May 1999.
U99-1658	BIBR 953 ZW/general pharmacology: effects of 10E-9 to 10E-5 mol/l on histamine, acetylcholine, bariumchloride and serotonin induced contractions in a smooth muscle preparation (isolated ileum) of the guinea pig. GP1997/024/PH5. 01 Oct 1999.
U99-1732	Effects of BIBR 953 ZW (0.01 to 10 µM) on action potential configuration in isolated guinea pig papillary muscle. GP1999/073/PH2. 08 Nov 1999.

ABBREVIATIONS

aPTT	Activated partial thromboplastin time
AUC	Area under the curve
Chbb: THOM	Rat strain
C_{max}	Maximum concentration
DLP	Data lock point
i.v.	Intravenous
MAH	Marketing authorisation holder
PT	Prothrombin time

MODULE SIII CLINICAL TRIAL EXPOSURE

Estimated cumulative exposure from clinical trials and the enrolment/randomisation schemes for completed and ongoing clinical trials are provided in SIII.Table 1 below. Exposure was calculated based on the number of subjects randomised that received at least 1 dose of the respective trial drug (dabigatran, comparators, placebo). Exposure in the completed trials and ongoing trials are added together. For completed trials, the actual enrolment numbers are included. For ongoing blinded trials, the randomisation scheme was applied to the number of subjects enrolled by the DLP to provide an estimated exposure in each treatment arm.

SIII.Table 1 Estimates of cumulative subject exposure from clinical trials

Treatment	**Estimated number of subject exposed - including paediatric patients (number of subjects)** [1]	**Estimated number of subject exposed - paediatric patients (number of subjects)** [1][3]
Dabigatran	35 394	424 [2]
Comparators	18 754	90
Placebo	10 638	0
Total	64 786	514

Data from completed and ongoing trials as of DLP: 18 Mar 2020

[1] Exposure was calculated based on number of subjects who received at least one dose of study drug.

[2] Patients rolling over from trial 1160-0106 to 1160-0108 were counted both in trial 1160-0106 as well as in 1160-0108.

[3] Paediatric patients included in trials 1160-0088, 1160-0089, 1160-0105, 1160-0106, and 1160-108.

Containing data from studies: 1160-0001, 1160-0002, 1160-0003, 1160-0005, 1160-0006, 1160-0007, 1160-0010, 1160-0011, 1160-0014, 1160-0015, 1160-0016, 1160-0017, 1160-0019, 1160-0020, 1160-0023, 1160-0024, 1160-0025, 1160-0026, 1160-0028, 1160-0029, 1160-0030, 1160-0031, 1160-0032, 1160-0033, 1160-0034, 1160-0040, 1160-0042, 1160-0046, 1160-0047, 1160-0048, 1160-0049, 1160-0050, 1160-0051, 1160-0052, 1160-0053, 1160-0054, 1160-0055, 1160-0056, 1160-0057, 1160-00 58, 1160-0059, 1160-0060, 1160-0061, 1160-0063, 1160-0064, 1160-0066, 1160-0067, 1160-0070, 1160-0071, 1160-0073, 1160-0074, 1160-0075, 1160-0078, 1160-0081, 1160-0082, 1160-0083, 1160-0086, 1160-0087, 1160-0088, 1160-0089, 1160-0090, 1160-0100, 1160-0101, 1160-0105, 1160-0106, 1160-0108, 1160-0112, 1160-0113, 1160-0117, 1160-0121, 1160-0128, 1160-0138, 1160-0141, 1160-0142, 1160-0166, 1160-0173, 1160-0186, 1160-0189, 1160-0194, 1160-0204, 1160-0246, 1160-0248, 1160-0270, 1160-0271

Source: Table 1

The cumulative subject exposure to dabigatran from completed clinical trials by age, gender and racial group is presented in the tables below.

SIII.Table 2 Cumulative subject exposure to dabigatran from completed clinical trials by age and gender

	Subjects exposed [n (%)]		
	Male	**Female**	**Total**
Number of subjects [n (%)]	20 794 (100.0)	14 211 (100.0)	35 005 (100.0)
Age [years] [n (%)]			
<18	17 (0.1)	18 (0.1)	35 (0.1)
18 to <65	8820 (42.4)	4764 (33.5)	13 584 (38.8)
65 to <75	7240 (34.8)	5106 (35.9)	12 346 (35.3)
75 to <80	2924 (14.1)	2510 (17.7)	5434 (15.5)
80 to <85	1388 (6.7)	1370 (9.6)	2758 (7.9)
≥85	405 (1.9)	443 (3.1)	848 (2.4)

Data from completed trials as of DLP: 18 Mar 2020 including all subjects who received at least one dose of study drug.

Containing data from trials: 1160-0001, 1160-0002, 1160-0003, 1160-0005, 1160-0006, 1160-0007, 1160-0010, 1160-0011, 1160-0014, 1160-0015, 1160-0016, 1160-0017, 1160-0019, 1160-0020, 1160-0023, 1160-0024, 1160-0025, 1160-0026, 1160-0028, 1160-0029, 1160-0030, 1160-0031, 1160-0032, 1160-0033, 1160-0034, 1160-0040, 1160-0042, 1160-0046, 1160-0047, 1160-0048, 1160-0049, 1160-0050, 1160-0051, 1160-0052, 1160-0053, 1160-0054, 1160-0055, 1160-0056, 1160-0057, 1160-00 58, 1160-0059, 1160-0060, 1160-0061, 1160-0063, 1160-0064, 1160-0066, 1160-0067, 1160-0070, 1160-0071, 1160-0073, 1160-0074, 1160-0075, 1160-0078, 1160-0081, 1160-0082, 1160-0083, 1160-0086, 1160-0087, 1160-0088, 1160-0089, 1160-0090, 1160-0100, 1160-0101, 1160-0105, 1160-0112, 1160-0113, 1160-0117, 1160-0121, 1160-0128, 1160-0138, 1160-0141, 1160-0142, 1160-0166, 1160-0173, 1160-0186, 1160-0189, 1160-0194, 1160-0204, 1160-0246, 1160-0248, 1160-0270, 1160-0271

Source: Table 2

SIII.Table 3 Number of patients in trials 1160.106 and 1160.108 by age group – RS, TS

	Dabigatran			**Standard of care**		
Age stratum	Birth to <2 years	2 to <12 years	12 to <18 years	Birth to <2 years	2 to <12 years	12 to <18 years
Randomised in 1160.106	22	43	112	13	21	56
Treated in 1160.106	22	43	111	13	21	56
Treated in 1160.160 only	21	31	63	12	17	31
Treated in both trials (roll-over)	1	12	48	1	4	25
Treated in 1160.108 only	8	27	87	--	--	--
Total of treated patients	30	70	198	13	21	56

Data source: [c29773859-01], Table 10.1: 3

SIII.Figure 1 Source of patients in trials 1160.106 and 1160.108 by age group – TS

Data source: [c29773859-01], Figure 10.1: 2

SIII.Table 4 Cumulative subject exposure to dabigatran from completed clinical trials by racial group

	Subjects exposed [n (%)]
Number of subjects [n (%)]	35 005 (100.0)
Race [n (%)]	
Asian[1]	4718 (13.5)
Black	445 (1.3)
White	28 147 (80.4)
Other[2]	1585 (4.5)
Missing	110 (0.3)

Data from completed trials as of DLP: 18 Mar 2020.

[1] Asian includes Asian, American Indian or Alaska native and Native Hawaiian or other Pacific Islander.

[2] Other includes Native Latin.

Containing data from trials: 1160-0001, 1160-0002, 1160-0003, 1160-0005, 1160-0006, 1160-0007, 1160-0010, 1160-0011, 1160-0014, 1160-0015, 1160-0016, 1160-0017, 1160-0019, 1160-0020, 1160-0023, 1160-0024, 1160-0025, 1160-0026, 1160-0028, 1160-0029, 1160-0030, 1160-0031, 1160-0032, 1160-0033, 1160-0034, 1160-0040, 1160-0042, 1160-0046, 1160-0047, 1160-0048, 1160-0049, 1160-0050, 1160-0051, 1160-0052, 1160-0053, 1160-0054, 1160-0055, 1160-0056, 1160-0057, 1160-00 58, 1160-0059, 1160-0060, 1160-0061, 1160-0063, 1160-0064, 1160-0066, 1160-0067, 1160-0070, 1160-0071, 1160-0073, 1160-0074, 1160-0075, 1160-0078, 1160-0081, 1160-0082, 1160-0083, 1160-0086, 1160-0087, 1160-0088, 1160-0089, 1160-0090, 1160-0100, 1160-0101, 1160-0105, 1160-0112, 1160-0113, 1160-0117, 1160-0121, 1160-0128, 1160-0138, 1160-0141, 1160-0142, 1160-0166, 1160-0173, 1160-0186, 1160-0189, 1160-0194, 1160-0204, 1160-0246, 1160-0248, 1160-0270, 1160-0271

Source: Table 3

SIII.1 REFERENCES

SIII.1.1 Published references

Not applicable.

SIII.1.2 Unpublished references

c29773859-01 Open-label, randomized, parallel-group, active-controlled, multi-centre, non-inferiority study of dabigatran etexilate versus standard of care for venous thromboembolism treatment in children from birth to less than 18 years of age: The DIVERSITY study. 1160-0106. 27 Apr 2020.

ABBREVIATIONS

DLP	Data lock point
RS	Randomised set
TS	Treated set

MODULE SIV POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 EXCLUSION CRITERIA IN PIVOTAL CLINICAL TRIALS WITHIN THE DEVELOPMENT PROGRAMME

Hypersensitivity

Reason for exclusion:	Hypersensitivity reactions are a listed side effect for Pradaxa.
Is it considered to be included as missing information?	No
Rationale:	Pradaxa is contraindicated in patients with known hypersensitivity to dabigatran, dabigatran etexilate, or to one of the excipients of the product. Therefore, there is no scientific rationale for inclusion of this population as missing information, as use of Pradaxa is not targeted for this population.
Renal impairment	**Adult patients** Severe renal impairment: CrCl ≤30 mL/min **Paediatric patients** Renal dysfunction: eGFR <50ml/min
Reason for exclusion:	Increased risk of haemorrhage.
Is it considered to be included as missing information?	Yes, for the paediatric VTE indication
Rationale:	For adult patients only: severe renal impairment is a contraindication for Pradaxa and is considered an important identified risk.

Active clinically significant bleeding

Reason for exclusion:	Increased risk of haemorrhage.
Is it considered to be included as missing information?	No
Rationale:	Haemorrhage is a contraindication for Pradaxa and is considered an important identified risk.

Increased risk of major bleeding

Reason for exclusion:	Increased risk of haemorrhage.
Is it considered to be included as missing information?	No

Rationale:	Haemorrhage is a contraindication for Pradaxa and is considered an important identified risk.

Severe hepatic impairment

Reason for exclusion:	Potential risk due to lack of experience on use of Pradaxa in these patients.
Is it considered to be included as missing information?	No
Rationale:	It is not expected that patients with severe hepatic impairment would have a different safety profile from the rest of population, since dabigatran is not primarily metabolised by the liver and does not interact with the CYP P450 enzyme system. A single dose (150 mg) hepatic impairment study comparing moderate hepatic impairment with matched healthy volunteers indicated that chronic hepatic disease does not change the elimination of dabigatran [U06-1705]. Use of Pradaxa is not recommended in patients with severe hepatic impairment according to EU-SmPC. There is no scientific rationale for inclusion of this population as missing information, as use of Pradaxa is not targeted for this population.

Heart valve disorders, especially prosthetic heart valves

Reason for exclusion:	Increased risk of thromboembolic events.
Is it considered to be included as missing information?	No
Rationale:	**Adult patients** Patients with prosthetic hearth valves were enrolled in specific studies (1160.113, RE-ALLIGN, and 1160.138, RE-ALIGN extension) to investigate safety and efficacy of Pradaxa in patients in this indication. The results of these studies led to a contraindication of the use of Pradaxa in patients with prosthetic hearth valves. Therefore, these patients were excluded from the subsequent studies. Due to the contraindication, there is no scientific rationale for inclusion of this population as missing information, as use of Pradaxa is not targeted for this population. **Paediatric patients** In the paediatric studies, subjects with prosthetic heart valves requiring anticoagulation were excluded. Due to the contraindication, there is no scientific rationale for inclusion of this population as missing information, as use of Pradaxa is not targeted for this population.

Recent severe stroke

Reason for exclusion:	Increased risk of intracranial haemorrhage.
Is it considered to be included as missing information?	No
Rationale:	Patients with a recent ischaemic stroke of unknown origin were investigated in the clinical trial 1160.189, RESPECT-ESUS, while patients with atrial fibrillation and previous stroke were investigated in a subgroup analysis of the clinical trial 1160.26, RE-LY. The studies' results did not warrant restrictions of Pradaxa use in patients with recent ischaemic stroke.

Active meningitis, encephalitis or intracranial abscess (Paediatric patients only)

Reason for exclusion:	Increased risk of haemorrhage.
Is it considered to be included as missing information?	No
Rationale:	There is no concern regarding use in patients with intracranial infections after over 17.2 million patient-years of Pradaxa use. According to the EU-SmPC, Pradaxa can be used in paediatric patients with active meningitis, encephalitis, and intracranial abscess if the expected benefit outweighs bleeding risks.

Pregnant and breastfeeding women

Reason for exclusion:	Lack of information on the safety of use of Pradaxa in pregnant women.
Is it considered to be included as missing information?	No
Rationale:	The EU-SmPC contains a recommendation that pregnant women should not be treated with Pradaxa unless the expected benefit is greater than the risk and that, as a precaution, breastfeeding should be stopped. Therefore, there is limited post-marketing use in this population. During the long cumulative safety experience with Pradaxa of over 17.2 million patient-years, there has been no new information that suggested any safety concern for this population. Therefore, this is not considered to be missing information.

Unstable cardiovascular disease

Reason for exclusion:	Insufficient information available at time of studies.

Is it considered to be included as missing information?	No
Rationale:	Controlled clinical data do not support a contraindication. Pradaxa has been used without restriction in terms of cardiovascular disease for more than 17.2 million patient-years; therefore, use in such patients is not considered missing information. No safety concern has been raised after 13 years of close monitoring of myocardial infarction.

Patients 0 to 2 years of age with gestational age at birth <37 weeks or with body weight lower than the 3rd percentile (according to the WHO Child growth standards)

Reason for exclusion:	Lack of information on the safety in these patients (patients <37 weeks or with body weight lower than the 3rd percentile according to the WHO Child growth standards were excluded from clinical trials).
Is it considered to be included as missing information?	Yes
Rationale:	Not applicable.

SIV.2 LIMITATIONS TO DETECT ADVERSE REACTIONS IN CLINICAL TRIAL DEVELOPMENT PROGRAMMES

The clinical development programme is unlikely to detect certain types of adverse reactions such as adverse reactions with a long latency or those caused by prolonged or cumulative exposure.

SIV.3 LIMITATIONS IN RESPECT TO POPULATIONS TYPICALLY UNDER-REPRESENTED IN CLINICAL TRIAL DEVELOPMENT PROGRAMMES

SIV.Table 1 Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure	
	Number	Person-time
Pregnant women	Not included in the clinical development programme	-
Breastfeeding women	Excluded from the clinical development programme	n.a.
Patients with relevant co-morbidities		
• Patients with severe hepatic impairment	Excluded from the clinical development programme	n.a.
• Patients with severe renal impairment	Excluded from the clinical development programme	n.a.

SIV.Table 1 (cont'd) Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure	
	Number	Person-time
Patients with a disease severity different from inclusion criteria in clinical trials	Excluded from the clinical development programme	n.a.
Population with relevant different ethnic origin	See SIII.Table 3 for information on ethnic origin.	n.a.
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development programme	n.a.
Other		
• Patients under 18 years	Trial 1160.88: 9 children aged 12 to <18 years treated for 3 days twice daily Trial 1160.89: 6 children aged 1 year to <2 years treated with a single dose; 9 children aged 2 to <12 years treated with a single dose; 3 children aged 2 to <12 years treated for 3 days twice daily Trial 1160.105: 8 children aged <1 year treated with a single dose Trial 1160.106: 22 children aged <2 years treated with multiple doses; 43 children aged 2 to <12 years treated with multiple doses; 111 children aged 12 to <18 years treated with multiple doses Trial 1160.108: 9 children aged <2 years treated with multiple doses; 43 children aged 2 to <12 years treated with multiple doses; 161 children aged 12 to <18 years treated with multiple doses	
• Elderly population	See SIII.Table 2	-
• Patients with low body weight (<50 kg)	Trial 1160.26 (RE-LY): 250 patients (2.1% of 12 091 patients treated with either dabigatran etexilate 110 mg b.i.d. or 150 mg b.i.d.) Trial 1160.53: 8 patients DE150, 10 patients VKA Trial 1160.46: 18 patients DE150, 21 patients VKA Trial 1160.47: 10 patients DE150, 5 patients VKA Trial 1160.63: 8 patients DE150, 10 patients placebo	-

Data source: RMP v36.0 [s00017740-46], [U12-3378-01], [c29773859-01], and [c29754273-01].

SIV.4 REFERENCES

SIV.4.1 Published references

Not applicable.

SIV.4.2 Unpublished references

c29754273-01 Open label, single arm safety prospective cohort study of dabigatran etexilate for secondary prevention of venous thromboembolism in children from 0 to less than 18 years. 1160.108. 24 Apr 2020.

c29773859-01 Open-label, randomized, parallel-group, active-controlled, multi-centre, non-inferiority study of dabigatran etexilate versus standard of care for venous thromboembolism treatment in children from birth to less than 18 years of age: The DIVERSITY study. 1160.106. 27 Apr 2020.

s00017740-46 Risk Management Plan for Pradaxa (Dabigatran Etexilate), Version 36.0. 02 May 2018.

U06-1705 Pharmacokinetics, pharmacodynamics, safety and tolerability of 150 mg dabigatran etexilate p.o. in patients with moderate hepatic impairment compared to subjects with normal hepatic function in a monocentric, open, parallel-group design. 17-Oct-2006.

U12-3378-01 Open-label safety and tolerability study of dabigatran etexilate given for 3 days at the end of standard anticoagulant therapy in children aged 12 years to less than 18 years. 1160.88. 05 Jul 2012.

ABBREVIATIONS

b.i.d	Bis in die (twice daily)
CrCl	Creatinine clearance
DE150	Dabigatran etexilate 150 mg
eGFR	Epidermal growth factor receptors
n.a.	Not applicable
RE-LY	Randomized Evaluation of Long term anticoagulant therapy (1160.26 trial)
VKA	Vitamin K antagonist
VTE	Venous thromboembolism
WHO	World Health Organisation

MODULE SV POST-AUTHORISATION EXPERIENCE

SV.1 POST-AUTHORISATION EXPOSURE

SV.1.1 Method used to calculate exposure

BI bases its estimate of post-marketing patient exposure to Pradaxa on ex-factory sales of commercial product excluding samples and free goods.

Exposure in PY was calculated based on the number of capsules sold (ex-factory sales), assuming that all capsules have been used by patients and that each patient was treated with 2 capsules per day. Therefore, the total number of days of medication was calculated by dividing the number of capsules by 2. Sales to Japan are an exception to this: for Japan, 2 capsules a day is assumed for 110 mg capsules, and 4 capsules a day is assumed for 75 mg capsules (as 150 mg capsules are not on the market there in order to arrive at the daily dose of 300 mg). The total number of days of medication was then divided by 365.25 to calculate exposure in PY. Calculated cumulative and interval exposure are presented by dose and region in the tables below.

At the DLP of this RMP, the paediatric formulations (pellets and oral solution) were not yet on the market.

SV.1.2 Exposure

SV.Table 1 Cumulative exposure from marketing experience by dose and region for Pradaxa based on ex-factory sales (18 Mar 2008 to 29 Feb 2022)

	Cumulative exposure [PY][1]						
Dose	**Australia**	**EEA excl. Germany[2]**	**Germany**	**US**	**Japan**	**ROW[2]**	**Total**
75 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1 070 760
110 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	8 391 107
150 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	7 804 375
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**17 266 242**

[1]All numbers are rounded to the nearest integer

[2]UK exposure, previously considered under 'EEA excl. Germany' is now included in the ROW

Data source: PBRER [s001048841-01], Table 4

The cumulative patient exposure to marketed Pradaxa is estimated to be 17 266 242 PY for the time period from 18 Mar 2008 (IBD) to 29 Feb 2022.

SV.Table 2 Cumulative exposure from marketing experience by formulation, dose, and EU/EEA country for Pradaxa (18 Mar 2008 to 29 Feb 2022)

	Cumulative exposure [PY]		
EU/EEA country	**110 mg**	**150 mg**	**75 mg**
Denmark	[redacted]	[redacted]	[redacted]
Finland	[redacted]	[redacted]	[redacted]
Norway	[redacted]	[redacted]	[redacted]
Sweden	[redacted]	[redacted]	[redacted]
United_Kingdom	[redacted]	[redacted]	[redacted]
Ireland	[redacted]	[redacted]	[redacted]
Malta	[redacted]	[redacted]	[redacted]
Netherlands	[redacted]	[redacted]	[redacted]
Belgium	[redacted]	[redacted]	[redacted]
France	[redacted]	[redacted]	[redacted]
Germany	[redacted]	[redacted]	[redacted]
Italy	[redacted]	[redacted]	[redacted]
Croatia	[redacted]	[redacted]	[redacted]
Slovenia	[redacted]	[redacted]	[redacted]
Austria	[redacted]	[redacted]	[redacted]
Spain	[redacted]	[redacted]	[redacted]
Portugal	[redacted]	[redacted]	[redacted]
Bulgaria	[redacted]	[redacted]	[redacted]
Poland	[redacted]	[redacted]	[redacted]
Romania	[redacted]	[redacted]	[redacted]
Hungary	[redacted]	[redacted]	[redacted]
Czech Republic	[redacted]	[redacted]	[redacted]
Slovak Republic	[redacted]	[redacted]	[redacted]
Greece	[redacted]	[redacted]	[redacted]
Cyprus	[redacted]	[redacted]	[redacted]
Estonia	[redacted]	[redacted]	[redacted]
Latvia	[redacted]	[redacted]	[redacted]
Lithuania	[redacted]	[redacted]	[redacted]
Total	4 041 867	3 240 501	138 371

[1]All numbers are rounded to the nearest integer

Data source: data on file, EA-006 Pradaxa exposure (2022 02)

As there is only 1 formulation for Pradaxa, a presentation by this variable is not applicable. For estimation of exposure by indication, age, and gender only very limited data was

available so that a presentation by these variables is not considered to provide information relevant for the safety or benefit-risk evaluation.

SV.2 OFF-LABEL USE

Off-label use of Pradaxa can be defined as

- Use of the product despite contraindication
- Use of the product in an unapproved population
- Use of the product in an unapproved indication

Use of the product despite contraindication refers to use in patients with prosthetic heart valves and in patients with severe renal failure.

SV.2.1 Off-label use in unapproved indications

As a follow-up measure to the EMA approval of the SPAF indication for dabigatran etexilate, BI carried out a non-interventional retrospective study (1160-0144) in 3 EU countries (France, Denmark, UK) to evaluate potential off-label use of dabigatran in Europe. Due to methodological challenges potential overestimation of off-label use results regarding treatment indication occurred in this study.

Therefore, a signal evaluation was initiated in 2017, including analysis of cumulative safety data in the BI pharmacovigilance database and a literature search to assess whether the findings on off-label use for indications as reflected in the study 1160-0144, concur with the off-label use information derived from ICSRs reported to/received by the company from global post marketing sources as well as within the concerned 3 countries. The results of the post-marketing safety data analysis revealed 93% to 99% on-label use in the EEA (with due consideration to the limitations of spontaneous reporting). These results did not reflect and do not support the 1160-0144 study findings, the signal was therefore rejected.

SV.2.1.1 Data from the PBRERs covering the reporting period 19 Mar 2012 – 18 Mar 2020

Since 2012, the EMA GVP Guidelines require collection of any report of off-label use with or without an ADR. Therefore, off-label use of dabigatran has been under continuous monitoring. The table below lists the results of evaluation of off-label use described and submitted in the PBRERs covering the period between 19 Sep 2012 and 18 Mar 2020. Off-label describes both cases which report only off-label use as well as off-label use in combination with labelled indications.

SV.Table 3 Off-label use evaluated for PBRER intervals 19 Mar 2012 – 18 Mar 2020

Document	Interval	% Off-label
PBRER 8	19 Mar 2012 – 18 Sep 2012	1.0
PBRER 9	19 Sep 2012 – 18 Mar 2013	1.8
PBRER 10	19 Mar 2013 – 18 Sep 2013	1.5
PBRER 11	19 Sep 2013 – 18 Mar 2014	2.0
PBRER 12	19 Mar 2014 – 18 Sep 2014	1.5
PBRER 13	19 Sep 2014 – 18 Mar 2015	2.3
PBRER 14	19 Mar 2015 – 18 Sep 2015	2.9
PBRER 15	19 Sep 2015 – 18 Mar 2016	2.5
PBRER 16	19 Mar 2016 – 18 Sep 2016	1.7
PBRER 17	19 Sep 2016 – 18 Mar 2017	2.8
PBRER 18	19 Mar 2017 – 18 Sep 2017	1.9
PBRER 19	19 Sep 2017 – 18 Mar 2018	2.9
PBRER 20	19 Mar 2018 – 18 Mar 2019	2.3
PBRER 21	19 Mar 2019 – 18 Mar 2020	3.1

Conclusion
Off-label use for reported indications ranged between 1.0% and 3.1% of all assessable cases (see table above). Contraindicated off-label use in patients with prosthetic heart valves remains low. The off-label use of Pradaxa showed no trends of concern.

SV.3 REFERENCES

SV.3.1 Published references

Not applicable.

SV.3.2 Unpublished references

s001048841-01 Periodic Benefit-Risk Evaluation Report for Pradaxa (dabigatran etexilate), Reporting Period from 19 Mar 2021 to 18 Mar 2022. 02 May 2020.

ABBREVIATIONS

ADR	Adverse drug reaction
AE	Adverse event
AF	Atrial fibrillation

BI	Boehringer Ingelheim
CABG	Coronary artery bypass graft
CCDS	Company Core Data Sheet
CIOMS	Council for International Organizations of Medical Sciences (WHO)
DLP	Data lock point
DVT	Deep vein thrombosis
EEA	European Economic Area
EMA	European Medicines Agency
EU	European Union
GI	Gastrointestinal
GSP	Global Safety Platform
GVP	Good Pharmacovigilance Practice
HCP	Healthcare professional
IBD	International birthdate
MAH	Marketing authorisation holder
MedDRA	Medical Dictionary for Regulatory Activities
NOAC	New oral anticoagluant drug
NVAF	Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation
NYHA	New York Heart Association
PBRER	Periodic Benefit-Risk Evaluation Report
PE	Pulmonary embolism
PT	Preferred term
PY	Patient years
ROW	Rest of world
SAE	Serious adverse event
SOC	System organ class
SPAF	Prevention of stroke and systemic embolism in adult patients with NVAF, with one or more risk factors, such as prior stroke or TIA; age ≥ 75 years; heart failure (NYHA Class ≥ II); diabetes mellitus; hypertension
TIA	Transient ischaemic attack
UK	United Kingdom

US(A)	United States
vs.	versus
VTE	Venous thromboembolic event

MODULE SVI ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

SVI.1 POTENTIAL FOR MISUSE FOR ILLEGAL PURPOSES

There is no potential for abuse of dabigatran etexilate.

SVI.2 REFERENCES

Not applicable.

ABBREVIATIONS

Not applicable.

MODULE SVII IDENTIFIED AND POTENTIAL RISKS

SVII.1 IDENTIFICATION OF SAFETY CONCERNS IN THE INITIAL RMP SUBMISSION

The following safety concerns were identified in the initial RMP submission according to EMEA/ CHMP/ 96268/ 2005 [U06-0269]:

- Important identified risks “Bleeding / Haemorrhage dose dependent”
- Important potential risks “Hepatotoxicity”
- Missing information: None.

SVII.2 NEW SAFETY CONCERNS AND RECLASSIFICATION WITH A SUBMISSION OF AN UPDATED RMP

As a consequence of the removal of the oral formulation for the paediatric population from this RMP, the list of safety concerns for Pradaxa has been revised to remove the related important potential risk “Medication error due to complexity of reconstitution of and dosing with the oral solution (paediatric population below 1 year of age)”.

SVII.3 DETAILS OF IMPORTANT IDENTIFIED RISKS, IMPORTANT POTENTIAL RISKS, AND MISSING INFORMATION

Pradaxa has been approved for the following indications:

- Primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery (referred to as **pVTEp** in the following)
- Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF), with one or more risk factors, such as prior stroke or transient ischemic attack (TIA); age ≥ 75 years; heart failure (NYHA Class ≥ II); diabetes mellitus; hypertension (referred to as **SPAF** in the following)
- Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults (referred to as **aVTEt** and **sVTEp**, respectively, in the following)
- Treatment of venous thromboembolic events (VTE) and prevention of recurrent VTE in paediatric patients from the time the child is able to swallow soft food to less than 18 years of age (referred to as **Paediatric VTE** in the following)

Where applicable, data on the important identified and potential risks are presented by indication.

SVII.3.1 Presentation of important identified risks and important potential risks

SVII.3.1.1 Important identified risk Haemorrhage

SVII.3.1.1.1 Potential mechanisms

For all indications, this identified ADR is linked directly to the pharmacological activity of the drug.

SVII.3.1.1.2 Evidence sources and strength of evidence

Anticoagulation bears an inherent risk of haemorrhage. Based on clinical and post-marketing data, haemorrhage was defined as an important identified risk for Pradaxa. Dabigatran (the active substance of Pradaxa) is eliminated through the kidneys, and kidney function diminishes with increasing age. Therefore, the rates of haemorrhages depend on the dose and are related to renal (kidney) failure and age.

Sources of evidence:

- pVTEp: Clinical trials (1160-0019, 1160-0024, .1160-0025, 1160-0048, 1160-0064, 1160-0050), SCS for pVTEp, spontaneous reporting, BI GSP
- SPAF: Clinical trials (1160-0026, 1160-0071, 1160-0186, 1160-0204), observational studies (1160-0129, 1160-0136), spontaneous reporting, BI GSP
- aVTEt: Clinical trials (1160-0046, 1160-0053, 1160-0248), BI GSP
- sVTEp: Clinical trials (1160-0047, 1160-0063), BI GSP
- Paediatric VTE: Phase III clinical trials (1160-0106, 1160-0108)

SVII.3.1.1.3 Characterisation of the risk

Clinical trial and study data

Indication: pVTEp

For the indication primary VTE prevention, the active controlled trials 1160-0019, 1160-0024, 1160-0025, 1160-0048, 1160-0064 and 1 placebo-controlled phase II trial (1160-0050) in Japanese patients were considered. Only results with patients treated with the suggested therapeutic dose (220 mg/day) and the results of the active comparator/placebo treated patients are presented in the following. In 2 of these trials (1160-0024, 1160-0050), the patients were randomised following surgery whereas in the remaining trials (1160-0019, 1160-0025, 1160-0048, and 1160-0064) the patients were randomised prior to surgery. These data are presented separately because the time point of randomisation may influence the incidence of haemorrhagic events.

In both post-operative randomisation trials, the number of patients with MBEs was low (≤2.3%) and none of the events was fatal. Fewer patients with MBEs were observed in the dabigatran etexilate 220 mg treatment group than in the enoxaparin 30 mg b.i.d. group (0.6% vs. 1.4%, respectively), the observed difference not being statistically significant. In trial

1160-0050, more patients with MBEs were observed in the dabigatran etexilate 220 mg treatment group than in the placebo group (2.3% vs. 0.8%, respectively). Further details are given in SVII.Table 1 and SVII.Table 2.

In the pooled pre-operative randomisation trials, the number of patients with MBEs was low and comparable between both treatment groups (1.7% dabigatran etexilate 220 mg vs. 1.4% enoxaparin 40 mg q.d.), the observed difference not being statistically significant. Further details are given in SVII.Table 3 and SVII.Table 4.

SVII.Table 1 Summary of haemorrhagic events for trials 1160-0024 and 1160-0050 (Japanese patients) - post-operative randomisation

	Trial 1160-0024		Trial 1160-0050	
	Dabigatran etexilate 220 mg	Enoxaparin 30 mg b.i.d.	Dabigatran etexilate 220 mg	Placebo
	n (%)	n (%)	n (%)	n (%)
Total treated patients	857 (100.0)	868 (100.0)	129 (100.0)	124 (100.0)
Patients with MBEs	5 (0.6)	12 (1.4)	3 (2.3)	1 (0.8)
Number of MBEs	5	14	4	1
Fatal haemorrhagic event	0	0	0	0
Haemorrhage leading to re-operation	0	1	1	0
Symptomatic haemorrhage in critical organ	1	0	0	0
Requiring treatment cessation	0	1	4	1
Leading to >2 units transfusion in excess of what investigator expected	4	12	n/a	n/a
Leading to >4.5 units transfusion in excess of what investigator expected	n/a	n/a	1	0
Greater than 20 g/L fall in haemoglobin in excess of what investigator expected	4	13	0	0

MBEs defined by meeting at least 1 of the following: 1) fatal bleeding, 2) clinically overt bleeding in excess of what was expected and associated with >20g/L fall in haemoglobin in excess of what was expected, 3) clinically overt bleeding in excess of what was expected and leading to transfusion of >2 units of packed cells or whole blood in excess of what was expected, 4) symptomatic retroperitoneal, intracranial, intraocular or intraspinal bleeding, 5) bleeding requiring treatment cessation bleeding leading to re-operation
Data source: Trial 1160-0024 (RE-MOBILIZE) CTR [U06-1616], Table 15.3.1.2: 2, and 1160-0050 CTR [U07-3436-01], Table 15.3.2.2: 4

SVII.Table 2 Number (%) of patients with haemorrhages incl. 95% CI for study 1160-0024 - post-operative randomisation

	Dabigatran etexilate 220 mg	Enoxaparin 30 mg b.i.d.
Total treated patients, n (%)	857 (100.0)	868 (100.0)
Patients with MBEs, n (%)	5 (0.6)	12 (1.4)
95% CI	0.2, 1.4	0.7, 2.4
p-value vs. enoxaparin	0.1416	--
Patients with MBEs or CRBE, n (%)	28 (3.3)	33 (3.8)
95% CI	2.1, 4.5	2.5, 5.1
p-value vs. enoxaparin	0.5475	--
Patients with any haemorrhage, n (%)	74 (8.6)	84 (9.7)
95% CI	6.8, 10.5	7.7, 11.6
p-value vs. enoxaparin	0.4527	--

MBEs defined by meeting at least 1 of the following: 1) fatal bleeding, 2) clinically overt bleeding in excess of what was expected and associated with >20g/L fall in haemoglobin in excess of what was expected, 3) clinically overt bleeding in excess of what was expected and leading to transfusion of >2 units of packed cells or whole blood in excess of what was expected, 4) symptomatic retroperitoneal, intracranial, intraocular or intraspinal bleeding, 5) bleeding requiring treatment cessation bleeding leading to re-operation
CRBE defined as either: 1) spontaneous skin haematoma >25 cm2, 2) wound haematoma >100 cm2, 3) spontaneous epistaxis lasting >5 minutes, 4) spontaneous macroscopic haematuria or that lasting >24 hours if associated with an intervention, 5) spontaneous rectal bleeding (more than a spot on toilet paper), 6) gingival bleeding lasting >5 min, 7) any other bleeding event judged as clinically relevant by the investigator
Data source: SCS [U07-3034] Table 2.1.1.1.1.1.12

SVII.Table 3 Summary of haemorrhagic events for trials 1160-0019, 1160-0025, 1160-0048, and 1160-0064 - pre-operative randomisation

	Dabigatran etexilate 220 mg n (%)	Enoxaparin 40 mg q.d. n (%)
Total treated patients	2835 (100.0)	3243 (100.0)
Patients with MBEs	47 (1.7)	44 (1.4)
Number of MBEs	48	45
Fatal haemorrhagic events	1	0
Haemorrhage leading to re-operation	5	4
Symptomatic haemorrhage in critical organ	1	0
Requiring treatment cessation	3	1
Leading to >2 units transfusion in excess of what investigator expected	41	27
Greater than 20 g/L fall in haemoglobin in excess of what investigator expected	38	26

ents in trial 1160-0019 did not receive dabigatran etexilate in the 220 mg dose. Consequently, there are more patients treated with enoxaparin displayed.
MBEs defined by meeting at least 1 of the following: 1) fatal bleeding, 2) clinically overt bleeding in excess of what was expected and associated with >20g/L fall in haemoglobin in excess of what was expected, 3) clinically overt bleeding in excess of what was expected and leading to transfusion of >2 units of packed cells or whole blood in excess of what was expected, 4) symptomatic retroperitoneal, intracranial, intraocular or intraspinal bleeding, 5) bleeding requiring treatment cessation bleeding leading to re-operation
Data source: data on file: RMP update tables 2010, Table 13.9

SVII.Table 4 Number (%) of patients with haemorrhages incl.95% CI for trials 1160-0019, 1160-0025, 1160-0048, and 1160-0064 - pre-operative randomisation

	Dabigatran etexilate 220 mg	Enoxaparin 40 mg q.d.
Total treated patients, n (%)	2835 (100.0)	3243 (100.0)
Patients with MBEs, n (%)	47 (1.7)	44 (1.4)
95% CI	1.2, 2.2	1.0, 1.8
p-value vs. enoxaparin	0.3427	--
Patients with MBEs or CRBE, n (%)	158 (5.6)	151 (4.7)
95% CI	4.8, 6.5	4.0, 5.4
p-value vs. enoxaparin	0.1140	--
Patients with any haemorrhage, n (%)	349 (12.3)	375 (11.6)
95% CI	11.1, 13.6	10.5, 12.7
p-value vs. enoxaparin	0.3827	--

defined by meeting at least 1 of the following: 1) fatal bleeding, 2) clinically overt bleeding in excess of what was expected and associated with >20g/L fall in haemoglobin in excess of what was expected, 3) clinically overt bleeding in excess of what was expected and leading to transfusion of >2 units of packed cells or whole blood in excess of what was expected, 4) symptomatic retroperitoneal, intracranial, intraocular or intraspinal bleeding, 5) bleeding requiring treatment cessation bleeding leading to re-operation
CRBE defined as either: 1) spontaneous skin haematoma >25 cm^2, 2) wound haematoma >100 cm^2, 3) spontaneous epistaxis lasting >5 minutes, 4) spontaneous macroscopic haematuria or that lasting >24 hours if associated with an intervention, 5) spontaneous rectal bleeding (more than a spot on toilet paper), 6) gingival bleeding lasting >5 min, 7) any other bleeding event judged as clinically relevant by the investigator
Data source: data on file, RMP update tables 2010, Table 13.10

Indication: SPAF

For the indication prevention of stroke and systemic embolism in patients with AF, the following studies were included in the analyses: 1160-0026 (RE-LY), 1160-0071 (RELY-ABLE), 1160-0186 (RE-DUAL PCI), and 1160-0204 (RE-CIRCUIT).

Trial 1160-0026 (RE-LY)

1160-0026: Randomized Evaluation of Long term anticoagulant therapy (RE-LY®) comparing the efficacy and safety of two blinded doses of dabigatran etexilate with open label warfarin for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation: prospective, multi-centre, parallel-group, non-inferiority trial (RE-LY® STUDY) [U09-3249-02]

Trial 1160-0026 (RE-LY) as a large trial allows for a better and more meaningful interpretation of the data. As the treatment in this indication is considered a long-term treatment the haemorrhagic event rates were calculated as yearly event rate. Fewer patients with MBEs were reported in the dabigatran etexilate treatment groups than in the warfarin treatment group, the rate of MBEs being dose-dependent: 2.92% dabigatran etexilate 110 mg

b.i.d. vs. 3.40% dabigatran etexilate 150 mg b.i.d. vs. 3.61% warfarin. Further details on haemorrhagic events are given in the following tables.

SVII.Table 5 Hazard ratio and 95% CI for patients with haemorrhages in trial 1160-0026 (RE-LY)

	Dabigatran etexilate 110 mg b.i.d.	Dabigatran etexilate 150 mg b.i.d.	Warfarin
Total treated patients, n (%)	6015 (100.0)	6076 (100.0)	6022 (100.0)
PY	11 899	12 033	11 794
Patients with MBEs, n (%)	347	409	426
HR vs. warfarin	0.81	0.94	--
95% CI	0.70, 0.93	0.82, 1.08	--
HR 110 vs. 150 mg b.i.d.	0.85	--	--
95% CI	0.74, 0.98	--	--
Patients with life-threatening MBEs, n (%)	151	183	221
HR vs. warfarin	0.68	0.81	--
95% CI	0.55, 0.83	0.67, 0.99	--
HR 110 vs. 150 mg b.i.d.	0.83	--	--
95% CI	0.67, 1.03	--	--
Patients with ICH, n (%)	27	38	90
HR vs. warfarin	0.29	0.42	--
95% CI	0.19, 0.45	0.29, 0.61	--
HR 110 vs. 150 mg b.i.d.	0.70	--	--
95% CI	0.43, 1.14	--	--

MBEs defined by meeting at least 1 of the following: 1) fatal bleeding, 2) clinically overt bleeding in excess of what was expected and associated with >20g/L fall in haemoglobin in excess of what was expected, 3) clinically overt bleeding in excess of what was expected and leading to transfusion of >2 units of packed cells or whole blood in excess of what was expected, 4) symptomatic retroperitoneal, intracranial, intraocular or intraspinal bleeding, 5) bleeding requiring treatment cessation bleeding leading to re-operation
Data source: Clinical Overview Statement [c02921655-02], Table 5.1.1, Table 5.1.2, Table 5.1.3

Several post-hoc analyses with data from the RE-LY trial were performed and published. The results of these analyses are summarised in the following.

Guidance adherent dabigatran etexilate treatment vs. warfarin in the RE-LY population: an analysis on the basis of the European label recommendations for dabigatran etexilate [P13-10972]

In the RE-LY trial (1160-0026), patients were randomised to treatment arms independent of baseline characteristics; DE 150 was associated with significantly fewer strokes and DE 110 with significantly fewer MBEs, compared to well-controlled warfarin. The European label recommends DE 150 in patients <80 years without an increased risk for bleeding or

concomitant verapamil, and DE 110 in other patients. In this analysis of the RE-LY dataset, the authors simulated how dabigatran etexilate, when used according to the European label, would compare to well-controlled warfarin. In this post-hoc, non-randomised analysis, the authors simulated the outcomes of patients receiving dabigatran etexilate with a dose selected according to the European label and compared them to the warfarin-treated patients. 'European label simulated dabigatran etexilate treatment' was associated with significant reductions in stroke and systemic embolism, haemorrhagic stroke, death and vascular death compared to warfarin; also with significant reductions in major and life-threatening bleeding and ICH, but not GI major bleeding, compared to warfarin. European label simulated dabigatran etexilate outcomes were not significantly different from those of patients receiving DE 150 in RE-LY.

In conclusion, this *post-hoc*, non-randomised analysis of the RE-LY trial suggests that 'European label adherent dabigatran etexilate treatment' may be associated with superior efficacy and safety compared with warfarin.

Causes of death and influencing factors in patients with AF: a competing risk analysis from the RE-LY trial 1160-0026 [P13-11205]

The authors analysed the specific causes of death and their predictors among patients with AF under effective anticoagulant therapy in the RE-LY trial. All deaths were categorised by the investigators using prespecified definitions followed by central adjudication. Overall, 1371 deaths occurred (annual mortality rate of 3.84%, 95% CI 3.64, 4.05). Cardiac deaths (sudden cardiac death and progressive heart failure) accounted for 37.4% of all deaths, whereas stroke and haemorrhage-related deaths represented 9.8% of the total mortality. In conclusion, the majority of deaths were not related to stroke in a contemporary anticoagulated AF population. These results emphasise the need to identify interventions beyond effective anticoagulation, to further reduce mortality in AF.

SVII.Table 6 Effect of Dabigatran Compared with Warfarin on Incidence of Different Causes of Death (Cox Proportional Hazard Model)

Causes of Death	Dabigatran (n=12 091), n (%/y)	Warfarin (n=6022), n (%/y)	HR (95% CI)	*P*-Value
Cardiovascular	542 (2.26)	300 (2.54)	0.89 (0.77-1.02)	0.105
Cardiac	338 (1.41)	174 (1.48)	0.96 (0.80-1.15)	0.638
Sudden cardiac death	202 (0.84)	103 (0.87)	0.97 (0.76-1.23)	0.789
Progressive heart failure	136 (0.57)	71 (0.66)	0.94 (0.71-1.25)	0.677
Vascular Death	78 (0.33)	61 (0.52)	0.63 (0.45-0.88)	0.007
Stroke/peripheral embolism	54 (0.23)	42 (0.36)	0.63 (0.42-0.94)	0.025
Hemorrhage	22 (0.09)	17 (0.14)	0.64 (0.34-1.21)	0.167
Pulmonary embolism	2 (0.01)	2 (0.02)	0.49 (0.07-3.50)	0.480
Other cardiovascular/unknown	126 (0.53)	65 (0.55)	0.95 (0.71-1.29)	0.758
Noncardiovascular death	321 (1.34)	170 (1.44)	0.93 (0.77-1.12)	0.423
Cancer	131 (0.55)	60 (0.51)	1.07 (0.79-1.45)	0.659
Respiratory failure	51 (0.21)	28 (0.24)	0.89 (0.56-1.46)	0.613
Trauma	7 (0.03)	5 (0.04)	0.69 (0.22-2.19)	0.533
Infection	42 (0.18)	19 (0.16)	1.09 (0.63-1.87)	0.766
Other	90 (0.38)	58 (0.49)	0.76 (0.55-1.06)	0.110
Undetermined death	21 (0.09)	17 (0.14)	0.60 (0.32-1.14)	0.118

The total follow-up time for the dabigatran patients is 24 047 PY and for the warfarin patients is 11 839 PY.

Efficacy and safety of dabigatran compared with warfarin in relation to baseline renal function in patients with atrial fibrillation: a RE-LY trial analysis (1160-0026) [P13-16527]

The present pre-specified analysis from RE-LY (1160-0026) evaluated the efficacy and safety of dabigatran compared with warfarin in relation to renal function in patients with AF. Glomerular filtration rate was estimated with the CKD-EPI, and MDRD equations in all randomised patients with available creatinine at baseline (n=17 951), and cystatin C-based GFR was estimated in a subpopulation with measurements available (n=6190).

Safety
There were 1157 major bleeds, 155 intracranial bleeds, and 543 life-threatening bleeds in total in the entire cohort. Based on the Cockcroft-Gault equation, patients with eGFR

≥80 mL/min had annual major bleeding rates of 1.98% compared with 3.30% in patients with eGFR 50 to <80 mL/min and 5.48% in patients with eGFR <50 mL/min. Similarly, the incidence of intracranial bleeding increased substantially with worsening renal function (0.20%, 0.51%, and 0.69%, respectively). Life-threatening bleedings were 3.2 times higher in patients with eGFR <50 mL/min than in subjects with eGFR ≥80 mL/min (2.64% vs. 0.83%, respectively). The associations between decreased renal function and increased incidence of major, intracranial, and life-threatening bleedings were consistent by all 3 methods of GFR estimation. Rates of major bleeding increased with decreasing renal function with dabigatran (both doses) and with warfarin.

Conclusion
Rates of stroke, mortality, and major bleeding increase as renal function deteriorates. Relative to warfarin, dabigatran etexilate 110 mg b.i.d. and dabigatran etexilate 150 mg b.i.d. displayed an efficacy consistent with the overall trial across the range of renal function with regard to the primary outcome of stroke or systemic embolism. When GFR was estimated with the newer CKD-EPI equation, a significantly greater relative reduction in major bleeding risk was displayed for both dosages of dabigatran in patients with eGFR ≥80 mL/min.

Dabigatran etexilate compared with warfarin in patients with AF and symptomatic heart failure: a subgroup analysis of the RE-LY trial (1160-0026) [P13-08160]

The authors evaluated the effects of dabigatran etexilate compared with warfarin in the subgroup of patients with previous symptomatic heart failure in the RE-LY trial. RE-LY compared 2 fixed and blinded doses of dabigatran etexilate (DE 110 and DE 150) with open label warfarin in 18 113 patients with AF at increased risk for stroke. Among 4904 patients with heart failure, annual rates of major bleeding were 3.90% for the group on warfarin, compared with 3.26% for DE 110 (HR 0.83, 95% CI 0.64 - 1.09) and 3.10% for DE 150 (HR 0.79, 95% CI 0.60 - 1.03). Rates of intracranial bleeding were significantly lower for both dabigatran etexilate dosages compared with warfarin in patients with heart failure (DE 110 vs. warfarin, HR 0.34, 95% CI 0.14, 0.80; DE 150 vs. warfarin, HR 0.39, 95% CI 0.17, 0.89). The relative effects of dabigatran etexilate vs. warfarin on the occurrence of stroke or systemic embolism and major bleeding were consistent among those with and without heart failure and those with low (40%) left ventricular ejection fraction. In conclusion, the overall benefits of dabigatran etexilate for stroke/systemic embolism prevention, and major and intracranial bleeding, relative to warfarin in the RE-LY trial were consistent in patients with and without heart failure.

The effect of dabigatran plasma concentrations and patient characteristics on the frequency of ischaemic stroke and major bleeding in AF patients [P13-12662] (PK analysis of the RE-LY trial [1160-0026])

The aims of this PK analysis of the RE-LY trial were to explore whether there is an association between plasma concentrations and outcomes. Also, factors affecting the variability of plasma concentrations of dabigatran and their impact on outcome events in AF patients with an indication for oral anticoagulation were investigated. In this study, peak and

trough samples at steady state were collected for determination of drug concentration, aPTT, and ECT at 1-month post-randomisation in all dabigatran etexilate subjects regardless of the time of any ischaemic or bleeding event that occurred. Additional samples were taken at 3, 6, and 12 months from 2143 subjects. Plasma concentrations of nonconjugated (free) dabigatran and of total dabigatran were determined by a validated high-performance liquid chromatography tandem mass spectrometry method. Logistic regression of events (ischaemic stroke/SEE and major and minor bleedings) and associated log-transformed trough plasma concentrations was performed with and without covariates. The impact of the covariates age, sex, BMI, CrCl, CAD, diabetes mellitus, prior stroke or TIA, hypertension, heart failure, CHADS2 score, concomitant aspirin (ASA) use, and concomitant clopidogrel use were investigated. Only covariates with $p < 0.2$ were retained. CrCL at baseline was calculated using the Cockroft-Gault equation.

Results
Plasma concentrations were obtained from 9183 patients, with 112 ischaemic strokes/systemic emboli (1.3%) and 323 major bleedings (3.8%) recorded. Dabigatran levels were dependent on renal function, age, weight, and female sex, but not ethnicity, geographic region, ASA use, or clopidogrel use. Renal function (CrCl) was a key determinant of plasma concentrations. The subjects with moderate renal impairment (between 30 and 50 mL/min CrCl) showed a 2.29-fold higher trough concentration than the subjects with renal function undiminished by age (CrCl ≥80 ml/min). In the subjects with mild renal impairment (between 50 and 80 mL/min CrCl), the trough concentrations were 47% higher compared with the subjects with CrCl ≥80 mL/min. Concentrations of dabigatran increased with age, with a 68% increase in trough concentrations in patients aged ≥75 years compared with those <65 years. Renal function was highly correlated with age.

In the group with subjects who had an MBE during the trial, there were more patients with higher plasma levels leading to higher median trough and peak concentration (55% and 36%, respectively). Plasma concentrations of dabigatran were higher in subjects with haemorrhagic stroke (n=11 with trough and n=13 with peak measurements) than in the subjects (n=8269 with trough and n=8971 with peak measurements) without haemorrhagic stroke (144 ng/mL vs. 78.4 ng/mL for trough and 241 ng/mL vs. 155 ng/mL for post-dose concentrations, respectively; $p>0.05$). Multiple logistic regression (c-statistic 0.715, 95% CI: 0.69, 0.74) showed major bleeding risk increased with dabigatran exposure ($p<0.0001$), age ($p<0.0001$), ASA use ($p< 0.0003$), and diabetes ($p=0.018$) as significant covariates.

Discussion
In this exposure response analysis from the 1160-0026 trial, the risks of major bleeding after dosing with dabigatran etexilate 110 mg b.i.d. or dabigatran etexilate 150 mg b.i.d. in patients with AF were related to several factors mainly including age, CrCl, and trough concentrations of dabigatran. Trough plasma concentrations increased approximately 67% in patients aged >75 years compared with those <65 years, but major bleed risk and stroke risk increased 2- to 3-fold. Concentrations were increased 1.8-fold and 1.2-fold for patients with CrCl of 30 or 50 mL/min, respectively, compared with the median CrCl of 69 mL/min in 1160-0026 patients. In 1160-0026, approximately 35% of patients ≥75 years had moderate renal dysfunction (CrCl 30 to 50 mL/min), and the median dabigatran concentration in patients ≥75

years was 39% higher than in patients <75 years. Despite increased rates of major bleeding with decreasing renal function in dabigatran etexilate patients, the RR of bleeding compared to warfarin did not change, suggesting that age and other factors in addition to anticoagulant effect or exposure play a role in the increased risk of stroke and bleeding seen in patients with renal dysfunction. In patients with risk factors for bleeding such as old age, reduced CrCl, or low body weight, better outcomes might be achieved by adjusting the dose. Across the 10th to 90th percentile range of steady-state trough plasma concentrations achieved for the 150 mg b.i.d. dose, the overall risk of major bleeding during the trial ranges from approximately 2% to 7% (approximately 1.0% to 3.5% per year), with substantial impact of age and concomitant antiplatelet use, with sex, history of diabetes, and CAD also significant covariates in the model. Older patients, those with multiple co-morbidities, or those with reduced renal function may be appropriate candidates for a lower dose such as 110 mg b.i.d. The large majority of patients achieve a favourable balance of benefit and risk with a fixed dose of dabigatran etexilate 110 mg b.i.d. or dabigatran etexilate 150 mg b.i.d. guided by a consideration of patient characteristics. This study has several limitations. Although the association of clinical outcomes with dabigatran concentrations was prespecified in the main study protocol, not all patients randomised to dabigatran etexilate contributed a blood sample. This may have introduced bias. There was no temporal proximity of PK sampling and time of event. Medication compliance was not assessed in this analysis, which may introduce additional variability. Thus, intra-individual variability in plasma concentrations over time may blur the associations between dabigatran concentration and outcomes.

Conclusion
In this 1160-0026 sub-study, specific demographic characteristics such as very elderly and/or poor renal function played the strongest role in determining risk of clinical events. Renal function was the predominant patient characteristic that determined plasma concentrations. There is no single plasma concentration range that provides optimal benefit-risk for all patients. The balance between stroke risk and bleeding risk was affected by several factors including plasma concentration. There might be a subset of AF patients who may improve their benefit–risk balance with dabigatran etexilate by a tailoring of the dose in relation to patient characteristics. Results from this targeted review of selected RE-LY data triggered the CCDS update to version 13 (dated 16 Sep 2014) and are included in the CCDS sections “side effects“ as well as “Pharmacological properties“. The EU-SmPC was updated accordingly (EMEA/H/C/000829/II/0073).

Additional clinical trials were performed to gain information on long-term effects of dabigatran and on the use of dabigatran in patients with AF who underwent PCI or ablation. These trials are presented below in ascending order.

1160-0071 (RELY-ABLE): Long term multi-center extension of dabigatran treatment in patients with atrial fibrillation who completed the RE-LY trial and a cluster randomised trial to assess the effect of a knowledge translation intervention on patient outcomes [U13-3509-01]

This long-term extension trial of the RE-LY trial evaluated the long-term safety of 2 doses of dabigatran etexilate (DE 110 and DE 150) and was conducted to address the safety concerns

'haemorrhage', 'hepatotoxicity', 'myocardial infarction' and 'pulmonary embolism'. Subjects remained on the randomised doses from RE-LY and continued double-blind treatment for up to 43 months. A total of 5883 subjects were treated, 2927 in the DE 110 group and 2956 were in the DE 150 group. As the objective of RELY-ABLE was safety, there were no primary efficacy endpoints. Secondary endpoints were stroke (including haemorrhagic), non-central nervous system systemic embolism, PE, acute MI, DVT, and all deaths (includes deaths from bleeding). All categories of bleeding generally occurred more frequently in the DE 150 group compared to the DE 110 group during RELY-ABLE. The risk of major bleedings was significantly lower for DE 110 treatment (0.77, 95% [CI] (0.64, 0.93) p=0.0055). For the RE-LY plus RELY-ABLE period, DE 110 and DE 150 had major bleeding rates of 2.08% and 2.49%, respectively. During the RELY-ABLE period, life-threatening bleedings, intracerebral haemorrhage, and major GI bleedings were consistent with the rates in RELY and were numerically lower for the DE 110 group. Similar patterns in the rates were shown in the RE-LY plus RELY-ABLE period, although the overall event rates were lower. DE 110 and 1.36% for DE 150. Haemorrhagic stroke was similar between the 2 groups and occurred at an annualised rate of 0.14% for DE 110 and 0.14% for DE 150. Renal dysfunction was associated with a higher risk of major bleeding for both treatments across the CrCl ranges evaluated. In all categories (except for CrCl <30 mL/min), the annualised rate for major bleeding was higher for subjects treated with DE 150 compared to DE 110. There were too few subjects with CrCl <30 mL/min to draw conclusions.

Haemorrhagic stroke was similar between the 2 groups and occurred at an annualised rate of 0.14% for DE 110 and 0.14% for DE 150.

During the RELY-ABLE period, reported SAEs were generally similar for both treatment groups. The reported incidence of SAEs was 35.3% and 37.7%, for DE 110 and DE 150, respectively.

Summary
The RE-LY extension study (RELY-ABLE) provided additional safety information for a large cohort of patients that continued the same dose of dabigatran etexilate as assigned in the RE-LY trial. During the additional 2.5 years of treatment in RELY-ABLE, with a maximum exposure of over 6 years (total exposure in RELY + RELY-ABLE), the long-term safety profile of dabigatran etexilate was confirmed for both test doses. No new safety findings were observed. The rates of outcome events, including major bleedings and other bleeding events, were consistent with those seen in RE-LY.

The trial 1160-0071 (RE-LY-ABLE) further supported the evaluations from the trial 1160-0026 (RE-LY). During more than 2.5 additional years of follow-up after trial 1160-0026 (RE-LY), rates of ischaemic and haemorrhagic stroke, and of major bleedings, on dabigatran etexilate 110 mg b.i.d. and on dabigatran etexilate 150 mg b.i.d. were consistent with the event rates reported during the trial 1160-0026 (RE-LY); providing evidence for long-term efficacy and safety of dabigatran etexilate in subjects with AF not caused by a heart valve problem at risk for stroke and blood clots. The risk of major bleedings was significantly lower for dabigatran etexilate 110 mg b.i.d. Annualised rates for major bleeding were 2.79%

and 3.59% for the dabigatran etexilate 110 mg b.i.d. and dabigatran etexilate 150 mg b.i.d. treatment groups, respectively. No new safety concerns were identified.

SVII.Table 7 Frequency (annualised rate) of subjects with bleedings-RELY-ABLE period

	DE 110 mg b.i.d.	**DE 150 mg b.i.d.**
	N (%)	**N (%)**
Subjects treated	2914	2937
Subject-years	7267	7297
Major bleedings	203 (2.79)	262 (3.59)
Life threatening MBEs	113 (1.55)	124 (1.70)
ICH	20 (0.28)	24 (0.33)
Fatal bleeding	19 (0.26)	16 (0.22)
Other MBEs	114 (1.57)	159 (2.18)
Minor bleedings	544 (7.49)	655 (8.98)
Any bleedings	686 (9.44)	817 (11.20)

Each subject with an event was counted once for the composite endpoint and once for each component of the composite endpoint.

In case of recurrent event, the first event was considered.

Subject-years=Sum (date of last visit—date of first dose study medication in RELY-ABLE + 1) of all treated subjects/ 365.25.

Annualised event rate (%)=100 * Number of subjects with event / subject-years.

Source data: 1160-0071 CTR [U13-3509-01], Table 15.3.2.1.1:1 and Table 15.3.2.1.1:3

SVII.Table 8 Frequency (annualised rate) of subjects with major bleedings by anatomic location-RELY-ABLE period SAF-FAS interval

	DE 110 mg b.i.d.	**DE 150 mg b.i.d.**
	N (%)	**N (%)**
Site/source		
Gastrointestinal	105 (1.44)	108 (1.48)
Intra-cranial (including sub-dural, sub-arachnoid, etx.)	20 (0.28)	24 (0.33)
Genito-urinary	10 (0.14)	15 (0.21)
Intramuscular	2 (0.03)	9 (0.12)
Intra-thoracic	6 (0.08)	6 (0.08)
Intraocular	4 (0.06)	7 (0.10)
Intra-abdominal (non-gastrointestinal)	3 (0.04)	3 (0.04)
Retroperioneal	4 (0.06)	1 (0.01)
ENT (ear-nose-throat)	2 (0.03)	2 (0.03)
Intra-articular	2 (0.03)	1 (0.01)
Pericardial	0	2 (0.03)
Intraspinal	1 (0.01)	0
Surgical bleeding (bleeding at the time of surgery, NOT surgery due to bleed)	19 (0.26)	33 (0.45)
Other, location not listed above	47 (0.65)	67 (0.92)

Site/source of bleeding was not collected for RELY-ABLE Visit 1.

In case of recurrent event, the first event was considered.

Subject-years=Sum (date of last visit—date of first dose study medication in RELY-ABLE + 1) of all treated subjects/ 365.25.

Annualised event rate (%)=100 * Number of subjects with event / subject-years.

Source data: 1160-0071 CTR [U13-3509-01], Table 15.3.2.1.1:3 and Table 15.3.2.1.2:2

1160-0186: A prospective Randomised, open label, blinded endpoint (PROBE) study to Evaluate DUAL antithrombotic therapy with dabigatran etexilate (110 mg and 150 mg b.i.d.) plus clopidogrel or ticagrelor vs. triple therapy strategy with warfarin (INR 2.0 – 3.0) plus clopidogrel or ticagrelor and aspirin in patients with non valvular atrial fibrillation (NVAF) that have undergone a percutaneous coronary intervention (PCI) with stenting (RE-DUAL PCI) [c13531195-01; P17-09776]

1160-0186 is a PROBE trial comparing a dual antithrombotic regimen of 110 mg dabigatran etexilate b.i.d. plus clopidogrel or ticagrelor (110 mg dabigatran dual therapy) and 150 mg dabigatran etexilate b.i.d. plus clopidogrel or ticagrelor (150 mg dabigatran dual therapy) with a triple antithrombotic therapy of warfarin plus clopidogrel or ticagrelor plus aspirin (warfarin triple therapy) in patients with NVAF undergoing a PCI with coronary stenting. The primary endpoint for this trial was time to first MBE or CRNMBE based on the ISTH definition and was analysed based on adjudicated data.

The following other safety endpoints complement the analysis of the primary endpoint:

- ISTH MBE
- ISTH CRNMBE
- Life-threatening bleedings
- Intracranial haemorrhage
- Fatal bleedings
- Clinically relevant bleeding measured using the following definitions
    - Bleeding Academic Research Consortium (BARC) ≥3
    - Thrombolysis in myocardial infarction (TIMI) group (i.e. major plus minor bleeding events)
    - Total bleedings

2725 patients with AF who underwent PCI were randomised to triple therapy with warfarin plus a P2Y12 inhibitor (clopidogrel or ticagrelor) and aspirin (for 1 to 3 months) (triple-therapy group) or dual therapy with dabigatran (110 mg or 150 mg b.i.d.) plus clopidogrel or ticagrelor and no aspirin (110 mg and 150 mg dual-therapy groups). Outside the United States, elderly patients (≥80 years of age; ≥70 years of age in Japan) were randomly assigned to the 110 mg dual-therapy group or the triple-therapy group only.

Primary endpoint (time to first ISTH MBE or CRNMBE)
The primary endpoint of this trial was time to first adjudicated ISTH MBE or CRNMBE. The treatment with 110 mg DE-DAT was found to be superior to warfarin-TAT (HR 0.52; 95% CI 0.42, 0.63), while 150 mg DE-DAT was found to be non-inferior to warfarin-TAT (HR 0.72; 95% CI 0.58, 0.88). The treatment with 150 mg DE-DAT treatment was nominally superior to warfarin-TAT (p=0.0020), but this hypothesis was not formally tested. See SVII.Table 9 for details. Sensitivity analyses confirmed the findings of the primary analysis. Results of primary endpoint were confirmed by subgroup analyses, with some heterogeneity among few subgroups.

SVII.Table 9 Cox regression for time to first ISTH MBE or CRNMBE (ITT period) - FAS

	110 mg DE-DAT	Warfarin-TAT	150 mg DE-DAT	Warfarin-TAT[1]
Randomised patients, N	981	981	763	764
Patients with an event, N (%)	151 (15.4)	264 (26.9)	154 (20.2)	196 (25.7)
HR vs. warfarin (95% CI)	0.52 (0.42, 0.63)		0.72 (0.58, 0.88)	
Superiority p-value	<0.0001		0.0020[2]	
Non-inferiority p-value[3]	<0.0001		<0.0001	

[1] Excluding elderly patients outside the USA

[2] Superiority was not formally tested; p-value provided for descriptive purposes only.

[3] Non-inferiority margin = 1.38

Data source: [c13531195-01] Table 6

The descriptive analysis of other safety endpoints was in line with the analyses of the primary endpoint. For most types of bleeding events, a nominally statistically significant decrease in bleeding events was observed for both treatment comparisons, favouring treatment with DE-DAT (SVII.Table 10 and SVII.Table 11).

SVII.Table 10 Cox regression for time to first ISTH MBE, life-threatening bleeding, intracranial haemorrhage, and fatal bleeding (ITT period) - FAS

	110 mg DE-DAT	Warfarin-TAT	150 mg DE-DAT	Warfarin-TAT[1]
Randomised patients, N	981	981	763	764
ISTH MBE				
Patients with an event, N (%)	49 (5.0)	90 (9.2)	43 (5.6)	64 (8.4)
HR vs. warfarin (95% CI)	0.52 (0.37, 0.74)		0.64 (0.43, 0.94)	
p-value[2]	0.0003		0.0220	
Life-threatening bleeding event				
Patients with an event, N (%)	19 (1.9)	38 (3.9)	16 (2.1)	30 (3.9)
HR vs. warfarin (95% CI)	0.49 (0.28, 0.85)		0.51 (0.28, 0.93)	
p-value[2]	0.0107		0.0286	
Intracranial haemorrhage				
Patients with an event, N (%)	3 (0.3)	10 (1.0)	1 (0.1)	8 (1.0)
HR vs. warfarin (95% CI)	0.30 (0.08, 1.07)		0.12 (0.02, 0.98)	
p-value[2]	0.0639		0.0474	
Fatal bleeding event				
Patients with an event, N (%)	4 (0.4)	5 (0.5)	3 (0.4)	4 (0.5)
HR vs. warfarin (95% CI)	0.79 (0.21, 2.93)		0.73 (0.16, 3.26)	
p-value[2]	0.7202		0.6802	

[1] Excluding elderly patients outside the USA

[2] Wald 2-sided p-value from (stratified) Cox proportional hazards model; provided for descriptive purposes only.

Data source: [c13531195-01] Table 7

SVII.Table 11 Cox regression for time to first ISTH CRNMBE, clinically relevant bleeding, and any bleeding (ITT period) - FAS

	110 mg DE-DAT	Warfarin-TAT	150 mg DE-DAT	Warfarin-TAT[1]
Randomised patients, N	981	981	763	764
ISTH CRNMBE				
Patients with an event, N (%)	115 (11.7)	193 (19.7)	126 (16.5)	148 (19.4)
HR vs. warfarin (95% CI)	0.55 (0.44, 0.69)		0.79 (0.63, 1.01)	
p-value[2]	<0.0001		0.0581	
Clinically relevant bleeding event (BARC ≥3)				
Patients with an event, N (%)	37 (3.8)	75 (7.6)	34 (4.5)	53 (6.9)
HR vs. warfarin (95% CI)	0.48 (0.32, 0.71)		0.61 (0.40, 0.94)	
p-value[2]	0.0002		0.0240	
Clinically relevant bleeding event (TIMI major and minor)				
Patients with an event, N (%)	29 (3.0)	69 (7.0)	27 (3.5)	48 (6.3)
HR vs. warfarin (95% CI)	0.41 (0.26, 0.63)		0.53 (0.33, 0.85)	
p-value[2]	<0.0001		0.0090	
Total bleeding events				
Patients with an event, N (%)	266 (27.1)	421 (42.9)	254 (33.3)	316 (41.4)
HR vs. warfarin (95% CI)	0.54 (0.46, 0.63)		0.72 (0.61, 0.84)	
p-value[2]	<0.0001		<0.0001	

[1] Excluding elderly patients outside the USA

[2] Wald 2-sided p-value from (stratified) Cox proportional hazards model; provided for descriptive purposes only.

Data source: [c13531195-01] Table 8

Conclusion

Following PCI in atrial fibrillation, dual-therapy with DE and a P2Y12 antagonist significantly reduced risk of bleeding versus warfarin triple-therapy, with non-inferiority for overall secondary thromboembolic events. Results from this trial triggered the CCDS update to version 18 (dated 23 Nov 2017) and are included in the CCDS section “Dosage and Administration”, "Special Warnings and Precautions", and "Clinical trials". The EU-SmPC has been updated accordingly (EMEA/H/C/000829/II/0108). In 2017, findings from this trial were published in the New England Journal of Medicine [P17-09776].

A summary of a subgroup analysis by treatment with clopidogrel or ticagrelor from this trial was published in 2019 [P19-01595] and is presented separately in this document.

1160-0204:Randomised Evaluation of dabigatran etexilate Compared to warfarIn in pulmonaRy vein ablation: assessment of an uninterrupted periproCedUral antIcoagulation sTrategy (The RE-CIRCUIT Trial) [c14388942-01; P17-03137]

The primary objective of this trial was to assess the safety of an uninterrupted dabigatran etexilate periprocedural anticoagulant regimen compared with an uninterrupted periprocedural warfarin regimen in NVAF patients undergoing ablation of AF in a PROBE (Prospective, randomised, open label, blinded end point) active controlled trial.

Secondary objectives were to assess additional safety endpoints and efficacy in this clinical setting. A total of 704 patients were enrolled in the trial. Of these, 678 patients were randomised and 676 were treated, and 26 were screening failures. Of the treated patients, 635 patients started the ablation procedure. The following text summarises the disposition, compliance, and patient characteristics based on the ablation set.

Primary endpoint
Treatment with DE resulted in a statistically significant reduction of the occurrence of ISTH MBEs compared with warfarin treatment in the patients in the ablation set (exploratory analysis). The frequency of MBEs was 1.6% in the DE group and 6.9% in the warfarin group (see table below). The risk difference was -5.3% (95% CI -8.4, -2.2%). The HR of DE vs. warfarin based on the unstratified Cox proportional hazards model was 0.224 (95% CI 0.08, 0.59). Analyses of the primary endpoint in a variety of subgroups by demographics, baseline characteristics, and type of ablation showed results that were generally consistent with the results for the overall population.

SVII.Table 12 Adjudicated ISTH MBEs during the ablation procedure and up to 2 months post-ablation - AS

	DE 150 mg	Warfarin
Patients in the ablation set, N (100%)	317	318
Patients with event, N (%)	5 (1.6)	22 (6.9)
95% CI [%][1]	(0.2, 2.9)	(4.1, 9.7)
Risk difference vs. warfarin [%]	-5.3	
95% CI [%]	(-8.4, -2.2)	
p-value[2]	0.0009	
HR vs. warfarin[3]	0.224	
95% CI[4]	(0.08, 0.59)	

[1]Based on the normal approximation of independent binomial distributions
[2]Based on the chi-square test
[3]Cox proportional hazards model
[4]Wald confidence limits
Data source: [c14388942-01]

Secondary endpoints of safety
The composite endpoint of ISTH MBE/SSE/TIA occurred more frequently in the warfarin group during the ablation procedure and up to 2 months post-ablation (SVII.Table 14). This result was driven by the treatment imbalance seen for MBEs. There were similar frequencies of minor bleedings in both treatment groups. Subgroup analyses of the secondary endpoints showed results that were consistent with those for the overall population.

SVII.Table 13 Secondary endpoints of safety, N (%)

	DE 150 mg	Warfarin
Patients in the ablation set, N (100%)	317	318
SSE/TIA (composite)	0	1 (0.3)
ISTH MBE/SSE/TIA (composite)	5 (1.6)	23 (7.2)
Minor bleeding	59 (18.6)	54 (17.0)

Data source: [c14388942-01]

Secondary endpoint of efficacy
Only 1 event was observed for the composite endpoint of SSE/TIA during the ablation procedure and up to 2 months post-ablation. It was a TIA event in the warfarin group. No MI or stroke was reported in the trial.

Further endpoints of efficacy
Further endpoints assessed during the ablation procedure and up to 1 month postablation were analysed based on the ablation set. Further endpoints assessed over the whole treatment period were analysed based on the treated set. The composite endpoint of SSE/TIA was reported for only 1 patient overall (warfarin group) up to 1 month post-ablation and for 3 patients over the whole treatment period (DE: 1 patient, warfarin: 2 patients); see table below.

SVII.Table 14 Further endpoints of efficacy, N (%)

	DE 150 mg	Warfarin
Endpoints during the ablation procedure and up to 1 month post-ablation		
Patients in the ablation set, N (100%)	317	318
SSE/TIA (composite)	0	1 (0.3)
Endpoints assessed over the whole treatment period		
Patients in the treated set, N (100%)	338	338
SSE/TIA (composite)	1 (0.3)	2 (0.6)
TIA	1 (0.3)	1 (0.3)
Systemic embolism	0	1 (0.3)

Data source: [c14388942-01]

Further endpoints of safety

ISTH MBEs were less frequent in the DE group than the warfarin group, both up to 1 month post-ablation (1.3 vs. 6.6%) and over the whole treatment period (1.8 vs. 6.8%); see SVII.Table 14. The location of MBEs over the whole treatment period was most commonly reported as 'other MBE' (DE: 2 events, warfarin: 12 events) or pericardial (2 vs. 6 events). Note that events were categorised based on pre-defined locations or otherwise categorised as 'other MBE'. For minor bleedings there were similar frequencies in both treatment groups over the whole treatment period. The composite endpoint of ISTH MBE/SSE/TIA occurred more frequently in the warfarin group over the whole treatment period; once again this result was driven by the treatment imbalance seen for MBEs. Pericardial tamponade up to 1 month post-ablation was less frequent in the DE group (0.3 vs. 1.9%). There were similar frequencies of vascular access complications across treatments (10.7% and 13.2%). No patient died.

SVII.Table 15 Further endpoints of safety, N (%)

	DE 150 mg	Warfarin
Endpoints during the ablation procedure and up to 1 month post-ablation		
Patients in the ablation set, N (100%)	317	318
ISTH MBEs	4 (1.3)	21 (6.6)
Pericardial tamponade	1 (0.3)	6 (1.9)
Vascular access complication	34 (10.7)	42 (13.2)
Endpoints assessed over the whole treatment period		
Patients in the treated set, N (100%)	338	338
MBEs (ISTH)	6 (1.8)	23 (6.8)
Location of MBEs [events], total	6	24
Other major bleeding event	2	12
Pericardial	2	6
Gastrointestinal	2	2
Intracranial	0	2
Intramuscular with compartment syndrome	0	1
Retroperitoneal	1	1
ISTH MBE/SSE/TIA (composite)	7 (2.1)	24 (7.1)
Minor bleedings	69 (20.4)	66 (19.5)

Data source: [c14388942-01]

Adverse events

AE frequencies were generally comparable between treatment groups (see SVII.Table 16 for an overview). The majority of AEs were mild or moderate in intensity. Severe AEs were less frequent in the DE group than the warfarin group (3.3 vs. 6.2%). AEs leading to treatment discontinuation were reported for 27 patients (4.0%) in the treated set. They were numerically more frequent in the DE group than the warfarin group (5.6 vs. 2.4%). The imbalance was largely driven by gastrointestinal disorders (8 patients/2.4% vs. 1 patient/0.3%); all of these 8 gastrointestinal events in the DE group were mild or moderate in intensity. AEs leading to treatment discontinuation that were reported for at least 2 patients in a treatment group were gastritis (DE: 4 patients/1.2%, warfarin: 0 patients) and atrial thrombosis (DE: 2 patients/0.6%, warfarin: 1 patient/0.3%). There were notably fewer AEs leading to treatment discontinuation in the ablation set (10 patients/1.6%) than in the treated set (27 patients/4.0%). In the ablation set, there were no marked differences between the treatment groups for such AEs (DE: 1.9%, warfarin: 1.3%).

Drug-related AEs as assessed by the investigator were reported for 20.7% of patients in the DE group and 17.5% of patients in the warfarin group. The only drug-related AE with an overall frequency >2% was haematoma (DE: 1.8%, warfarin: 3.3%).

SAEs were reported for 18.6% of patients in the DE group and 22.2% of patients in the warfarin group. The only SAEs with a frequency >2% in any treatment group were atrial flutter (DE: 5.9%, warfarin: 5.6%) and atrial fibrillation (DE: 1.8%, warfarin: 3.8%).

SVII.Table 16 Adverse event overall summary, N (%)

	DE 150 mg	Warfarin	Total
Patients in the treated set, N (100%)	338	338	676
Patients with any AE	225 (66.6)	242 (71.6)	467 (69.1)
Severe AEs	11 (3.3)	21 (6.2)	32 (4.7)
Investigator-defined drug-related AEs	70 (20.7)	69 (17.6)	129 (19.1)
Other significant AEs (according to ICH E3)	11 (3.3)	8 (2.4)	19 (2.8)
AEs leading to discontinuation of trial medication	19 (5.6)	8 (2.4)	27 (4.0)
SAEs	63 (18.6)	76 (22.2)	138 (20.4)
Fatal	0	0	0
Immediately life-threatening	1 (0.3)	2 (0.6)	3 (0.4)
Disability/incapacity	0	1 (0.3)	1 (0.1)
Requiring hospitalisation	26 (7.7)	34 (10.0)	60 (8.9)
Prolonged hospitalisation	13 (3.8)	22 (6.5)	35 (5.2)
Congenital anomaly	0	0	0
Other	29 (8.6)	27 (8.0)	56 (8.3)

Patients could be counted in more than 1 seriousness criterion.
Data source: [c14388942-01]

In this exploratory study, treatment with dabigatran etexilate resulted in a statistically significant reduction in adjudicated ISTH MBEs when compared with INR-adjusted warfarin. This clinically relevant difference was noted from the time of the ablation and was sustained until 8 weeks after the ablation (end of follow up). No thromboembolic events occurred in the dabigatran etexilate group during or after the ablation and the incidence of minor bleedings was similar in both treatment groups. Periprocedural anticoagulation with uninterrupted dabigatran etexilate 150 mg b.i.d. was a safe, effective, and well-tolerated treatment option in patients undergoing AF ablation compared with uninterrupted vitamin K antagonist. Results from this trial triggered the CCDS update to version 17 (dated 13 Apr 2017) and are included in the CCDS sections “Dosage and Administration” as well as “Clinical trials“. The final CTR for 1160-0204 and respective update of the EU-SmPC were submitted on 19 Apr 2017 (Type II variation procedure EMEA/H/C/000829/II/0103, Positive Opinion: 14 Sep 2017). In 2017, findings from the RE-CIRCUIT trial were published in the New England Journal of Medicine [P17-03137].

Investigation of effectiveness of additional risk minimisation measures

1160-0149: Post authorisation study to evaluate the effectiveness of additional risk minimisation activities in the treatment of SPAF [c08929115-01]:

In accordance with FUM 026 and in order to investigate the efficacy of PG and PAC, BI initiated a 'Post authorisation study to evaluate the effectiveness of additional risk minimisation activities in the treatment of SPAF" with special reference to the PG and PAC.

The objective of this survey was to provide data on

1. Physician's knowledge and recommendations to their patients on appropriate dosing and minimising the risk of bleeding when treated with Pradaxa as provided by educational material (Pradaxa "Prescriber Guide").
2. Patients' understanding of the disease, bleeding signs, what to do in case of bleeding and how to deal with emergency situations as provided by educational material ("Patient Alert Card").

Results from this study which was finalised on 12 Feb 2016 and submitted to the EMA on 10 Mar 2016 were summarised in PBRER 16. During the reporting interval for PBRER 17 (19 Sep 2016 to 18 Mar 2017), BI took steps to implement the recommendations from this study including an action plan with defined standard measures of coverage, timing of logistical implementation of locally (re)-approved educational material (PG and PAC) and tracking of local HA approval and logistical implementation. The minimum standard of communication after an update of PG and PAC should include publication on a company webpage (similar to e.g. Pradaxa.co.uk) + emailing to HCPs + distribution by customer facing functions.

Because improvement in the distribution of educational material (both PG and PAC) is considered by BI to be the key for better understanding of the safest and most efficacious use of Pradaxa by HCPs and patients, the action plan was updated based on results of study 1160-0149, with focus on the processes of final distribution of PAC and Patient Guide to HCPs.

With this, BI has implemented an end-to-end tracking tool (VEEVA) of the RMM documents PG and PAC. Within this tool, the distribution pathway via customer facing function for the EEA region was outlined including key parameters for tracking the activity.

Since 2017, this activity included an active distribution of the PG and PAC through face to face interaction and discussion between the MAH's customer facing functions and HCPs. The results from this activity have been discussed in PBRERs 19 and 20 with DLPs of 18 Mar 2018 and 18 Mar 2019, respectively). As agreed with the PRAC (EMEA/H/C/PSUSA/00000918/201903) the face to face interaction was conducted in the entire EEA region until 31 Dec 2019. Since 1 Jan 2020, the MAH has initiated the switch to digital availability of the PG and PAC. The digital switch of PG and PAC was finalised by the first half of 2021. Upon request, the HCPs are still provided with hard copies of the PG and PAC.

Indication: aVTEt

For this indication, the following clinical trials were considered: 1160-0046 (RE-COVER II), 1160-0053 (RE-COVER) and 1160-0248 (RE-SPECT CVT)

In the 2 active controlled clinical trials 1160-0053 (RE-COVER) and 1160-0046 (RE-COVER II), 5107 patients were treated with dabigatran etexilate 150 mg b.i.d. or warfarin for up to 6 months. Fewer patients with haemorrhages were reported in the dabigatran etexilate 150 mg b.i.d. treatment group than in the warfarin treatment group: MBEs 1.0% vs. 2.0%, MBEs/CRBE 4.4% vs. 8.5%, and any haemorrhagic event 14.4% vs. 22.2%, respectively. Further details are provided in the tables below.

SVII.Table 17 Summary of haemorrhagic events for trials 1160-0053 (RE-COVER) and 1160-0046 (RE COVER II) from start of double-dummy treatment (oral only treatment)

	Dabigatran etexilate 150 mg b.i.d.	Warfarin
	n (%/a)	n (%/a)
Total treated patients	2456	2462
PY	1127.0	1124.9
Patients with MBEs	24 (1.0)	40 (1.6)
Fatal haemorrhagic event	1 (0.0)	2 (0.1)
Life-threatening haemorrhagic event	4 (0.2)	6 (0.2)
Symptomatic haemorrhage in critical area or organ	4 (0.2)	11 (0.4)
Haemorrhage causing fall ≥20 g/L fall in haemoglobin or leading ≥2 units of transfusion of whole blood or red cells	20 (0.8)	30 (1.2)

= yearly event rate
MBEs defined by meeting at least 1 of the following: 1) fatal bleeding, 2) clinically overt bleeding in excess of what was expected and associated with >20g/L fall in haemoglobin in excess of what was expected, 3) clinically overt bleeding in excess of what was expected and leading to transfusion of >2 units of packed cells or whole blood in excess of what was expected, 4) symptomatic retroperitoneal, intracranial, intraocular or intraspinal bleeding, 5) bleeding requiring treatment cessation bleeding leading to re-operation
Data source: [U12-2617-01], Table 2.1.3.2: 2 and [U12-2653-01], Table 4.13.2.1.3

SVII.Table 18 Number (%) of patients with haemorrhages incl. 95% CI for trials 1160-0053 (RE-COVER) and 1160-0046 (RE COVER II) from start of double-dummy treatment (oral only treatment)

	Dabigatran etexilate 150 mg b.i.d.	Warfarin
Total treated patients, n (%)	2456 (100.0)	2462 (100.0)
Patients with MBEs, n (%)	24 (1.0)	40 (1.6)
HR vs. warfarin	0.60	--
95% CI	0.36, 0.99	--
Patients with life-threatening MBEs, n (%)	4 (0.2)	6 (0.2)
HR vs. warfarin	0.66	--
95% CI	0.19, 2.36	--
Patients with MBEs/CRBE, n (%)	109 (4.4)	189 (7.7)
HR vs. warfarin	0.56	--
95% CI	0.45, 0.71	--
Patients with any haemorrhagic event, n (%)	354 (14.4)	503 (20.4)
HR vs. warfarin	0.67	--
95% CI	0.59, 0.77	--

MBEs defined by meeting at least 1 of the following: 1) fatal bleeding, 2) clinically overt bleeding in excess of what was expected and associated with >20g/L fall in haemoglobin in excess of what was expected, 3) clinically overt bleeding in excess of what was expected and leading to transfusion of >2 units of packed cells or whole blood in excess of what was expected, 4) symptomatic retroperitoneal, intracranial, intraocular or intraspinal bleeding, 5) bleeding requiring treatment cessation bleeding leading to re-operation
CRBE defined as either: 1) spontaneous skin haematoma >25 cm2, 2) wound haematoma >100 cm2, 3) spontaneous epistaxis lasting >5 minutes, 4) spontaneous macroscopic haematuria or that lasting >24 hours if associated with an intervention, 5) spontaneous rectal bleeding (more than a spot on toilet paper), 6) gingival bleeding lasting >5 min, 7) any other bleeding event judged as clinically relevant by the investigator
Data source: [U12-2617-01], Table 2.1.3.2: 2

Safety of dabigatran etexilate vs. warfarin for acute VTE: pooled analyses of RE-COVER (1160-0053) and RE-COVER II (1160-0046) trials [P13-09153]

The authors present a pooled analysis of the safety of dabigatran etexilate vs. warfarin for acute VTE based on results of the RE-COVER and RE-COVER II trials (dabigatran etexilate vs. warfarin). In these trials, patients with confirmed acute VTE were started on parenteral therapy approved for this indication and were then randomised to receive overlapping warfarin or warfarin-placebo (single-dummy). After discontinuing parenteral therapy, they either continued warfarin or received dabigatran etexilate, respectively (double-dummy = oral only treatment), for 6 months. The authors analysed bleeding events in the pooled RECOVER and RE-COVER II trials using 3 different counting scenarios. Scenario 1 included bleeding events related to parenteral therapy alone (before any administration of dabigatran etexilate), scenario 2 excluded events associated with parenteral therapy in the dabigatran etexilate arm, thus assessed safety of dabigatran etexilate itself, and scenario 3 compared dabigatran etexilate with warfarin at its full pharmacological potential.

Outcome measures were MBEs, defined as clinically overt bleeding associated with a fall in haemoglobin of ≥20 g/l that resulted in the need for transfusion of ≥2 units of red blood cells, that involved a critical site or that was fatal. CRBEs included at least one of spontaneous skin haematoma of ≥25 cm, gingival bleeding, or spontaneous nose bleeding (with a duration >5 minutes), macroscopic haematuria, spontaneous rectal bleeding, bleeding leading to hospitalisation and/or requiring surgical treatment, bleeding leading to transfusion of ≥2 units of whole blood or red blood cells, or any other bleeding events considered clinically relevant by the investigator. Bleeding events were counted until 6 days after the last intake of study drug.

For MBEs, the authors found in scenario 1, 1.4% and 2% for dabigatran etexilate and warfarin, respectively (HR 0.73, 95% CI 0.48, 1.11). For scenario 2, 1% and 2% of MBEs were found for dabigatran etexilate and warfarin, respectively (HR 0.48, 95% CI 0.29, 0.78), and for scenario 3, there were 1% vs. 1.6% of MBEs for dabigatran etexilate and warfarin, respectively (HR 0.60 (95% CI 0.36, 0.99). The HRs for combined MBE/CRBEs also favoured dabigatran etexilate, and for all scenarios the upper bounds of the CIs were below 1.0. In the pooled analysis of RE-COVER and RE-COVER II, there was no statistically significant difference in the incidence of symptomatic VTE and VTE-related mortality (DE 150: 68/2553 [2.7 %] vs. warfarin: 62/2554 [2.4 %]; HR 1.09, 95% CI 0.77, 1.54).

In conclusion, 3 safety comparisons were made, and regardless of the calculation, pooled data from RE-COVER and RE-COVER II consistently showed a profile of numerically or even statistically significantly lower MBE rates with dabigatran etexilate than with warfarin. No other new relevant safety information was identified.

1160-0248 (RE-SPECT CVT): a randomised, open-label, exploratory trial with blinded endpoint adjudication (PROBE), comparing efficacy and safety of oral dabigatran etexilate versus oral warfarin in patients with cerebral venous and dural sinus thrombosis over a 24-week period [c24502871-01; P19-07958]

RE-SPECT CVT was a phase III randomised, open label, exploratory trial with 2 parallel groups over 24 weeks with blinded endpoint adjudication (PROBE) design. The primary objective of this trial was to compare the net clinical benefit of the treatment arms, as measured by the composite of VTE (recurring CVT; DVT of any limb, PE, or splanchnic vein thrombosis) or MBEs according to ISTH criteria, after up to 24 weeks of treatment. 120 patients were randomised and treated in this trial, 60 with dabigatran and 60 with warfarin.

The frequency of MBEs and VTEs was low during this trial, with MBEs reported for 1 patient (1.7%) on DE and 2 patients (3.3%) on warfarin over the full observation period. There were no reported VTEs in either treatment group. Clinically relevant non-MBEs were reported for no patient (0.0%) on DE and for 1 patient (1.7%) on warfarin. The overall frequency of MBEs or clinically relevant non-MBEs was 1.7% on DE (95% CI: 0.0, 8.9) and 5.0% on warfarin (95% CI: 1.0, 13.9). Minor bleeding events were reported for 11 patients (18.3%; 95% CI 9.5, 30.4) in the DE group and 10 patients (16.7%; 95% CI 8.3, 28.5) in the

warfarin group. The frequencies of any bleeding events as reported by the investigator (non-adjudicated data) were identical in the DE and warfarin groups (12 patients, 20.0% for each group; 95% CI: 10.8, 32.3).

New ICH or worsening of the haemorrhagic components of a previous lesion were similar in the 2 groups: 1 patient (1.8%; 95% CI: 0.0, 9.6) in the DE group; 2 patients (3.8%; 95% CI: 0.5, 13.0) in the warfarin group.

In assessments of recanalisation, 33/55 DE patients with data and 35/52 warfarin patients with data showed an improvement in total occlusion scores from baseline to end of treatment.

The frequency of AEs was 78.3% in the DE group and 70.0% in the warfarin group. In the DE group, the most frequently reported AEs by MedDRA SOC were GI disorders (30.0%), nervous system disorders (28.3%), infections and infestations (15.0%), and respiratory, thoracic and mediastinal disorders (10.0%). In total, 7 patients (11.7%) in the DE group experienced AEs leading to discontinuation of trial medication compared with no patient in the warfarin group. All AEs leading to discontinuation of trial medication were each reported for only a single patient (7 patients in total [1.7%]) in the DE group, as follows (note, patients could have more than 1 AE leading to discontinuation): abdominal discomfort, ALT increased, AST increased, cerebral haemorrhage, cerebral infarction, epigastric discomfort, gastrointestinal necrosis, intracranial venous sinus thrombosis, intestinal haematoma, thrombocytopenia, urticaria, and vomiting. SAEs were reported for 13.3% of patients on DE and 10.0% on warfarin. There were no fatal AEs in either treatment group. The most frequent SAEs by MedDRA SOC were nervous system disorders, reported for 5 (8.3%) patients on DE vs. 1 (1.7%) on warfarin.

Based on the frequency of major bleedings or venous thrombosis, there were no clinically noteworthy differences comparing the net clinical benefit of oral DE vs. oral warfarin in patients with cerebral venous and dural sinus thrombosis over a 24-week treatment period. Results from this trial were published by Ferro et al in 2019 [P19-07958].

Indication: sVTEp

For this indication, the following clinical trials were analysed: 1160-0047 (RE-MEDY) and 1160-0063 (RE-SONATE).

1160-0047 (RE-MEDY), 1160-0063 (RE-SONATE)

In total, 4199 patients were treated with either dabigatran etexilate 150 mg b.i.d., warfarin, or placebo for up to 36 or 18 months. Fewer patients with haemorrhages were reported in the dabigatran etexilate 150 mg b.i.d. treatment group than in the warfarin treatment group: MBEs 0.9% vs. 1.8%, MBEs/CRBE 5.6% vs. 10.2% and any haemorrhagic event 19.4% vs. 26.2%. The difference between treatment groups was statistically significant for MBEs/CRBE and any haemorrhagic events ($p<0.0001$). Compared with placebo, more patients in the dabigatran etexilate 150 mg b.i.d. group were reported with haemorrhagic events: MBEs 0.3% vs. none, MBEs/CRBE 5.3% vs. 2.0% and any haemorrhagic event

10.5% vs. 6.1%. The difference between treatment groups was statistically significant for MBEs/CRBE and any haemorrhagic events. Further details are provided in the tables below.

SVII.Table 19 Summary of haemorrhagic events for trials 1160-0047 (RE-MEDY) and 1160-0063 (RE-SONATE) (pooled data)

	Dabigatran etexilate 150 mg b.i.d.	Warfarin	Placebo
	n (%/a)	n (%/a)	n (%/a)
Total treated patients	2114	1426	659
PY	2191.6	1867.0	303.1
Patients with MBEs	15 (0.7)	25 (1.8)	0 (0.0)
Fatal haemorrhagic event	0 (0.0)	1 (0.1)	0 (0.0)
Life-threatening haemorrhagic event	1 (0.0)	3 (0.2)	0 (0.0)
Symptomatic haemorrhage in critical area or organ	9 (0.4)	11 (0.8)	0 (0.0)
Haemorrhage causing fall ≥20 g/L fall in haemoglobin or leading ≥2 units of transfusion of whole blood or red cells	7 (0.3)	16 (1.1)	0 (0.0)

%/a = yearly event rate
MBEs defined by meeting at least 1 of the following: 1) fatal bleeding, 2) clinically overt bleeding in excess of what was expected and associated with >20g/L fall in haemoglobin in excess of what was expected, 3) clinically overt bleeding in excess of what was expected and leading to transfusion of >2 units of packed cells or whole blood in excess of what was expected, 4) symptomatic retroperitoneal, intracranial, intraocular or intraspinal bleeding, 5) bleeding requiring treatment cessation bleeding leading to re-operation
Data source:[U12-2617-01], Tables 4.1.1.6 and 4.2.1.6

SVII.Table 20 Number (%) of patients with haemorrhages incl. 95% CI for trials 1160-0047 (RE-MEDY) and 1160-0063 (RE-SONATE) (pooled data)

	1160-0047 (RE-MEDY)		1160-0063 (RE-SONATE)	
	Dabigatran etexilate 150 mg b.i.d.	Warfarin	Dabigatran etexilate 150 mg b.i.d.	Placebo
Total treated patients, n (%)	1430 (100.0)	1426 (100.0)	684	659
Patients with MBEs, n (%)	13 (0.9)	25 (1.8)	2 (0.3)	0 (0.0)
HR vs. warfarin/placebo	0.54	--	1.0	--
95% CI	0.25, 1.16	--	0.00, 1.00	--
p-value for superiority	0.1135	--	0.9964	--
Patients MBEs/CRBE, n (%)	80 (5.6)	145 (10.2)	36 (5.3)	13 (2.0)
HR vs. warfarin/placebo	0.55		2.69	
95% CI	0.41, 0.72	--	1.43, 5.07	--
p-value for superiority	<0.0001	--	0.0022	--
Patients with any haemorrhagic event, n (%)	278 (19.4)	373 (26.2)	72 (10.5)	40 (6.1)
HR vs. warfarin/placebo	0.71	--	1.77	--
95% CI	0.61, 0.83	--	1.20, 2.61	--
p-value for superiority	<0.0001	--	0.0038	--

MBEs defined by meeting at least 1 of the following: 1) fatal bleeding, 2) clinically overt bleeding in excess of what was expected and associated with >20g/L fall in haemoglobin in excess of what was expected, 3) clinically overt bleeding in excess of what was expected and leading to transfusion of >2 units of packed cells or whole blood in excess of what was expected, 4) symptomatic retroperitoneal, intracranial, intraocular or intraspinal bleeding, 5) bleeding requiring treatment cessation bleeding leading to re-operation
CRBE defined as either: 1) spontaneous skin haematoma >25 cm2, 2) wound haematoma >100 cm2, 3) spontaneous epistaxis lasting >5 minutes, 4) spontaneous macroscopic haematuria or that lasting >24 hours if associated with an intervention, 5) spontaneous rectal bleeding (more than a spot on toilet paper), 6) gingival bleeding lasting >5 min, 7) any other bleeding event judged as clinically relevant by the investigator
Data source: data on file: Pradaxa Mastersheet Version 15 Nov 2012 Tables 13 and 14

Paediatric indication: Acute treatment and secondary prevention of VTE

Phase I- Bioavailability

1160-0194: Relative bioavailability of dabigatran after administration of different dosage forms of multiple doses of 150 mg dabigatran etexilate (hard capsule, granules resolved in reconstitution solution, pellets on food) in healthy male volunteers (an open label, randomised, multiple-dose, 3-way crossover study) [c02248557-02]

The primary objective of this trial, which was performed in the context of the paediatric programme, was to determine the relative bioavailability of 150 mg of dabigatran etexilate as pellets on food and of 150 mg of dabigatran etexilate as granules resolved in reconstitution solution, both compared with 150 mg of dabigatran etexilate as hard capsule. The secondary objective was the assessment of palatability of pellets on food and granules resolved in

reconstitution solution. The assessment of safety and tolerability was an additional objective of this trial. Deaths, SAEs, other significant AEs according to ICH E3, AEs of special interest, or severe AEs were not reported in this study and there were no AEs leading to trial discontinuation.

7 subjects experienced a total of 9 drug-related AE. 5 of the 9 drug-related AEs concerned events of bleeding (2 cases of haematoma, 2 of epistaxis, and 1 of haemorrhage), 2 were GIS (vomiting and diarrhoea), and 2 were headache. All drug-related AEs had recovered, except for 1 AE (haematoma), which was not yet recovered by the end of the study, but was expected to recover without sequelae.

Multiple 150 mg doses of dabigatran etexilate administrated as pellets on food (T1), granules resolved in reconstitution solution (T2), or as hard capsules (R) were safe and well tolerated by the healthy subjects. The trial results did not provide new relevant safety findings.

Results from this trial triggered the CCDS update to version 15 (dated 5 May 2015) and are included in the CCDS section “Pharmacokinetics”. The EU-SmPC has been updated accordingly (EMEA/H/C/000829/II/0080).

Phase Ib/IIa

1160-0088: Open-label safety and tolerability study of dabigatran etexilate mesilate given for 3 days at the end of standard anticoagulant therapy in children aged 12 years to less than 18 years [U12-3378-01]

Trial 1160-0088, which assessed safety in adolescents, has been completed. In this trial, the PK and PD of dabigatran etexilate administered b.i.d. for 3 consecutive days (total 6 doses) were assessed in 8 stable adolescents (12 to <18 years). All patients received an initial oral dose of 1.71 mg/kg (± 10%) of dabigatran etexilate (80% of the adult dose of 150 mg/70 kg adjusted for the patient's weight). Based on dabigatran concentrations as determined by the diluted thrombin time test and clinical assessment, the dose was adjusted to the target dose of 2.14 mg/kg (± 10%) of dabigatran etexilate (100% of the adult dose adjusted for the patient's weight). In this small population of patients, dabigatran etexilate capsules were well tolerated with only 3 mild and transient gastrointestinal adverse events reported by 2 patients. Exposure in this adolescent population was slightly lower compared to the exposure seen in adults. However, the PK/PD relationship in this population was similar to the relationship seen in adult VTE patients.

1160-0089: Single dose open-label PK/PD, safety and tolerability study of dabigatran etexilate mesilate given at the end of standard anticoagulant therapy in successive groups of children aged 2 years to less than 12 years followed by 1 year to less than 2 years [c09069268-01]

Trial 1160-0089 explores an oral liquid preparation (oral liquid formulation (6.25 mg/mL) after reconstitution from dabigatran etexilate granules (167.5 mg) and solvent for oral liquid formulation) as a single dose in children between 2 and 12 years and has been completed.

18 patients who were entered into the study were treated with dabigatran etexilate. All 6 patients aged 1 to <2 years who entered the study were treated with a single dose of dabigatran etexilate. In the age group of 2 to <12 years, 9 entered patients received a single dose of dabigatran etexilate and 3 entered patients were treated with a multiple dose of dabigatran etexilate (3 days, b.i.d.). None of the 18 treated patients prematurely discontinued the trial medication or the trial. The dose was adjusted based on age and weight and was equivalent to the adult dose of 150 mg dabigatran etexilate (multiple dose, 3 days b.i.d.), with 80% of the paediatric target dose for dose 1 on day 1, followed by 100% of the target dose for all subsequent 5 doses. Single dose on 1 day (100% of the target dose).

All 6 patients in the single dose group aged 1 to <2 years were treated with the planned single dose of dabigatran etexilate which was adjusted based on age and weight of the individual patient. In the single dose group aged 2 to <12 years, 7 patients received their planned single dose of dabigatran etexilate and 2 patients received less than the planned dose but more than the minimum required dose. All 3 patients in the multiple dose group were to receive 80% of the target dose on dose 1, followed by 100% for all subsequent 5 doses. Of these 3 patients, 2 patients received the planned dose with very minor deviations in volume and 1 patient received a higher volume for all 6 doses (Dose 1: 4.96 mL instead of 4.4 mL; Doses 2 to 6: 6.24 mL instead of 5.4 mL).

Adverse events
A total of 3 patients (16.7%) in this study had AEs during screening (respiratory tract infection, nasopharyngitis, ear pain, and back pain) and 1 patient (5.6%) had AEs during the on-treatment period (leukopenia and dizziness). All AEs were of mild intensity, non-serious and considered to be not related to study drug intake in the opinion of the investigator; all patients recovered. None of the patients had a VTE during this study.

There were no AEs during the post-treatment or post-study periods. There were no deaths, no AEs leading to discontinuation of trial drug, no drug-related AEs (in the opinion of the investigator), no AEs of special interest, and no other significant AEs according to ICH E3 at any time of the trial.

Bleeding events
During the entire study, no bleeding events were reported for the 20 screened patients.

Laboratory assessment and vital signs
Laboratory analyses (haematology and clinical chemistry) did not reveal any clinically significant findings compared to baseline. Regarding transitions relative to the reference range, no clinically relevant or unexpected findings were observed for any of the measured parameters. Regarding vital signs, there were no clinically meaningful findings or changes from baseline to each measured time point in blood pressure or pulse rate values.

1160-0105 Open-label, single dose, tolerability, pharmacokinetic/ pharmacodynamics and safety study of dabigatran etexilate given at the end of standard anticoagulant therapy in children aged less than 1 year old [c09085437-01]

Trial 1160-0105 is an open-label, single dose, tolerability, PK/PD and safety study of dabigatran etexilate given at the end of standard anticoagulant therapy in children aged less than 1 year old. Dabigatran etexilate oral liquid formulation (6.25 mg/mL) after reconstitution from dabigatran etexilate granules (167.5 mg) and solvent for oral liquid formulation (26 mL out of 30 mL provided in solvent bottle, dose: adjusted based on age and weight).

A total of 10 patients were screened / enrolled. Of these, 2 patients were screening failures. All 8 patients who were entered into the study were treated with dabigatran etexilate. None of the 8 patients prematurely discontinued the trial medication or prematurely discontinued the trial.

All 8 patients who were entered into the study were treated with a single dose of dabigatran etexilate which was adjusted based on their age and weight. All 8 patients received at least the minimum required dose. Of these, 2 patients received slightly less than the planned dose (5.5 mL instead of 6.0 mL; 2.5 mL instead of 3.0 mL) and 1 patient received slightly more than the planned dose (4.0 mL instead of 3.0 mL).

Adverse events
During screening and the on-treatment period, none of the patients were documented with any AE. There were no deaths, no AEs leading to discontinuation of trial drug, no drug-related AEs (in the opinion of the investigator), no AEs of special interest, and no other significant AEs according to ICH E3 at any time of the trial.

During the post-treatment period, 1 of 8 patients (12.5%) was documented with an SAE (preferred term aortic stenosis, system organ class vascular disorders). The event was of severe intensity, not drug related according to the investigator, was immediately life-threatening, and required/prolonged hospitalisation. The SAE occurred 7 days after intake of dabigatran etexilate.

Bleeding events
During the entire study, no bleeding events were reported for the 10 screened patients.

Global assessment of acceptability and tolerability of the study medication
The majority of patients were assessed with ‘good’ tolerability (6 patients, 75.0%). 1 patient each (12.5%) was evaluated with a satisfactory tolerability or tolerated the study medication badly.

Conclusion
In this small population of infants (children aged less than 1 year), dabigatran etexilate as oral liquid formulation was well tolerated without AEs or bleeding events during the on-treatment period. The 1 reported SAE (aortic stenosis), occurred 7 days after taking dabigatran etexilate and was not considered related to study medication by the investigator.

The variability of total dabigatran plasma concentrations was moderate at 2 hours after dosing and low at 12 hours after dosing. The projected steady-state dabigatran trough concentrations of the present study were largely comparable to those observed in adult patients with VTE. The relationships between total dabigatran concentration and ECT or dTT were linear; the PK/PD relationship for aPTT can be described by a non-linear model. The observed PK/PD relationships in this study were similar to those observed in adult and adolescent patients with VTE.

Phase IIb/III studies

1160-0106 Open-label, randomised, parallel-group, active-controlled, multicentre,non-inferiority study of dabigatran etexilate [DE] versus standard of care for venous thromboembolism treatment in children from birth to less than 18 years of age: The DIVERSITY study [c29773859-01, P20-11143]

This study is an active-controlled, open-label, randomised, parallel-group trial for treatment of paediatric VTE. Clinically stable patients diagnosed with acute VTE who had completed an initial parenteral treatment with an unfractionated or a low molecular weight heparin for a minimum of 5 to 7 days (but not longer than 21 days) and who had an anticipated need for continued anticoagulation therapy for at least 3 months (including the initial parenteral therapy) were eligible to enter the study. Patients aged ≥8 years received age- and weight-adjusted DE dosing via capsules using 50 mg, 75 mg, 110 mg, and 150 mg doses. For patients aged <8 years or for patients who cannot take capsules even if older than 8 (but <12 years of age) there was age- and weight-adjusted dosing via DE pellets. Patients aged <12 months received age- and weight-adjusted dosing via DE oral liquid formulation. There was a 2:1 randomisation to DE vs. standard of care. Investigators decided on SoC treatment at the time of randomisation: either LMWH, VKA, or fondaparinux. Study treatment was planned for 3 months which included the initial parenteral therapy. Outcome events were adjudicated by an independent blinded adjudication committee.

Overall, 267 patients entered the trial and 266 were treated. Of those, 176 patients were treated with dabigatran etexilate and 90 patients according to standard of care. 168 patients were 12 to <18 years old, 64 patients 2 to <12 years old, and 35 patients were younger than 2 years. Of those, 21 patients were 6 months to <2 years old and 14 patients were <6 months old.

The frequency of bleeding events (major, minor, CRNM, or any bleeding event) was generally comparable between treatment groups. In total, 38 patients (21.6%) in the DE arm and 22 patients (24.4%) in the standard of care arm had any adjudication-confirmed bleeding event, most of them categorised as minor. The rate difference for the probability of freedom from any bleeding event and the HR of events showed that there was no difference in risk of any bleeding events between the 2 treatment groups. The combined endpoint of adjudication-confirmed MBE or CRNM was reported for 6 (3.4%) patients in the DE group and 3 (3.3%) patients in the standard of care group. In 2019, Albisetti et. al. presented this study at the 27th Congress of the ISTH [P19-06030]

1160-0108 Open label, single arm safety prospective cohort study of dabigatran etexilate for secondary prevention of venous thromboembolism in children from 0 to less than 18 years [c29754273-01, P19-11322]

Trial 1160-0108 was a multi-centre, multinational, open-label, single arm phase III trial of DE to evaluate safety in the secondary prevention of VTE in children from 0 to <18 years. Recruitment was first initiated in the adolescent group (12 to <18 years) and was consecutively opened to younger age groups (2 to <12 years of age; 0 to <2 years). This trial included patients who required further anticoagulation due to the presence of a clinical risk factor after completing the initial treatment for confirmed VTE (for at least 3 months) or after completing the DIVERSITY trial. Patients with active meningitis, encephalitis, or intracranial abscess were excluded from trials 1160-0106 and 1160-0108 due to the potential for ICH in this patient population [c26571231-01, c26496086-01].

Eligible patients received age and weight adjusted doses of an age-appropriate formulation (capsules, coated granules or oral solution) of dabigatran etexilate until the clinical risk factor resolved, or up to a maximum of 12 months. The primary endpoints of the study included the recurrence of VTE, major and minor bleeding events, and mortality (overall and related to thrombotic or thromboembolic events) at 6 and 12 months. Outcome events were adjudicated by an independent blinded adjudication committee.

214 patients entered the study and 213 were treated.The mean age at screening was 12.8 years (SD 4.6 years), with 161 patients in the 12 to <18 years age group, 43 patients in the 2 to <12 years age group, and 9 patients in the 0 to 2 years age group. The youngest patient was 6 months old.

During the on-treatment period, 3 patients (1.4%) had an adjudication-confirmed recurrent VTE within the first 12 months after treatment start. The overall probability of being free from recurrence of VTE during the on-treatment period was 0.984 (95% CI 0.950, 0.995) at 6 months and 0.984 (95% CI 0.950, 0.995) at 12 months.

In 3 patients (1.4%), an adjudication-confirmed major bleeding event occurred within the first 12 months. 3 patients (1.4%) had an adjudication-confirmed clinically relevant non-major bleeding within the first 12 months. Overall, adjudication-confirmed bleeding events (major, minor, and clinically relevant non-major bleeding) during the ontreatment period were reported for 48 patients (22.5%) within the first 12 months. The probability of being free from bleeding events was 0.785 (95% CI 0.718, 0.838) at 6 months and 0.723 (95% CI 0.645, 0.787) at 12 months.

No on-treatment deaths occurred. The safety profile of DE was consistent with the known profile of the drug, and no new safety signal for DE has been identified. In 2019, Brandao et. al published a manuscript based on an interim data snapshot from this trial [P19-11322].

Special populations

Renal impairment

1160-0086: An open label, non-comparative, pharmacokinetic and pharmacodynamic study to evaluate the effect of dabigatran etexilate on coagulation parameters including a calibrated thrombin time test in patients with moderate renal impairment (creatinine clearance 30-50 mL/min) undergoing primary unilateral elective total knee or hip replacement surgery [c01954741-02]

The 1160-0086 study, a phase IV, multi-centre, multi-national study in patients with moderate renal impairment (CrCl 30-50 mL/min) undergoing TKR or THR was a PK/PD study to compare the estimated dabigatran etexilate concentration in plasma measured by local/central calibrated Hemoclot Thrombin Inhibitor assay with the concentration measured in a central laboratory via HPLC-MS/MS. The study also evaluated the correlation between total dabigatran etexilate plasma concentration and coagulation parameters using Hemoclot, aPTT, and ECT. This study confirmed that Hemoclot is an adequate assay to estimate dabigatran concentrations and is comparable with the HPLC-MS/MS reference method in the calibrated range of approximately 50 to 500 ng/mL, if adequately calibrated.

Safety data from the 112 patients who received trial medication included bleeding events for 20 patients (17.9%), most of which occurred at the surgical site; only few patients (n=5; 4.5%) experienced gastrointestinal bleeding. More than half of the bleeding events were classified as clinically relevant; MBEs were reported for only 4 (3.6%) patients. One third of the patients received blood transfusions as surgical routine and only 12 patients due to other bleeding events or reasons. None of the treated patients had a thromboembolic event. 4 patients (3.6%) were reported with signs of DVT, but none of these were confirmed as DVT.

The most common AEs were nausea, vomiting, and arthralgia; AEs leading to discontinuation were most frequently reported in the SOC ‘GI disorders’ including gastric ulcer and haematemesis. The most frequently reported drug-related AEs were haematoma and wound haematoma. Most AEs were mild or moderate in intensity; only 7 patients (6.3%) had AEs that were assessed as severe. SAEs were reported for 10 patients during treatment with dabigatran etexilate; 6 SAEs were considered to be related to the study drug by the investigator and led to treatment discontinuation (diverticulitis, gastritis haemorrhagic, and 2 cases each of gastric ulcer and haematemesis); 1 SAE was fatal (acute MI).

The overall profile of AEs was expected in this population of patients with advanced age (mean age 79.1 years). The safety profile of dabigatran etexilate in patients who underwent THR or TKR was consistent with the safety profile as described in the current Pradaxa EU-SmPC.

1160-0121: Open label, non-randomized, multiple dose phase I study to investigate the elimination, pharmacokinetics, pharmacodynamics and safety of dabigatran etexilate (Pradaxa) under steady state conditions before, during and after haemodialysis in patients with End Stage Renal Disease (ESRD) undergoing regular haemodialysis [U11-2257-01]

The aim of this study was to assess effects of 2 different haemodialysis procedures on PK, PD, and elimination rate of dabigatran in subjects with ESRD. In each trial period, dabigatran etexilate was administered on days 1, 2, and 3, and haemodialysis was performed on days 1, 3, and 5. During haemodialysis on day 3, target rate of blood flow was 200 mL/min in treatment period 1 and 400 mL/min in treatment period 2. Dabigatran etexilate doses for these subjects were selected to obtain plasma concentrations of dabigatran comparable to steady-state concentrations in typical patients treated b.i.d. with 150 mg of dabigatran etexilate.

7 subjects with ESRD were included. All 7 subjects entered in the trial completed the planned observation time for the trial; no important protocol violations or violations of inclusion/exclusion criteria were identified for any subject.

The dosing scheme employed for subjects with ESRD resulted in gMean maximum plasma levels of dabigatran on day 3 (after the third dose of dabigatran etexilate) that were similar to those observed at steady state in patients with normal renal clearance receiving 150 mg of dabigatran etexilate b.i.d. In subjects with ESRD, however, geometric mean predose concentrations of dabigatran were substantially higher (40 to 55%) due to reduced clearance in these subjects.

Haemodialysis clearly resulted in marked decreases in plasma concentrations of both free and total dabigatran. Increasing the blood flow rate during Day 3 dialysis (from 200 mL/min in treatment period 1 to almost 400 mL/min in treatment period 2) increased dialysis clearance of total dabigatran from blood and plasma by approximately 50% and the fraction of dabigatran removed from plasma by 20%. In treatment period 1, individual fractions of dabigatran removed from plasma ranged from 41.3% to 58.0%; in treatment period 2, values ranged from 54.3% to 64.9%.

In both treatment periods, pharmacodynamic assessment indicated that aPTT and anti-FIIa increased after administration of dabigatran etexilate, and that dialysis reduced aPTT and anti-FIIa times. The presence of heparin during dialysis affected the aPTT ratio, whereas the anti-FIIa ratio was not affected by heparin.

In both treatment periods, all 7 subjects received all 3 planned doses of dabigatran. No deaths, serious AEs, other significant AEs, or AEs of severe intensity were reported. Over the course of the trial, AEs were reported for 2 subjects (28.6%). During dabigatran treatment, mild epistaxis was reported in 1 subject. It was considered by the investigator as minor bleeding and as related to trial medication. Other AEs reported were mild headache for one subject during dabigatran treatment and one subject experienced mild nasopharyngitis for the 6-week washout period between treatment periods. Neither of these AEs was considered treatment-related by the investigator. All 3 AEs resolved without concomitant therapy.

During haemodialysis on day 3, heparin was administered at half the normal dose due to subjects' concomitant exposure to dabigatran. No bleeding-related AEs and no coagulation-related dialysis complications were reported for subjects receiving low-dose heparin.

No relevant elevations in ALT or AST were observed. No transitions in individual clinical laboratory values were of clinical relevance or reported as an AE by the investigator. The investigator assessed tolerability of trial treatment as 'good' for all 7 subjects.

Conclusion
The dosing scheme for subjects with ESRD produced gMean maximum plasma levels of dabigatran on day 3 that were similar to steady state levels in patients with normal renal clearance receiving 150 mg of dabigatran etexilate b.i.d. The haemodialysis procedures employed in the trial resulted in substantial clearance of total plasma dabigatran. Dialysis clearance of dabigatran was higher for higher dialysis blood flow rates. Dialysis was also successful in reducing the pharmacodynamic effect of dabigatran. Treatment was well-tolerated, and safety analysis did not indicate a safety risk for subjects with ESRD participating in the trial.

1160-0166: "An exploratory study to investigate the PK and effects of DABIgatran etexilate in patients with stable severe RENAL disease: DabiRenal" [c02161791-02]

This open-label, single centre trial was performed in patients with a chronic need for anticoagulation and concomitant severe CKD (as defined by a CrCl between 15 and 30 mL/min over the last 3 months before trial participation) to evaluate the PK and PD of dabigatran etexilate, based on the FDA exposure response model. A total of 16 patients received 75 mg dabigatran etexilate (1 capsule) b.i.d. for 7.5 days (corresponding to a total of 15 capsules).

The primary PK endpoints $C_{max,ss}$ and $AUC_{tau,ss}$ (=$AUC_{0-12,ss}$) had geometric mean values of 207 ng/mL (gCV of 53.9%, N=15) and 2140 ng*h/mL (gCV of 51.9% N=15), respectively. The observed total exposure (AUC) is similar to the gMean AUC0-∞ of 2460 ng*h/mL seen in subjects with CrCl from 30 to 50 mL/min after receiving a single dose of 150 mg DE in trial 1160-0023 [U06-1704], which demonstrated that 75 mg DE b.i.d. is the appropriate dosing regimen when targeting the exposure levels seen in patients with moderate renal impairment receiving 150 mg DE b.i.d. As expected, prolonged elimination of dabigatran in subjects with severe renal impairment was shown by an increase in terminal half-life with a gMean $t_{1/2,ss}$ of 28.3 hours (gCV: 13.0%) compared to $t_{1/2,ss}$ values of 14 to 17 hours in healthy volunteers. This observation is also consistent with the previously reported half-life of 27.2 hours in patients with severe renal impairment [U06 1704]. Overall, twice daily administration of 75 mg dabigatran etexilate for 7.5 days was safe and well tolerated by the subjects with severe CKD in this trial.

No clinically relevant finding was reported as an AE regarding safety laboratory measurements, ECG recordings, physical examinations, and vital sign measurements. No

bleeding event was reported as an AE, but 1 AE (wound) led to a minor bleeding, which lasted 30 to 45 min and did not require any therapy.

1160-0173: A prospective, open label study to evaluate the pharmacokinetics of dabigatran in non-valvular atrial fibrillation (NVAF) patients with severely impaired renal function on dabigatran etexilate 75 mg b.i.d. therapy [c04596002-01]:

This trial was conducted to assess dabigatran exposure (at trough and peak) in NVAF patients with severe renal impairment (defined as CrCl 15-30 mL/min) receiving dabigatran etexilate 75 mg b.i.d. therapy.

60 patients were treated with Pradaxa and 59 (98.3%) of these patients completed the planned observation time. No patient prematurely discontinued from the trial medication. 1 patient was treated but died in the post-treatment phase and the termination visit was not done. All 60 patients received at least 12 doses of trial drug and were therefore were included in the pharmacokinetic set and pharmacokinetic modelling set. There were no important protocol violations in this trial.

Pharmacokinetics – primary endpoints:
B.i.d. administration of 75 mg dabigatran etexilate in patients with severe renal impairment resulted in a gMean $C_{pre,ss}$ of 155 ng/mL (gCV of 76.9%) and gMean $C2_{,ss}$ of 202 ng/mL (gCV of 70.6%) on Day 8 (Visit 3).

Observed plasma concentrations were predicted reasonably well by the RE-LY population PK model, although with a tendency towards under-prediction of median and higher concentrations. When only accounting for between-patient variability, there was also a tendency to over-predict the 10th concentration percentile.

Summary of AEs
Overall, 11/60 (18.3%) patients in this trial had at least 1 AE during the treatment period through 3 days after the last drug intake of the treatment period. 1 patient (1.7%) had a severe AE (acute MI). A total of 4 (6.7%) patients had AEs that were considered to be drug-related. No patients had AEs leading to premature discontinuation of trial drug or significant AEs (significant according to ICH E3). There were no pre-specified events outlined in the protocol for this trial. 2 patients reported SAEs during the treatment period that required hospitalisation (one of which was also considered to be immediately life-threatening). No deaths were reported during the treatment period through 3 days after the last drug intake of the treatment period. 1 death of a patient was reported in the post-treatment phase.

Bleeding events
Bleeding events were reported in a total of 5 patients during the trial. All bleeding events were considered by the investigator to be minor. 2 (3.3%) patients each reported an oral bleeding (mouth hemorrhage and gingival bleeding) and a subcutaneous bleeding (contusion in one patient and ecchymosis and fall in a second patient). 1 (1.7%) patient reported a genito-urinary bleeding (haematuria). 1 (1.7%) patient who had experienced gingival bleeding (see above) also experienced other bleeding (haematoma and laceration).

No patients reported bleeding events associated with a drop in hemoglobin of ≥2 g/dL, associated with hypotension requiring use of an intravenous inotropic agent, requiring surgical intervention, or requiring a transfusion of blood or red blood cells.

Conclusion
The observed dabigatran plasma concentrations in patients with severe renal impairment (defined as CrCl 15 to 30 mL/min) following 75 mg dabigatran etexilate (Pradaxa) b.i.d. were generally in agreement with those predicted by models developed from data in previous trials, although with a tendency towards under-prediction of median and higher concentrations. The safety profile of Pradaxa 75 mg b.i.d. for at least 7 days in NVAF patients with severe renal impairment in this trial was consistent with the patient population and the known safety profile of the drug, with no unexpected safety concerns. These findings support a 75 mg b.i.d. dosing regimen for Pradaxa in patients with severe renal impairment.

EMA requested in the frame of variation procedure EMEA/H/C/000829/II/0097 to include study data in the EU-SmPC under section “Pharmacokinetics”. Results regarding 1160-0173 have been included in the EU-SmPC.

Non-interventional and investigator-initiated studies

Non-interventional studies conducted by BI

pVTEp

The non-interventional studies 1160-0084, 1160-0085, 1160-0102 and 1160-0118 were pertinent for the indication primary VTE prevention and are described below.

*1160-0084: Observational cohort study to evaluate the safety and efficacy of Pradaxa (dabigatran etexilate) in patients with moderate renal impairment (creatinine clearance 30-50 mL/min) undergoing elective total hip replacement surgery or total knee replacement surgery [**Error! Reference source not found.**, c01853156-02].*

This was a phase IV, open-label, prospective, observational, single-arm study (1160-0084) in patients with moderate renal impairment (calculated CrCl 30-50mL/min) undergoing elective hip or knee replacement surgery was conducted to collect data on the safety and efficacy of dabigatran etexilate (Pradaxa) administered at a dose of 150 mg once daily, in accordance with the current European label.

The incidence of symptomatic VTEs including all cause death in this study was 0.70% overall (95% CI 0.14%, 2.03%). The incidence of MBEs in patients with moderate renal impairment was 2.10% (95% CI: 0.97%, 3.95%) and the incidence of treatment-emergent AEs in all treated patients was 36.3%, higher than in a more general population of patients undergoing elective orthopaedic surgery and treated with dabigatran etexilate, reflecting the older and more fragile patient population included in an observational study conducted in a

real world setting. Overall, the safety profile in this population was consistent with the known safety profile for dabigatran etexilate.

Dabigatran etexilate administered to patients with moderate renal impairment undergoing elective hip or knee replacement surgery in accordance with the locally approved label, in a routine clinical setting, was safe and well tolerated.

1160-0085: Observational cohort study to evaluate the safety and efficacy of Pradaxa (dabigatran etexilate) for the prevention of venous thromboembolism in patients undergoing elective total hip replacement surgery or total knee replacement surgery in a routine clinical setting [U12-1556-01]

1160-0085 was a phase IV, open-label, prospective, observational, single-arm study with the aim to assess the safety (MBEs) and efficacy (symptomatic VTE) of dabigatran etexilate 220 mg once daily, in accordance with the European product label in defined subgroups of patients from the general population (with potentially an increased risk) who were undergoing elective THR or TKR surgery in a routine clinical setting. This study was performed in accordance with the EMA recommendation to conduct a post approval study to evaluate the risk of bleeding in the more general population of patients with an increased risk of bleeding.

The study provided safety and efficacy data in more than 5000 patients undergoing major orthopaedic surgery (2701 hip surgery patients and 2527 knee surgery patients). The demographic characteristics of patients in study 1160-0085 were generally comparable with patients in phase III knee or hip replacement studies. Approximately 40% of patients were in at least 1 sub-population of patients at an increased risk for bleeding or VTE (i.e. patients with co-morbidities of particular interest or taking concomitant medications of particular interest). The most common co-morbidities were chronic use of NSAIDs (15.9%), active smokers (13.3%), concomitant ASA use (6.9%), and CAD (6.0%). Other risk factors (history of CHF, history of VTE) were reported for fewer than 5% of patients.

The incidence of the primary efficacy endpoint was 1.04% (95% CI: 0.78%, 1.35%). It was lower for patients undergoing hip surgery (0.55%, 95% CI: 0.31%, 0.90%) than for patients undergoing knee surgery (1.56%, 95% CI: 1.12%, 2.12%). With the exception of patients with a history of VTE (a known risk factor for recurrent VTE), the risk factors that were evaluated in the protocol-defined subgroups of special interest had little impact on the incidence of the primary endpoint. Patients with a history of VTE had a higher incidence of the primary endpoint (4.84%) than patients with no history of VTE (0.90%), OR for the composite endpoint for patients with vs. those without a history of VTE was 5.59 (95% CI: 2.53, 11.08). Hence, a history of VTE was the only variable found to have a significant impact on the risk of an event (symptomatic VTE or all-cause death) in a univariate logistic regression analysis at a 5% level.

In total, 38 patients had 40 MBEs during the treatment period. The incidence of MBEs for all patients in the study was 0.72% (95% CI: 0.51%, 0.98%) and was comparable for patients undergoing hip surgery (0.69%, 95% CI: 0.42%, 1.08%) and patients undergoing knee

surgery (0.74%, 95% CI: 0.45%, 1.16%). None of the protocol defined subgroup variables appeared to have a significant effect on occurrence of MBEs based on logistic regression analyses at a 5% level.

The overall incidence of major extra-surgical bleeding events was 0.32% (95% CI: 0.19%, 0.51%). Overall, only 17 major extra-surgical site bleedings were observed. The most common sites for extra-surgical bleeding events were gastrointestinal sites (n=13). A stratified analysis of incidences by protocol-defined subgroups showed there was a more than a 2-fold increase in the odds of major extra-surgical bleeding events for the subgroups of patients with CAD or CHF, for patients with concomitant use of ASA, and for patients within the combined subgroup of CAD, CHF, or history of VTE. The incidence of any bleeding event was 3.82% (95% CI: 3.32%, 4.37%). The most common sites for any bleeding event were the surgical site (n=144) and GI bleedings (n=43). None of the protocol-defined subgroup variables showed a marked effect on the occurrence of any bleeding event and the 95% CIs overlapped across all subgroups.

In summary, dabigatran etexilate administered to patients undergoing hip or knee replacement surgery in accordance with the current European label, in a routine clinical setting, was safe and well tolerated. The pattern of AE reporting was similar to that observed in the corresponding phase III studies. However, the overall incidence of treatment-emergent AEs (which included bleeding events and efficacy outcome events), drug-related AEs, and SAEs was lower. The incidences of any bleeding events were also lower. None of the risk factors appeared to have a significant effect on occurrence of MBEs at a 5% level.

1160-0102 Cohort study in prevention of venous thromboembolic events after orthopaedic surgery in patients treated with Pradaxa: PETRO study [c05079154-04]

Study 1160-0102, a non-interventional PASS conducted to address the safety concern ‘haemorrhage’ (important identified risk), was a cohort study in prevention of venous thromboembolic events after orthopaedic surgery in patients treated with dabigatran etexilate. This study was designed to respond to a request from the French Transparency Committee, dated 16 July 2008 [P10-03367], to follow-up a cohort of patients treated with dabigatran etexilate in France in order to ascertain the characteristics of treated patients, the actual conditions of use of dabigatran etexilate, the frequency of clinical (symptomatic) VTE events, the safety in terms of MBEs and the impact of dabigatran etexilate on the organisation of care. The primary endpoints were the occurrence of symptomatic clinical venous thromboembolic events (primary variable) and MBEs (primary covariate). 2 main subgroups were defined by the type of surgery: TKR or THR. A total of 1676 consecutive patients undergoing either THR (n=929) or TKR (n=747) were recruited.

The incidence of symptomatic VTEs was within the expected range for patients who underwent THR and was slightly higher than that expected in those that underwent TKR from the results from clinical trials but was similar to the range reported in the 2012 American College of Chest Physicians guidelines [P12-02756] and the FOTO study [R09-2242]. This may be due to differences in the percentage of patients who underwent TKR who had a history of VTE, which is a known to be a major risk factor for recurrent symptomatic VTE.

The patients who underwent THR in 1160-0102 had a higher rate of MBEs compared with that in the observational cohort study 1160-0085 (1.7% vs. 0.7%). Noteworthy is that patients aged >75 years were excluded from the 1160-0085 study. This is in contrast to the 1160-0102 study where the observed incidence of MBEs was higher in patients aged ≥75 years than in younger patients (2.9% vs. 1.2%). The observed incidence of MBEs is compatible with the results from clinical trial 1160-0048 for patients who received 220 mg of Pradaxa. The incidences as well as the estimated upper limits of the 95% CI were lower than or equal to the estimated upper limit of the 95% CI in the 1160-0048 trial (220 mg/day). The analyses of the subgroups defined by type of anaesthesia, age, sex and centre activity did not show any differences in the observed incidences.

The observed incidence of MBEs for patients who underwent TKR, was higher in patients aged ≥75 years than in younger patients (1.3% vs. 1.0%). There was a slightly higher rate of MBEs in 1160-0102 compared to the 1160-0085 study (1.1% vs. 0.7%), but patients aged >75 years were excluded from the 1160-0085 study. The observed incidence of MBEs in patients who underwent TKR in 1160-0102 was consistent with that reported for the clinical trial 1160-0025 taking into consideration the 95% CI, the incidences as well as the estimated upper limits of the 95% CIs were lower than or equal to the estimated upper limit of the 95% CI in trial 1160-0025. The rate of MBEs observed in study 1160-0102 was consistent to those observed in other studies (varying from 0.7 in the 1160-0085 study to 2.0 in trial 1160-0048 with 220 mg/day).

In conclusion, the incidence rates of MBEs observed during the study were consistent with those reported in the randomised clinical trials, and therefore were of no major concern.

1160-0118: Observational cohort study to evaluate the safety and efficacy of switching from Lovenox (enoxaparin) 40 mg to Pradaxa (dabigatran etexilate) 220 mg in patients undergoing elective total hip or knee replacement surgery [c03541877-01]

This post-marketing surveillance study was performed to evaluate the safety and efficacy of a switch from enoxaparin 40 mg to Pradaxa 220 mg q.d. for prevention of VTE after elective hip or knee replacement surgery. Due to slower than anticipated recruitment, the study was terminated prematurely. Prior to trial discontinuation, 163 patients had received dabigatran for a median of 36.0 days

Only 1 MBE occurred in 1 patient. There were no occurrences of symptomatic VTE or all-cause mortality in any of the patients during any of the treatment periods. Thus, the estimated incidence for symptomatic VTE or all-cause mortality during switch-/post switch treatment period (i.e. from last enoxaparin administration to last dabigatran administration +24 h) was 0.0% with a 95% CI ranging from 0.00% to 2.24%.

For the 163 patients who received dabigatran during this post-marketing surveillance study, the types of AEs, SAEs, and AEs leading to discontinuation of dabigatran reported were consistent with the known safety profile for dabigatran; incidence of bleeding events was low and, along with results of laboratory and other safety measures, did not raise any new safety

issues for the switch from enoxaparin to dabigatran etexilate in patients undergoing elective hip or knee replacement surgery.

Indication: aVTEt

1160-0188: ChaRactErisation of patients following aCute venous thromboembolism (VTE) and assessment of safety and effectiveness of dabigatran etexilate (DE) in the tReatment and secondarY prevention of acute deep vein thrombosis (DVT) and pulmonary embolism (PE) in comparison to vitamin K antagonist (VKA) in routine clinical practice - RE-COVERY DVT/PE

The RE-COVERY DVT/PE was the first non-interventional, prospective study providing long-term safety and effectiveness outcome data comparing dabigatran with VKA treatment in a large cohort of consecutively enrolled patients with DVT, PE, or both. The incidence rates of major bleeding, CRNMBE, recurrent VTE, life-threatening bleeding, and all-cause mortality were low and consistent with results from pivotal trials. Compared with VKA, the risks of primary safety and effectiveness outcome events among patients receiving dabigatran were lower but not statistically significant based on the 95% CI of the HR. In summary, results from this study were consistent with those from controlled, pivotal trials supporting an effective and favourable safety profile of dabigatran for the treatment and secondary prevention of VTE in the routine clinical practice setting.

SPAF

The following non-interventional studies conducted by BI are presented in ascending order of BI internal clinical study numbers: 1160-0129 (GLORIA-AF), 1160-0136 (GLORIA-AF - Europe), 1160-0157, 1160-0162, 1160-0170, 1160-0183, 1160-0192, 1160-0207, 1160-0204 (RE-CIRCUIT), and 1160-0248 (RESPECT CVT).

GLORIA-AF (1160-0129 and 1160-0136)

GLORIA-AF is a global, multicentre, prospective, non-interventional registry programme including patients newly diagnosed with NVAF and at risk for stroke. The main objectives of GLORIA-AF were to investigate patient characteristics influencing the choice of antithrombotic treatment for the prevention of stroke in patients with AF; and to collect real-world data on important outcome events of antithrombotic treatments for the prevention of stroke.

GLORIA-AF phases II and III were conducted in global regions (study 1160-0129) and with focus on Europe (study 1160-0136). The main study design features within the respective protocols are identical.

GLORIA-AF was conducted in 3 phases:

- Phase I was conducted prior to the availability of non-VKA NOACs and was described elsewhere [c01955897-02]

- Phase II was conducted after the availability of DE. An interim CSR for 1160-0136 (Europe) was submitted to EMA in 2016 [c03697437-01] (a summary of the results is provided in the section below). Phase II was conducted in Asia, Europe, North America, Latin America, and Africa/Middle East. Phase II consisted of a baseline visit for all patients, and 2-year follow-up only for patients treated with DE. In total, 15 644 patients were enrolled. Interim analyses during phase II compared patients beginning treatment with DE or VKA at the baseline visit. These interim analyses were conducted approximately once or twice a year on a regional basis, based on the number of patients enrolled [U11-1638-03].
- Phase III was initiated after regional PS analyses of phase II data indicated that patients prescribed DE or VKA were sufficiently comparable in terms of baseline risk profile [c26500834-01]. Phase III was conducted in Asia, Europe, North America, and Latin America. Patients were followed up for 3 years regardless of antithrombotic therapy treatment status. Patients were required to be newly diagnosed with AF; thus, patients from phase II were not eligible for phase III. The main comparison of interest in phase III was the safety and effectiveness of DE vs. VKAs; this comparison is also the focus of this summary [c34109846-01].

As a non-interventional study, GLORIA-AF included patients who were managed according to the local label and routine clinical practice. No specific antithrombotic treatment was mandated, and no concomitant treatment was withheld. The choice of antithrombotic agent and dosing was according to local clinical practice at the discretion of the treating physician. Per entry criteria, patients were adults newly diagnosed with AF and at risk for stroke.

Phase II results

1160-0129 (Global): Interim results GLORIA-AF: Global Registry on Long-Term Oral Anti-thrombotic TReatment In PAtients with Atrial Fibrillation (Phase II/III); Final Phase II results of two-year outcomes of atrial fibrillation patients on dabigatran [c19461930-01]

At the data cut point of 17 Mar 2017, 15 308 patients were eligible for the final phase II analyses, including 4873 patients prescribed DE and 4859 patients taking DE (i.e. excluding 14 patients prescribed, but that never took a dose of DE). The majority of patients prescribed DE (n=4873) were enrolled in Europe (n=2682, 55.0%), followed by North America (n=843, 17.3%, of which 662 in the US) and Asia (n=655, 13.4%). DE was prescribed in combination with antiplatelet agents for 621 (12.7%) patients. Doses were 150 mg BID (2664, 54.7%), 110 mg BID (2096, 43.0%), 75 mg BID (87, 1.8%), and missing or reported to be other for 26 (0.5%) patients. Mean age was 70.2 ± 10.4 years (150 mg: 66.8 ± 9.5, 110 mg: 74.1 ± 10.0), 44.4% of patients were female (150 mg: 39.8%, 110 mg: 49.5%), stroke risk was high (CHA2DS2-VASc≥2) for 87.9% of patients (150 mg: 83.3%, 110 mg: 93.1%) and bleeding risk was known to be high (HAS-BLED≥3) for 6.8% of patients (150 mg: 5.8%, 110 mg: 7.5%). Patients taking DE (n=4859) had a mean on-treatment exposure time of 18.26±9.22 months; the probability of DE persistence at 2 years was 70.5%. During follow-up, 47 patients presented at least 1 stroke event (ischemic stroke: 31), 70 at least 1 major bleeding event (life-threatening: 33, intracranial: 12, gastrointestinal: 43), 36 at least 1 MI event and 179 died. The incidence rate of stroke was 0.65 events per 100 PY (% PY), 95% CI

0.48-0.87% PY (ischemic stroke: 0.43% PY, CI 0.29-0.61). The incidence rate was 0.97% PY (0.76-1.23) for major bleeding, 0.46% PY (0.32-0.64) for life-threatening bleeding, 0.17% PY (0.09-0.29) for intracranial bleeding and 0.60% PY (0.43-0.80) for gastrointestinal bleeding. The incidence rate was 0.50% PY (0.35-0.69) for MI, 0.07% PY (95% CI 0.02–0.16) for pulmonary embolism, and 2.48% PY (2.13-2.87) for all-cause mortality.

Conclusions: The probability of remaining on dabigatran was high and the incidence rates of stroke and major bleeding were low, confirming the sustained safety and effectiveness of DE over 2 years of follow-up. Results from this study triggered the CCDS update to version 19 (dated 19 Dec 2017) and are included in the CCDS section "Clinical trials".

1160-0136 (Europe): Interim results GLORIA–AF: Global Registry on Long-Term Oral Antithrombotic Treatment in Patients with Atrial Fibrillation (Phase II/III – Europe); Baseline data for all Phase II patients following enrollment completion (GLORIA) [c03697437-01]

Interim data from GLORIA-AF from patients with NVAF at risk for stroke show that NOACs have been highly adopted into practice, becoming more frequently prescribed than VKAs in Europe and North America. In Europe, the majority of the assessed patient population received OACs. Overall, DE treatment and dosing in Europe were generally consistent with EU-SmPC recommendations. Some patients at moderate to high risk of stroke remain untreated or undertreated; e.g. receiving VKA, ASA, or no treatment when a NOAC may be optimal, or are receiving DE 110 when DE 150 could be considered based on the approved SmPC.

Based on the reported baseline data from phase II, there was no impact on the overall DE benefit-risk profile, and no amendment to the Product Information was required. CHMP endorsed the post-authorisation measure EMEA/H/C/000829/MEA/044 on 15 Sep 2016.

Phase III results

The main comparison of interest in phase III was to evaluate the safety and effectiveness of DE vs. VKAs for a 3-year follow-up period. In the following sections, summaries of results from GLORIA-AF are provided separately for study 1160-0129 and 1160-0136. Complete information is provided in the CSRs for 1160-0129 (global results [c28497947-01]) and 1160-0136 (results for EU/EEA Member States, hereafter referred to as Europe) [c31140776-01]).

Analysis sets

Definitions of the analysis sets are provided in the table below. The restricted and matched sets were defined for DE and VKA treatment groups only, for the purpose of comparative analyses.

SVII.Table 21 Patient sets and definitions

Patient set	Patients included
All enrolled sets	All patients entered in the electronic data capture system who signed the informed consent
All eligible set	All patients who were enrolled and eligible (i.e. did not have any important protocol violation(s) related to eligibility criteria as defined in the SEAP and who met certain minimal data cleaning requirements)
Restricted set	All eligible patients within the trimmed patient set which were within the region of PS overlap, by trimming out patients in the non-overlap region. As the PS analysis was based on eligible patients who at least once took the prescribed treatment, the restricted population excluded patients prescribed the treatment who did not take it. The restricted set was defined for DE and VKA patients only. DE and VKA patients were shown to be comparable in Phase II and their comparison was the main focus in Phase III.
Matched set	The patient set used for PS-matched 1:1 pair analysis of DE vs. VKA.

Source: Data on file, Clinical Overview Statement for Pradaxa [c34109846-01], Table 4.1:1

1160-0129 (Global): GLORIA-AF: Global Registry on Long-Term Oral Antithrombotic Treatment in Patients with Atrial Fibrillation (Final Report of Phase III Results) [c34109846-01]

Patient disposition and treatment patterns

- 19 729 patients (92.6% of all enrolled patients) were eligible and treated
- By region, the largest proportion of eligible patients was from Europe (48.4%), followed by North America (24.0%), Asia (19.9%), and Latin America (7.6%)
- The most common antithrombotic treatment among eligible patients was VKA (22.7%), followed by apixaban (Apix) (21.2%), rivaroxaban (Riva) (18.8%), DE (18.0%), ASA (10.2%), edoxaban (Edox) (1.6%), and other antiplatelets (1.0%); and 6.5% of patients were not prescribed any antithrombotic treatment at baseline
- Among 3839 eligible patients who were prescribed DE, the majority (90.2%) were prescribed DE monotherapy, whereas 9.8% of the patients were prescribed DE as combination therapy (defined as DE plus other antithrombotics, with the exception of other NOACs or VKA). Most patients on DE received 150 mg b.i.d. (52.2% of patients), followed by 110 mg b.i.d. (45.0%), and 75 mg b.i.d. (1.4%). 1.3% of the patients received another another dose

Selected important effectiveness and safety outcome data

Incidence rates (95% CI) and frequencies of selected important effectiveness and safety outcome data for the restricted and matched sets are summarised in the table below.

SVII.Table 22 Incidence rates (95% CI) and frequencies of important outcomes – 1160-0129, restricted and matched sets

Outcome	Restricted set				Matched set			
	DE (N = 3611)		VKA (N = 4413)		DE (N = 3326)		VKA (N = 3326)	
	Pts with event, n (PY)	IR/ 100 PY (95% CI)	Pts with event, n (PY)	IR/ 100 PY (95% CI)	Pts with event, n (PY)	IR/ 100 PY (95% CI)	Pts with event, n (PY)	IR/ 100 PY (95% CI)
Composite Outcome	164 (7396)	2.21 (1.88, 2.57)	279 (8646)	3.23 (2.83, 3.62)	155 (6915)	2.24 (1.87, 2.60)	184 (6484)	2.83 (2.41, 3.27)
Vascular Composite Outcome	141 (7409)	1.91 (1.59, 2.24)	227 (8678)	2.62 (2.27, 2.96)	134 (6927)	1.93 (1.59, 2.28)	151 (6506)	2.32 (1.94, 2.74)
Stroke	57 (7425)	0.77 (0.58, 0.97)	83 (8724)	0.95 (0.76, 1.16)	52 (6942)	0.74 (0.55, 0.95)	58 (6541)	0.88 (0.64, 1.13)
MBE	51 (7440)	0.69 (0.51, 0.89)	126 (8696)	1.44 (1.20, 1.70)	49 (6953)	0.70 (0.52, 0.91)	79 (6526)	1.22 (0.93, 1.52)
MI	30 (7449)	0.40 (0.27, 0.55)	46 (8710)	0.53 (0.38, 0.68)	29 (6962)	0.41 (0.26, 0.57)	33 (6528)	0.50 (0.32, 0.69)
All-cause death	161 (7465)	2.16 (1.84, 2.49)	312 (8751)	3.56 (3.18, 3.94)	157 (6976)	2.24 (1.89, 2.59)	209 (6560)	3.18 (2.74, 3.63)
Vascular death	56 (7465)	0.75 (0.56, 0.95)	110 (8752)	1.26 (1.03, 1.50)	71 (6976)	1.02 (0.77, 1.28)	89 (6560)	1.36 (1.07, 1.69)

Source: Data on file, Clinical Overview Statement for Pradaxa [c34109846-01], Table 4.2.2.1: 2.

Composite Outcome included stroke, SE, MI, life-threatening bleeding events, and vascular death.

Vascular Composite Outcome included stroke, SE, MI, and vascular death.

For Composite Outcome and Vascular Composite Outcome, unknown death was imputed by multiple imputation.

The analysis was based on the initial treatment regimen episode.

For Composite Outcome and Vascular Composite Outcome, in case of multiple events for a patient, the first event was considered. For other outcomes, in case of recurrent event for a patient, the first event was considered.

Counts were based on the average of the 20 restricted/matched data sets. The average of the 20 incidence rates from the 20 imputed datasets were used to obtain the point estimate of the incidence rate. The bootstrapping approach was used to obtain the 95% CI of the incidence rate.

Comparative analyses: DE vs. VKA

For the main comparison of DE and VKA, a multivariable Cox regression model (per the study protocol [U11-1638-03]) was performed. Core covariates for each of the outcomes were prespecified in the SEAP and were adjusted for in the multivariable Cox regression analyses. These pre-specified covariates were deemed most relevant based on previous

knowledge particularly from the RE-LY trial as relevant covariates, and were therefore selected as core covariates.

Based on this primary analysis, patients on DE had a reduced risk of Composite Outcome, Vascular Composite Outcome, MBE, and all-cause death. Risks were similar between DE- and VKA-treated patients, for stroke and MI, though point estimates were in favour of DE vs. VKA with 95% CIs including 1.

SVII.Table 23 Multivariable Cox regression analysis of important outcomes – 1160-0129, restricted set

Outcome	**DE (N = 3611)**	**VKA (N = 4413)**	
	Patients with event, n (%)	**Patients with event, n (%)**	**HR(95% CI)**
Composite Outcome	164 (4.5)	279 (6.3)	0.74 (0.60, 0.90)
Vascular Composite Outcome	141 (3.9)	227 (5.2)	0.79 (0.63, 0.98)
Stroke	57 (1.6)	83 (1.9)	0.81 (0.57, 1.14)
MBE	51 (1.4)	126 (2.8)	0.52 (0.38, 0.73)
All-cause death	161 (4.5)	312 (7.1)	0.66 (0.54, 0.80)
MI	30 (0.8)	46 (1.0)	0.97 (0.60, 1.57)

Source: Data on file, Clinical Overview Statement for Pradaxa [c34109846-01], Table 4.2.2.2: 1.
The analysis was based on the initial treatment regimen episode.
Missing or unknown data was imputed using multiple imputation approach.
Counts were obtained by averaging over 20 imputed datasets and rounding.
Cox regression analysis was performed 20 times and the estimates were combined to obtain the final estimates.

Sensitivity analyses

Multiple sensitivity analyses consistently showed a reduced risks of MBE and all-cause death, as well as similar risks of stroke and MI in DE patients compared with VKA.Via usage of the PS, these analysis techniques allowed adjustment for a broader list of covariates as compared with the primary analysis.

For composite outcomes, sensitivity analyses showed similar risk between DE and VKA treated patients, with point estimates remaining in favour of DE but with CIs including 1 (PS adjustment, PS matching, PS matching + unbalanced variables, and different variable selection procedure) (see table below).

Post-hoc analyses

As the pre-specified PS-stratified analysis as per the SEAP method generated unstable HR estimates due to small number of events within individual strata, the analysis method was updated post-hoc to use a Mantel-Haenszel weighting. Strata were defined based on the

pre-specified PS and region. To check for robustness of results, one additional post-hoc PS stratified analysis was implemented for which an extended PS was used.

Common rate ratios, deemed as estimates of HRs, showed reduced risks of MBE and all cause death in DE-treated patients compared with VKA treated patients. Both analyses also showed similar risks of stroke and MI between DE and VKA-treated patients. Thus, results for these outcomes were consistent with the primary and sensitivity analyses.

For the composite outcomes, post-hoc analyses showed similar risks between DE and VKA treated patients, with point estimates in favour of DE and CIs sometimes including 1, as similarly observed in the primary and other sensitivity analyses (see table below).

SVII.Table 24 Sensitivity analyses – restricted and matched patient sets on DE or VKA

	Hazard ratio (95% CI)					
Sensitivity analysis	**Composite outcome**	**Vascular composite outcome**	**Stroke**	**MBE**	**MI**	**All-cause death**
PS adjustment[1]	0.79 (0.65, 0.97)	0.84 (0.67, 1.05)	0.79 (0.56, 1.12)	0.56 (0.40, 0.78)	1.00 (0.61, 1.62)	0.72 (0.59, 0.88)
PS matching[2]	0.80 (0.64, 1.00)	0.84 (0.65, 1.07)	0.85 (0.57, 1.26)	0.59 (0.40, 0.85)	0.84 (0.50, 1.41)	0.71 (0.57, 0.88)
PS matching + unbalanced variables[2,3]	0.85 (0.67, 1.07)	0.90 (0.69, 1.16)	0.89 (0.59, 1.34)	0.61 (0.42, 0.88)	0.89 (0.53, 1.48)	0.78 (0.63, 0.97)
Different variable selection procedure[4]	0.82 (0.67, 1.01)	NA	NA	NA	NA	NA
ITT[5]	0.78 (0.66, 0.92)	NA	NA	NA	NA	NA
Unknown death imputed as vascular cause[6]	0.74 (0.62, 0.89)	0.79 (0.65, 0.96)	NA	NA	NA	NA

SVII.Table 24 (cont'd) Sensitivity analyses – restricted and matched patient sets on DE or VKA

	Hazard ratio (95% CI)					
Sensitivity analysis	**Composite outcome**	**Vascular composite outcome**	**Stroke**	**MBE**	**MI**	**All-cause death**
Unknown death imputed as nonvascular cause[6]	0.74 (0.60, 0.91)	0.79 (0.63, 0.99)	NA	NA	NA	NA
Vascular death replaced with all-cause death[7]	0.71 (0.61, 0.84)	NA	NA	NA	NA	NA

Source: CSR of 1160-0129 [c28497947-01] Table 10.4.1.2: 3

The analyses were based on the initial treatment regimen episode, except for the ITT analysis. Missing or unknown data was imputed using multiple imputation approach. Cox regression analysis was performed 20 times and the estimates were combined to obtain the final estimates.

[1] The model was based on the same main model from the main analysis plus PS as an additional covariate. Analysis was performed on the restricted patient set.

[2] Treatment plus a frailty parameter were considered in the Cox regression model. Analysis was performed on the matched patient set.

[3] The variables of CrCl, previous OAC use, and type of AF were adjusted in the model as their standardized difference >10% in the matched datasets.

[4] Forward likelihood ratio selection procedure based on p-values was used. Analysis was performed on the restricted patient set.

[5] Patients were not censored at permanent discontinuation of initial antithrombotic treatment for stroke prevention. Analysis was performed on the restricted patient set.

[6] Analysis was performed on the restricted patient set.

[7] Composite Outcome was defined as “stroke, SE, MI, life-threatening bleeding events, and all-cause death,” where vascular death was replaced with all-cause death. Analysis was performed on the restricted patient set.

1160-0136: GLORIA-AF – Europe: Global Registry on Long-Term Oral Antithrombotic Treatment in Patients with Atrial Fibrillation (Final Report of Phase III Results for Europe) [c34109846-01]

Patient disposition and treatment patterns

- 9699 patients (94.2% of all enrolled patients) were eligible and treated
- By EU subregion, the majority of eligible patients were from Western Europe (88.9%), as compared with Eastern Europe (11.1%). The study included patients from the following countries: Austria, Belgium, Bulgaria, Croatia, Czech Republic, Denmark, Estonia, France, Germany, Greece, Ireland (Republic), Italy, Latvia, The Netherlands, Norway, Poland, Portugal, Romania, Slovenia, Spain, Switzerland, and the United Kingdom
- The most common antithrombotic treatment among eligible patients was VKA (26.8%), followed by Apix (21.3%), DE (20.1%), Riva (19.5%), ASA (4.9%), Edox (1.7%), and other antiplatelets (0.8%); 4.9% of patients were not prescribed any antithrombotic treatment at baseline
- A total of 2066 eligible patients were prescribed DE. Of those, the majority (93.2%) were prescribed DE monotherapy, whereas 6.8% of the patients were prescribed DE as combination therapy. Most patients on DE received 150 mg b.i.d. (59.6% of patients), followed by 110 mg b.i.d. (39.5%); none of the patients received DE 75 mg b.i.d. 0.8% of the patients received another dose

Selected important effectiveness and safety outcome data

Incidence rates (95% CI) and frequencies of selected important effectiveness and safety outcome data for the restricted and matched sets are summarised in the table below.

SVII.Table 25 Incidence rates (95% CI) and frequencies of important outcomes –1160-0136, restricted and matched sets

Outcome	Restricted set				Matched set			
	DE (N = 1946)		VKA (N = 2509)		DE (N = 1887)		VKA (N = 1887)	
	Pts with event, n (PY)	IR/ 100 PY (95% CI)	Pts with event, n (PY)	IR/ 100 PY (95% CI)	Pts with event, n (PY)	IR/ 100 PY (95% CI)	Pts with event, n (PY)	IR/ 100 PY (95% CI)
Composite Outcome	103 (4465)	2.30 (1.86, 2.73)	155 (5118)	3.02 (2.54, 3.54)	99 (4328)	2.28 (1.85, 2.73)	104 (3832)	2.70 (2.14, 3.29)
Vascular Composite Outcome	86 (4476)	1.91 (1.52, 2.32)	121 (5133)	2.36 (1.93, 2.82)	83 (4338)	1.91 (1.50, 2.33)	82 (3841)	2.14 (1.67, 2.66)
Stroke	29 (4482)	0.64 (0.42, 0.89)	49 (5165)	0.96 (0.70, 1.22)	27 (4344)	0.63 (0.41, 0.87)	36 (3865)	0.93 (0.62, 1.27)
MBE	33 (4488)	0.73 (0.49, 0.98)	73 (5145)	1.42 (1.09, 1.75)	31 (4350)	0.72 (0.48, 0.99)	46 (3856)	1.20 (0.86, 1.58)
MI	15 (4497)	0.34 (0.18, 0.53)	23 (5149)	0.45 (0.27, 0.64)	15 (4357)	0.35 (0.18, 0.53)	18 (3855)	0.46 (0.26, 0.67)
All-cause death	94 (4503)	2.08 (1.69, 2.51)	170 (5178)	3.27 (2.80, 3.77)	91 (4363)	2.09 (1.67, 2.52)	115 (3877)	2.96 (2.40, 3.59)

Source: Data on file, Clinical Overview Statement for Pradaxa [c34109846-01], Table 4.3.2.1: 2.

Composite Outcome included stroke, SE, MI, life-threatening bleeding events, and vascular death.

Vascular Composite Outcome included stroke, SE, MI, and vascular death.

For Composite Outcome and Vascular Composite Outcome, unknown death was imputed by multiple imputation.

The analysis was based on the initial treatment regimen episode.

For Composite Outcome and Vascular Composite Outcome, in case of multiple events for a patient, the first event was considered. For other outcomes, in case of recurrent event for a patient, the first event was considered.

Counts were based on the average of the 20 restricted/matched data sets. The average of the 20 incidence rates from the 20 imputed datasets were used to obtain the point estimate of the incidence rate. The bootstrapping approach was used to obtain the 95% CI of the incidence rate.

Comparative analyses: DE vs. VKA

For the main comparison of DE and VKA, a multivariable Cox regression model (per the study protocol [c01951554-12]) was performed. Core covariates for each of the outcomes were prespecified in the SEAP and were adjusted for in the multivariable Cox regression analyses. The prespecified core covariates were deemed most relevant based on previous knowledge particularly from the RE-LY trial.

Based on this primary analysis, patients on DE had a reduced risk of MBE compared with patients on VKA (see table below). The risks of other outcomes were similar between DE- and VKA-treated patients, though point estimates were in favour of DE vs. VKA with 95% CIs including 1.

SVII.Table 26 Multivariable Cox regression analysis of important outcomes – 1160-0136, restricted set

Outcome	**DE (N = 1946)**	**VKA (N = 2509)**	
	Patients with event, n (%)	**Patients with event, n (%)**	**HR (95% CI)**
Composite Outcome	103 (5.3)	155 (6.2)	0.83 (0.64, 1.08)
Vascular Composite Outcome	86 (4.4)	121 (4.8)	0.94 (0.70, 1.27)
Stroke	29 (1.5)	49 (2.0)	0.68 (0.43, 1.09)
MBE	33 (1.7)	73 (2.9)	0.58 (0.38, 0.88)
All-cause death	94 (4.8)	170 (6.8)	0.78 (0.60, 1.01)
MI	15 (0.8)	23 (0.9)	0.95 (0.49, 1.84)

Source: Data on file, Clinical Overview Statement for Pradaxa [c34109846-01], Table 4.3.2.2: 1.

The analysis was based on the initial treatment regimen episode.

Abnormal kidney disease was excluded from core covariates for Cox model as there was no patient with abnormal kidney disease history.

Missing or unknown data was imputed using the multiple imputation approach.

Counts were obtained by averaging over 20 imputed datasets and rounding.

Cox regression analysis was performed 20 times and the estimates were combined to obtain the final estimates.

Sensitivity analyses

Sensitivity analyses based on multivariable Cox regression for the Composite Outcome showed HRs of 0.88 (95% CI: 0.70, 1.10) and 0.74 (95% CI: 0.60, 0.91) as determined by ITT approach and by replacing vascular death with all-cause death, respectively.

Post-hoc analyses

To check for robustness of results, one additional post-hoc PS-stratified analysis as implemented for the global data set (1160-0129) was used.

Common rate ratios, deemed as estimates of HRs, showed reduced risks of MBE and all-cause death in DE-treated patients compared with VKA-treated patients. For other outcomes, similar risks between DE- and VKA-treated patients were generally observed, with point estimates in favour of DE and CIs including 1. With the exception of all-cause death, for which the 95% CI included 1 in the primary analysis, results for all selected outcomes based on these post-hoc analyses are consistent with those of the primary analysis.

For the composite outcomes, post-hoc analyses showed similar risks between DE-and VKA-treated patients, with point estimates in favour of DE and CIs sometimes including 1, as similarly observed in the primary and other sensitivity analyses.

SVII.Table 27 Common rate ratios by PS stratification – restricted patient set on DE or VKA

	Rate ratio (95% CI)	
Outcome	**PS stratification[1]**	**PS stratification with extended PS[2, 3]**
Composite outcome	0.86 (0.66, 1.11)	0.83 (0.64, 1.08)
Vascular composite outcome	0.92 (0.69, 1.23)	0.91 (0.68, 1.21)
Stroke	0.69 (0.43, 1.09)	0.68 (0.43, 1.06)
MBE	0.57 (0.37, 0.89)	0.53 (0.34, 0.83)
MI	0.92 (0.50, 1.72)	0.84 (0.44, 1.60)
All-cause death	0.71 (0.55, 0.92)	0.77 (0.59, 0.99)

[1] Average number of patients in the restricted dataset: DE, N = 1946; VKA, N = 2509.
[2] Additional variables adjusted for were concomitant antiplatelet use, NSAID use, previous OAC use, CrCl, and type of AF.
[3] Average number of patients in the updated restricted dataset: DE, N = 1904; VKA, N = 2468.
Composite outcome considered stroke, SE, MI, life-threatening bleeding events, and vascular death.
Vascular composite outcome considered stroke, SE, MI, and vascular death.
Note: Common rate ratios were deemed as estimates of HRs.
Source: Data on file, CSR 1160-0136 [c31140776-01], Table 10.5.3: 1.

GLORIA-AF phase III Europe (1160-0136), in the context of GLORIA-AF phase III Global (1160-0129) [c34109846-01]

The 1160-0136 (Europe) population was a subset of patients from the global GLORIA-AF phase III study 1160-0129.

In study 1160-0136 (Europe), clinically relevant findings were observed in comparative analyses, although the treatment groups (restricted set: DE, N=1946; VKA, N=2509) were smaller than in the global analyses (restricted set: DE, N=3611, VKA=4412). In the 1160-0136 study, the primary analysis showed reduced risk of MBE in DE-treated patients compared with VKA-treated patients, consistent with the 1160-0129 global results. The risk

of all-cause death and composite outcomes were reduced in the study 1160-0129, but not in study 1160-0136, as determined by the primary analysis, though point estimates were consistently in favour of DE vs VKA. It is noteworthy that post-hoc analyses for 1160-0136 showed reduced risk of all-cause death. The 1160-0136 study showed a similar risk of stroke, all-cause death, MI, Composite Outcome and Vascular Composite Outcome between DE- and VKA-treated patients; however point estimates were in favour of DE vs. VKA and 95% CIs included 1.

Conclusion

The final analysis of GLORIA-AF phase III provides long-term prospective data of a large cohort of consecutive, newly diagnosed patients with AF who were at risk for stroke and were treated in routine clinical practice. The main comparison of interest in phase III of GLORIA-AF was to evaluate the safety and effectiveness of DE vs. VKAs in patients with AF for a 3-year follow-up period. GLORIA-AF findings reinforce a favourable benefit-risk profile for DE compared with VKA in routine clinical practice among patients with newly diagnosed AF.

1160-0139: A regulatory requirement non-interventional study to monitor the safety and effectiveness of Pradaxa (Dabigatran etexilate mesilate, 110 mg or 150 mg b.i.d.) in Korean patients with non-valvular atrial fibrillation (SPARK: Safety study of Pradaxa in AF patients by Regulatory requirement of Korea) [c21807097-02]

The primary objective of this PASS was to monitor the safety profile of Pradaxa in Korean patients with non-valvular AF in a routine clinical setting. 3053 patients were included in the safety assessment and 2311 patients in the efficacy assessment. During the study period, 126 SAEs were reported in 104 (3.41%) patients. Classifying the SAEs by SOC, the most common SAEs were from the SOC ‘Nervous system disorders’ in 1.08% of the subjects, followed by ‘Cardiac disorders’ in 0.59% and ‘Gastrointestinal disorders’ in 0.39% of the patients. By PT, the most common SAE was ‘Cerebral infarction’ in 0.36% of patients, followed by ‘Transient ischaemic attack’ in 0.23% and ‘Atrial fibrillation’ in 0.20% of patients. Of these, 32 events from 27 (0.88%) patients were serious AEs whose causality to the drug could not be ruled out.

648 unexpected AEs were reported from 508 (16.64%) patients. Classifying the unexpected AEs by SOC, the most common unexpected AEs were from the SOC ‘Gastrointestinal disorders’ in 5.73% of patients, followed by ‘Nervous system disorders’ in 2.85% and ‘General disorders and administration site conditions’ in 2.00% of patients.

Of these, 240 events from 217 (7.11%) patients were unexpected ADRs whose causality to the drug could not be ruled out. Classifying the unexpected ADRs by SOC, the most common unexpected ADRs were from the SOC ‘Gastrointestinal disorders’ in 4.62% of patients, followed by ‘Nervous system disorders in’ 0.92% and ‘General disorders and administration site conditions’ in 0.79% of the patients. By PT, the most common unexpected ADR was ‘Gastrointestinal disorder’ in 2.72% of patients, followed by ‘Abdominal pain upper in 0.82% of patients and ‘Abdominal discomfort’ in 0.46% of patients.

During this surveillance period, 82 unexpected SAEs were reported in 70 patients (2.29%). The most common unexpected SAEs were from the SOC 'Cardiac disorders' in 0.52% of patients, followed by 'Infections and infestations' in 0.36% and 'Nervous system disorders' in 0.29% of patients. By PT, the most common unexpected SAE was 'Atrial fibrillation' in 0.20% of patients, followed by 'Dyspnoea' and 'Cellulitis' each occurring in 0.10% of patients and 'Acute kidney injury', 'Back pain', and 'Chronic obstructive pulmonary disease' each occurring in 0.07% of patients.

Of these, 10 events from 8 (0.26%) patients were unexpected SAEs whose causality to the drug could not be ruled out (i.e. serious ADRs). By PT, the most common serious ADRs were 'Acute kidney injury', 'Bursitis', and 'Arterial rupture' each occurring in 1 patient.

The efficacy assessment was conducted by calculating the frequency and percentage of patients experiencing stroke or systemic embolism among those on Pradaxa for 12 weeks or longer since the 1st visit. Of the patients on Pradaxa for 12 weeks or longer from the 1st visit (ordinary surveillance), stroke occurred in 0.30%, with no patient experiencing systemic embolism. Of the patients on Pradaxa for 24 weeks or longer from the 1st visit (long term administration), stroke occurred in 0.36%, with no patient experiencing systemic embolism.

The conclusion from this Pradaxa PMS study results showed no abnormal tendencies compared to previously reported AE incidences and no specific issues that could affect safety and efficacy. Therefore, it is considered that administration of Pradaxa to reduce the risk of stroke and systemic embolism in Korean patients with NVAF is safe and effective, and the use of the drug will continue to be monitored through spontaneous reports.

1160-0157: Comparative Effectiveness of Oral Anticoagulants: A Cohort Study [c02409758-01]

This study, which was completed in 2014, was the first part of a long-term study programme with Brigham and Women's Health to assess comparative safety and effectiveness of Pradaxa in the real world. This programme uses 2 large commercial US health insurance databases and propensity score matching to compare new users of dabigatran and warfarin with respect to ischaemic and bleeding events, with several planned interim analyses.

The first analysis included only 1 database (United Health Research Database). Following propensity score matching, new users of dabigatran and warfarin were compared to assess pre-specified stroke and bleeding events. 4158 patients were identified with NVAF and CHA2DS2-VASc scores ≥1 who initiated dabigatran, and 7724 patients who initiated warfarin from October 2010 – June 2012.

Propensity scores including known risk factors for the outcomes of interest produced matched groups with nearly identical characteristics: 2991 dabigatran initiators with 1237 PY follow-up and 2991 warfarin initiators with 950 PY follow-up. Average age was 63 years and 9% had a recent stroke. Follow-up ended at anticoagulant discontinuation, study event, or insurance disenrolment. Warfarin initiators discontinued earlier and more frequently. There

were 36 strokes among dabigatran users vs. 30 among warfarin users (Cox HR=1.05, 95% CI: 0.64, 1.70), along with 74 major bleedings among dabigatran users vs. 63 in warfarin users (HR=0.97, 0.69, 1.36).

These first feasibility results are limited by the small sample size, short follow-up and few events resulting in wide 95% CIs. No comparative conclusions on the safety and effectiveness of Pradaxa in clinical practice can be drawn at this stage due to limited sample size and observation time. After this feasibility analysis future data in the context of the subsequent protocol (study 1160-0207) will increase the number of patients and potential follow-up and also expand to additional data sources (Marketscan). The study results have been submitted to the EMA (procedure number EMEA/H/C/000829/II/0092).

1160-0162: An observational study assessing the management of gastrointestinal and urogenital bleeding events in patients with atrial fibrillation treated with dabigatran etexilate [c14372587-01]

1160-0162 was an observational study with the main objective to assess the clinical characteristics of GI and GU bleeding events in patients with NVAF taking dabigatran etexilate who present to Eds/Ers for management of such events. This study additionally collected information to describe the diagnostic evaluations and treatments provided to resolve these events, and the clinical outcomes of these events. The study was initiated and conducted prior to registration of the specific reversal agent of dabigatran.

Patients who presented to the ED/ER (index visit) with an acute GI and/or GU bleeding event (index event) at one of the participating study sites between 28 Oct 2010 and 01 Aug 2013 (eligibility period) were included in the chart review.

Site staff from 44 clinical sites collected data from the medical charts of 220 patients. The mean age (SD) of patients was 76.1 years (10.3) and 108 were female (49%). Of patients with known date of AF diagnosis (n=119), 99 (83.2%) were diagnosed with AF ≥6 months prior to ED/ER visits for the index bleeding events. 84 patients (38.3%) were taking one or more medications known to increase the risk of bleeding within 5 days prior to ED presentation.

Anatomic locations of the bleedings are described below by type of bleeding event; bleeding appearing in multiple locations was possible: n=4 patients (1.8%) had both GI and GU bleeding.

- GI bleeding: n=161 (73.2%)
    - Upper GI bleedings: 34 (15.5%)
    - Lower GI bleedings: 101 (45.9%)
    - Location unknown: 28 (12.7%)
- GU bleeding: n=63 (28.6%)

Overall, 127 patients had 228 diagnostic and evaluation procedures during their index visits, including endoscopy (n=50, 21.9%), colonoscopy (n=49, 21.5%), and FOBT/DRE (n=43, 18.9%).

For most patients (n=170, 77.3%), at least one intervention was documented in the charts, while 50 patients (22.7%) received no intervention to treat their bleeding events. The most common intervention was discontinuation of dabigatran (n=157, 71.4%) followed by transfusion/infusion (n=81, 36.8%, predominantly packed red blood cell transfusions: n=60/81, 74.1%). 3030 (13.6%) patients had medications documented in their medical record considered to have been used to treat the bleeding event. Those medications included proton pump inhibitors (PPIs, 25 patients, all with GI bleed), vitamin K (n=7), H2 antagonists (n=1), and factor concentrate (n=1). Surgery was reported for 15 patients (6.8%) and therapeutic procedures (e.g. colonoscopy) for 21 patients (9.5%). The mean duration of index visit was 7.6 hours (SD: 8.5). 148 (67.3%) patients were admitted to the hospital with a mean duration of stay of 5.7 days (SD: 6.6). 14 patients had a revisit beyond 7 days following the index discharge.

At the time of index discharge, 169 (76.8%) patients had their bleeding events resolved, 42 patients still had some symptoms of bleeding and their bleeding was classified as ongoing (19.1%), 9 (4.1%) patients had died. Primary causes of death were index event (n=1), sepsis (n=2), congestive heart failure (n=2), cancer (n=1), cardiac arrest (n=2), and ischaemic bowel (n=1).

As specified in the protocol, all adverse events, including the index GI/GU bleeding event leading to the enrolment of the patient, were considered. Overall, 651 AEs were documented in the medical charts for the 220 patients. Of those, 395 were considered serious, occurring in 184 patients (83.6%), while the remaining 256 were considered non-serious, occurring in 136 patients (61.8%). 11 patients (5.0%) had 14 fatal adverse events; 9 died during the index hospitalisation and 2 died beyond the end of individual patient's study period but before date of site close-out dates.

In these analyses based on 1034 patients (627 exposed to dabigatran), bleeding in patients receiving dabigatran was managed with comparable or superior effectiveness and lower 30-day mortality rates, as compared to bleeding in patients receiving warfarin.

The sample size (220 patients) and availability of data in the patients' ED/ER medical charts do not allow either for conclusions on the appropriateness of the measures taken to manage the bleeding events or for the assessment of their effectiveness. There is limited clinical knowledge to characterise the bleeding events and the rationale for treatment. However, it provides first insights into the characteristics of patients in the real-world setting in North America and on the treatment approaches prior to idarucizumab availability.

1160-0170: Use of Pradaxa (dabigatran etexilate) for stroke prevention in patients with NVAF and mild to moderate renal impairment [c02155743-03]

The aim of this cross-sectional, multicentre non-interventional study was to gain knowledge of the risk profile of patients in Germany with mild to moderate renal impairment who are intended to be treated with Pradaxa and to analyse the prescribing patterns of doctors in reference to this patient subpopulation. The primary endpoint was the CrCl at the prescription

time point according to the Cockcroft-Gault formula (re-calculated using age, gender, body weight, and serum creatinine as documented in the case report form). All analyses were descriptive. Overall, 4340 patients were observed at the point in time of Pradaxa prescription, i.e. before start of treatment.

More than half of the patients (N=2220; 51.2%) were excluded from the per protocol analysis since they did not meet the pre-defined inclusion criteria of documented NFAV (1042 patients [24.0%]) or mild or moderate renal impairment as assessed by the clinical judgment of the physician (1668 patients (38.4%)). 25 patients (0.6 %) were documented as suffering from severe renal impairment as assessed by the clinical judgment of the physician.

120 patients (2.8%) were documented as suffering from valvular AF. With regard to the primary endpoint of the NIS, the median CrCl of the patients was 55.2 (43.6; 68.3) mL/min. 226 (10.7%) patients had no renal impairment, 1003 (47.3%) patients had a mild degree of renal impairment, in 653 patients (30.8%) the renal impairment was moderate, and in 93 (4.4%) patients the renal impairment was documented as severe based on the re-calculated CrCl according to the Cockcroft-Gault formula. With regard to the primary endpoint, physicians predominantly prescribed Pradaxa to patients with mild renal impairment as assessed by re-calculated CrCl according to the Cockcroft-Gault formula. The study results have been disclosed on clinicaltrials.gov under the identifier NCT01721837.

The results of this local (German) observational study showed understanding of the importance of RF in Pradaxa therapy but insufficient appreciation of the role of the Cockcroft-Gault formula for optimal assessment of RF, due to the following:

- Percentage of renal contraindications: 22 out of 4340 patients (0.5% - all patient set) and 12 out of 2120 patients (0.6% - per protocol set) had a documented CrCl according to Cockcroft-Gault <30 ml/min
- Percentage of documented serum creatinine: in 4061 out of 4340 patients (93.6% - all patient set) and in 2065 out of 2120 patients (97.4% - per protocol set) serum creatinine was documented
- Percentage of documented CrCl according to Cockcroft-Gault: in 1917 out of 4340 patients (44.2% - all patient set) and in 1134 out of 2120 patients (53.5% - per protocol set) CrCl according to Cockcroft-Gault was documented

Subsequently, BI has proactively reviewed all training and educational materials concerning correct usage of Pradaxa and has confirmed that the assessment of renal status (measured according to Cockcroft-Gault) is emphasised in training, e.g. for sales representatives. Future clinical trials will include a measurement of RF using Cockcroft-Gault prior to enrolment.

1160-0183: The Comparative Safety and Effectiveness of Warfarin and Dabigatran Utilized in the Department of Defense (DoD) Non-Valvular Atrial Fibrillation (NVAF) Patient Population-A Retrospective Database Analysis [c03493519-01]

1160-0183 aimed to assess the safety and effectiveness of dabigatran compared to warfarin in patients diagnosed with NVAF in the Department of Defense population. The study included

treatment-naïve patients aged 18-89 years, with first prescription claim for dabigatran (either FDA-approved dose) or warfarin between 01 Oct 2010 and 31 Jul 2012 (index date) and a diagnosis of NVAF during the 12 months before index date. 12 793 patients per treatment group (dabigatran or warfarin) following PSM were analysed. The dabigatran group experienced fewer strokes (adjusted HR [95% CIs] of 0.73 [0.55, 0.97]); hemorrhagic strokes (0.32 [0.14, 0.73]); major intracranial bleeding (0.49 [0.30, 0.79]); major urogenital (0.36 [0.18, 0.74]) and other (0.38 [0.22, 0.66]) bleeding; Mis (0.65 [0.45, 0.95]); and deaths (0.64 [0.55, 0.74]) than the warfarin group. Major lower gastrointestinal bleeding events were more frequent (1.30 [1.04, 1.62]) in the dabigatran group.

The overall results of this study comparing the effectiveness and safety of dabigatran and warfarin in a large population of patients in clinical practice are consistent with those of the RE-LY randomised clinical trial. Compared with warfarin, dabigatran treatment was associated with fewer events across most outcomes measured, including stroke, major bleeding, MI, and death, but more frequent GI bleeding.

A supplemental analysis consisting of only patients taking dabigatran 150 mg at index date led to overall similar results, although with lowered statistical power. The fewer patients in this subset analysis were overall younger and healthier than the patients in the original analysis, and fewer outcome events were observed. The subset analysis also had slightly less follow-up time for the dabigatran patients due to ending follow-up if and when they started taking 75 mg dabigatran.

1160-0192: The Comparative Safety and Effectiveness of Warfarin and Dabigatran Utilized in the Humana Non-Valvular Atrial Fibrillation Patient Population – A Retrospective Database Analysis [c16197989-01]

1160-0192 is a non-interventional study based on existing data was conducted including OAC-naïve new dabigatran (75 mg or 150 mg capsules administered orally, b.i.d.) or warfarin (1 to 10 mg tablets administered orally) users. Propensity score matching was used to control for channelling bias. Patients were followed-up until treatment discontinuation, switch to another OAC, disenrollment, end of the observation period, or death.

A total of 7245 dabigatran and 14 490 warfarin users remained after PSM 1:2. Post-PSM dabigatran and warfarin cohorts showed no significant differences in baseline demographic characteristics. After PSM, dabigatran and warfarin users had mean (SD) ages of 73.9 (8.0) years and 74.0 (8.1) years, respectively, the proportion of males in both cohorts was 55.6% and the proportion of females in both cohorts was 44.4%. Comorbidity risk scores, stroke risk, and bleeding risk scores were not significantly different. Mean durations of follow up for dabigatran and warfarin patients were 207 and 224 days, respectively.

In the primary analysis of the primary outcomes, rates per 1000 PY of stroke (21.9 vs. 29.3, p=0.0111) and major bleeding (61.7 vs. 76.7, p=0.0011) were significantly lower in the dabigatran cohort compared to the warfarin cohort (SVII.Table 28). Similarly, based on HRs adjusted for covariates, risks for stroke (0.74, p=0.0149) and major bleeding (0.80, p=0.0023) were lower in the dabigatran cohort.

In the primary analysis of secondary outcomes, rates per 1000 PY of hemorrhagic stroke (1.5 vs. 4.4, p=0.0068), major extracranial bleeding (54.4 vs. 66.1, p=0.0055), venous thromboembolism (12.2 vs. 23.0, p<0.0001), and all-cause death (36.6 vs. 49.8, p=0.0004) were significantly lower in the dabigatran cohort (SVII.Table 28). Rates per 1000 PY of ischaemic stroke (21.7 vs. 26.4, p=0.0808), major intracranial bleeding (8.0 vs. 11.3, p=0.0749), TIA (10.7 vs. 13.0, p=0.261) and MI (13.6 vs. 16.1, p=0.2665) were not significantly different between the dabigatran and warfarin cohorts (SVII.Table 28). Based on HRs adjusted for covariates, lower risks for haemorrhagic stroke (0.32, p=0.0097), major extracranial bleeding (0.82, p=0.0108), venous thromboembolism (0.52, p<0.0001), and all-cause death (0.73, p=0.001) were observed in the dabigatran cohort. For ischaemic stroke, TIA and MI, the risk were lower though not statistically significant (p=0.081, 0.261, 0.267 respectively). In a post-hoc analysis that measured outcomes using an algorithm to define the principal diagnosis (the primary analysis used diagnosis codes in all service lines of medical claims in a hospitalisation, which could result in identification of multiple outcomes within a single hospitalisation), rates of stroke per 1000 PY were not significantly different between dabigatran and warfarin cohorts (12.4 vs. 16.1, p=0.0861, (SVII.Table 29). However, rates of major bleeding per 1000 PY were significantly lower in the dabigatran cohort compared to the warfarin cohort (35.6 vs. 46.9, p=0.0019, SVII.Table 29). Based on HRs adjusted for covariates, lower risk for major bleeding (0.75, p=0.0028) was observed in the dabigatran cohort compared to the warfarin cohort. There was no statistically significant difference in the risk for stroke (0.76, p=0.0904) in the dabigatran cohort compared to the warfarin cohort.

In the post-hoc analysis of secondary outcomes, rates per 1000 PY of hemorrhagic stroke (1.2 vs. 3.3, p=0.0271), major intracranial bleeding (4.4 vs. 8.6, p=0.0072), major extracranial bleeding (31.2 vs. 38.3, p=0.0284), and death (36.6 vs. 49.8, 0.0004) were significantly lower in the dabigatran cohort compared to warfarin cohort (SVII.Table 29). Rates per 1000 PY of ischaemic stroke (11.2 vs. 12.9, p=0.3502), TIA (3.4 vs. 4.4, p=0.4407) and MI (8.0 vs. 7.5, p=0.8017) were not significantly different between the dabigatran and warfarin cohorts (SVII.Table 29). Based on HRs adjusted for covariates, lower risks for hemorrhagic stroke (0.36, p=0.0366), major intracranial bleeding (0.50, p=0.0082), major extracranial bleeding (0.81, p=0.0394), and death (0.73, p=0.0007) were observed in the dabigatran cohort.

Similarly, for ischaemic stroke and TIA, the risks were lower though not statistically significant (p=0.350, 0.441, respectively).

SVII.Table 28 Incidence of Primary and Secondary Outcomes for Dabigatran vs. Warfarin (Primary Analysis)

Measure	Dabigatran N=7245	Warfarin N=14 490	p-value*
Primary Outcomes			
Stroke	90 (1.2%)	261 (1.8%)	0.0021
Rate per 1000 PY (95% CI)	21.9 (17.4, 26.5)	29.3 (25.7, 32.9)	0.0111
Major bleeding	253 (3.5%)	683 (4.7%)	0.0001
Rate per 1000 PY (95% CI)	61.7 (54.1, 69.3)	76.7 (70.9, 82.4)	0.0011
Secondary Outcomes			
Ischaemic Stroke	89 (1.2%)	235 (1.6%)	0.0241
Rate per 1000 PY (95% CI)	21.7 (17.2, 26.2)	26.4 (23.0, 29.8)	0.0808
Hemorrhagic Stroke	<10	39 (0.3%)	0.0044
Rate per 1000 PY (95% CI)	1.5 (0.3, 2.6)	4.4 (3.0, 5.8)	0.0068
Major intracranial bleeding	33 (0.5%)	101 (0.7%)	0.032
Rate per 1000 PY (95% CI)	8.0 (5.3, 10.8)	11.3 (9.1, 13.6)	0.0749
Major extracranial bleeding	223 (3.1%)	589 (4.1%)	0.0003
Rate per 1000 PY (95% CI)	54.4 (47.2, 61.5)	66.1 (60.8, 71.5)	0.0055
Major GI bleeding	182 (2.5%)	392 (2.7%)	0.4023
Rate per 1000 PY (95% CI)	44.4 (37.9, 50.8)	44.0 (39.7, 48.4)	0.907
Major upper GI bleeding	27 (0.4%)	80 (0.6%)	0.0748
Rate per 1000 PY (95% CI)	6.6 (4.1, 9.1)	9.0 (7.0, 10.9)	0.1534
Major lower GI bleeding	178 (2.5%)	381 (2.6%)	0.4488
Rate per 1000 PY (95% CI)	43.4 (37.0, 49.8)	42.8 (38.5, 47.1)	0.9573

SVII.Table 28 (cont'd) Incidence of Primary and Secondary Outcomes for Dabigatran vs. Warfarin (Primary Analysis)

Measure	Dabigatran N=7245	Warfarin N=14 490	p-value*
Secondary Outcomes			
Major urogenital bleeding	24 (0.3%)	108 (0.7%)	0.0002
Rate per 1000 PY (95% CI)	5.8 (3.5, 8.2)	12.1 (9.8, 14.4)	0.0006
Major other bleeding	52 (0.7%)	162 (1.1%)	0.0048
Rate per 1000 PY (95% CI)	12.7 (9.2, 16.1)	18.2 (15.4, 21.0)	0.0185
TIA	44 (0.6%)	116 (0.8%)	0.1162
Rate per 1000 PY (95% CI)	10.7 (7.6, 13.9)	13.0 (10.7, 15.4)	0.261
Myocardial infarction	56 (0.8%)	143 (1.0%)	0.1185
Rate per 1000 PY (95% CI)	13.6 (10.1, 17.2)	16.1 (13.4, 18.7)	0.2665
Venous thromboembolism	50 (0.7%)	205 (1.4%)	<.0001
Rate per 1000 PY (95% CI)	12.2 (8.8, 15.6)	23.0 (19.9, 26.2)	<.0001
Deep Vein Thrombosis	39 (0.5%)	142 (1.0%)	0.0007
Rate per 1000 PY (95% CI)	9.5 (6.5, 12.5)	15.9 (13.3, 18.6)	0.0023
Pulmonary Embolism	14 (0.2%)	81 (0.6%)	<.0001
Rate per 1000 PY (95% CI)	3.4 (1.6, 5.2)	9.1 (7.1, 11.1)	0.0003
Death	150 (2.1%)	444 (3.1%)	<.0001
Rate per 1000 PY (95% CI)	36.6 (30.7, 42.4)	49.8 (45.2, 54.5)	0.0004

*p-value for n/% is from chi-square test
Source: [c16197989-01]

SVII.Table 29 Incidence of Primary and Secondary Outcomes for Dabigatran vs. Warfarin (Post-hoc Analysis)

Measure	Dabigatran N=7245	Warfarin N=14 490	p-value*
Primary Outcomes			
Stroke	51 (0.7%)	143 (1.0%)	0.0365
Rate per 1000 PY (95% CI)	12.4 (9.0, 15.8)	16.1 (13.4, 18.7)	0.0861
Major bleeding	146 (2.0%)	418 (2.9%)	0.0001
Rate per 1000 PY (95% CI)	35.6 (29.8, 41.4)	46.9 (42.4, 51.4)	0.0019
Secondary Outcomes			
Ischaemic Stroke	46 (0.6%)	115 (0.8%)	0.1983
Rate per 1000 PY (95% CI)	11.2 (8.0, 14.5)	12.9 (10.6, 15.3)	0.3502
Hemorrhagic Stroke	<10	29 (0.2%)	0.0211
Rate per 1000 PY (95% CI)	1.2 (0.2, 2.3)	3.3 (2.1, 4.4)	0.0271
Major intracranial bleeding	18 (0.2%)	77 (0.5%)	0.0029
Rate per 1000 PY (95% CI)	4.4 (2.4, 6.4)	8.6 (6.7, 10.6)	0.0072
Major extracranial bleeding	128 (1.8%)	341 (2.4%)	0.005
Rate per 1000 PY (95% CI)	31.2 (25.8, 36.6)	38.3 (34.2, 42.3)	0.0284
Major GI bleeding	117 (1.6%)	256 (1.8%)	0.4165
Rate per 1000 PY (95% CI)	28.5 (23.4, 33.7)	28.7 (25.2, 32.3)	0.8208
Major upper GI bleeding	22 (0.3%)	61 (0.4%)	0.1862
Rate per 1000 PY (95% CI)	5.4 (3.1, 7.6)	6.8 (5.1, 8.6)	0.3055
Major lower GI bleeding	97 (1.3%)	202 (1.4%)	0.7418
Rate per 1000 PY (95% CI)	23.6 (18.9, 28.3)	22.7 (19.6, 25.8)	0.8465
Major urogenital bleeding	<10	40 (0.3%)	<.0001
Rate per 1000 PY (95% CI)	0.2 (0.0, 0.7)	4.5 (3.1, 5.9)	<.0001
Major other bleeding	11 (0.2%)	52 (0.4%)	0.0074
Rate per 1000 PY (95% CI)	2.7 (1.1, 4.3)	5.8 (4.3, 7.4)	0.0138
Transient Ischaemic Attack	14 (0.2%)	39 (0.3%)	0.2847
Rate per 1000 PY (95% CI)	3.4 (1.6, 5.2)	4.4 (3.0, 5.8)	0.4407
Myocardial infarction	33 (0.5%)	67 (0.5%)	0.9435
Rate per 1000 PY (95% CI)	8.0 (5.3, 10.8)	7.5 (5.7, 9.3)	0.8017
Venous thromboembolism	<10	31 (0.2%)	0.1457
Rate per 1000 PY (95% CI)	2.2 (0.8, 3.6)	3.5 (2.3, 4.7)	0.2083
Deep Vein Thrombosis	<10	12 (0.1%)	0.4793
Rate per 1000 PY (95% CI)	1.0 (0.0, 1.9)	1.3 (0.6, 2.1)	0.5331

* p-value for n/% is from chi-square test

Source: [c16197989-01]

SVII.Table 29 (cont'd) ''Incidence of Primary and Secondary Outcomes for Dabigatran vs. Warfarin (Post-hoc Analysis)

Measure	Dabigatran N=7245	Warfarin N=14 490	p-value*
Pulmonary Embolism	<10	19 (0.1%)	0.1937
Rate per 1000 PY (95% CI)	1.2 (0.2, 2.3)	2.1 (1.2, 3.1)	0.2646
Death	150 (2.1%)	444 (3.1%)	<.0001
Rate per 1000 PY (95% CI)	36.6 (30.7, 42.4)	49.8 (45.2, 54.5)	0.0004

* p-value for n/% is from chi-square test

Source: [c16197989-01]

Safety and efficacy of dabigatran compared to warfarin in treatment of patients with NVAF have been studied previously. The RE-LY trial found that dabigatran administered at a dose of 110 mg b.i.d. was associated with similar rates of stroke and systemic embolism as warfarin, as well as lower rates of major bleeding [P09-11669]. However, the 150 mg dose of dabigatran was associated with lower rates of stroke and systemic embolism, but similar rates of major bleeding compared to warfarin [P09-11669].

Final results from 1160-0207: Safety and effectiveness of dabigatran and warfarin in routine care of patients with atrial fibrillation [c25839310-01]

Study 1160-0207 has been completed and the final results are presented in the following: The final pooled analysis included new users of dabigatran (n=29 448) propensity score matched to an equal number of warfarin patients (n=29 448) identified between October 2010 and September 2015 in the MarketScan (n=23 323) and Optum Research Databases (n=6125). Among the matched dabigatran patients providing 14 981.1 PY of follow-up, there were a total of 104 strokes (MarketScan: 78 events, IR=0.64 per 100 PY, 95% CI=0.51-0.80; Optum: 26 events, IR=0.90 per 100 PY, 95% CI=0.60-1.30). Among the matched warfarin patients providing 12 114.2 PY of follow-up, there were a total of 120 stroke events (MarketScan: 97 events, IR=0.99 per 100 PY, 95% CI =0.80-1.20; Optum: 23 events, IR=1.01 per 100 PY, 95% CI=0.66-1.50). The pooled HR was 0.75 with 95% CI=0.58-0.98 (MarketScan: HR=0.69, 95% CI=0.52-0.94; Optum: HR=1.00, 95% CI=0.57-1.76). For the primary outcome of major bleeding, the pooled analysis provided 14 880.4 PY of follow-up among dabigatran initiators and 12 012.1 PY of follow up among warfarin initiators. There were a total of 593 major bleeding events among dabigatran users (MarketScan: 523 events, IR=4.36 per 100 PY, 95% CI=4.00-4.74; Optum: 70 events, IR=2.43 per 100 PY, 95% CI=1.91-3.05) vs. 709 events among warfarin users (MarketScan: 591 events, IR=6.06 per 100 PY, 95% CI=5.58-6.56; Optum: 118 events, IR=5.23 per 100 PY, 95% CI=4.35-6.24), leading to a pooled HR of 0.72, 95% CI=0.65-0.80 (MarketScan: HR=0.76, 95% CI=0.68-0.86, Optum: HR=0.51, 95% CI=0.38-0.69).

Pooled HRs for dabigatran versus warfarin with corresponding 95% CI for secondary outcomes are listed below:

SVII.Table 30 Pooled hazard ratios for dabigatran versus warfarin

	Dabigatran events	Warfarin events	HR	95% CI
Stroke or systemic embolism	137	137	0.87	0.69 – 1.11
Systemic embolism	35	17	1.85	1.03 – 3.30
Ischemic stroke	94	97	0.84	0.63 – 1.12
Hemorrhagic stroke	10	23	0.37	0.18 – 0.78
TIA	32	52	0.53	0.34 – 0.82
MI	72	73	0.83	0.60 – 1.15
VTE	100	138	0.65	0.50 – 0.84
DVT	69	95	0.65	0.47 – 0.88
PE	43	56	0.70	0.47 – 1.04
Major Intracranial bleeding	32	71	0.39	0.25 – 0.59
Major Extracranial bleeding	563	645	0.75	0.67 – 0.84
Major GI bleeding	357	340	0.89	0.77 – 1.04
Major upper GI bleeding	77	109	0.60	0.44 – 0.80
Major lower GI bleeding	326	299	0.93	0.79 – 1.08
Major urogenital bleeding	1	0	NA*	NA*
Other major bleeding	346	441	0.68	0.59 – 0.78
Hepatotoxicity	26	36	0.63	0.38 – 1.05
Death	115	118	0.83	0.64 – 1.08

*Major urogenital bleeding: Across databases, only one event was observed among dabigatran initiators versus no event among warfarin initiators. Therefore HR estimation is not possible.
Data source: [c25839310-01], Table11

The suggested increased risk of systemic embolism for dabigatran as compared to warfarin in the pooled analysis based on the primary analysis (as-treated approach) could be a chance finding. The estimate is based on a relatively small number of events (35 in the dabigatran group vs. 17 in the warfarin group). The effect is therefore imprecisely estimated as reflected in the width of the CI, and although the point estimates were all elevated, the CI included the null for several of the sensitivity analyses performed in the study.

The results from the final analyses remain consistent with what was observed in the interim analyses that suggested a reduced risk of both primary outcomes (stroke and major bleeding) with dabigatran relative to warfarin. The final results were also comparable to the results seen in RE-LY for dabigatran 150 mg b.i.d. Of note is that in the US, only the 150 mg b.i.d. and the 75 mg b.i.d. dose for patients with severe renal impairment are approved.

1160-0261: Non-interventional study describing patients' perception on anticoagulant treatment and treatment convenience when treated with Pradaxa or vitamin K antagonist for stroke prophylaxis in atrial fibrillation [c20654895-01]

This was a multicentre, multinational, non-interventional study in NVAF patients in Asia who had been treated with a VKA and were then switched to Pradaxa (Cohort A) or patients who were newly diagnosed with NVAF and initiated on either Pradaxa or VKA (Cohort B).

This non-interventional study, which was conducted in 5 SEASK countries, aimed at collecting real world data on how Asian patients with NVAF perceive their anticoagulant treatment with Pradaxa in comparison to treatment with a VKA.

The safety data collected in this study did not give rise to any new safety concerns.

1160-0274: The Comparative Safety and Effectiveness of Dabigatran, versus Rivaroxaban, and Apixaban Utilized in the Department of Defense (DoD) Non-Valvular Atrial Fibrillation Patient Population-A Retrospective Database Analysis [c22067736-01]

This was a non-interventional PASS based on existing data with propensity score matching designed to assess the safety and effectiveness of newly initiated dabigatran NVAF patients in comparison to newly initiated rivaroxaban patients and newly initiated apixaban patients in 2 separate study cohorts in the US:

- dabigatran vs. rivaroxaban
- dabigatran vs. apixaban

This study sampled patients with NVAF from a US database of 10 million active patients to assess incident stroke and major bleedings associated with pharmacy dispensing of 3 drugs, dabigatran, rivaroxaban and apixaban. The study considered only patients who were prescribed standard doses for each of the NOACs (dabigatran 150 mg, rivaroxaban 20mg and apixaban 5mg). Primary outcomes in the study were the occurrence of stroke (haemorrhagic, ischemic, uncertain) and major bleeding.

42 534 unique patients (12 763 on dabigatran, 17 177 on rivaroxaban, and 12 594 on apixaban) were included before PSM. After 12 763 dabigatran patients were propensity-score matched to 12 763 rivaroxaban patients, event rates per 100 PY for stroke were 5.2 in dabigatran patients and 6.9 in rivaroxaban patients. In Cox proportional-hazards regression analysis using the same PSM sample, the HR for stroke comparing dabigatran to rivaroxaban was 0.77 (95% CI 0.57 to 1.04, p=0.08). Rates for major bleeding were 18.2 and 22.4 per 1000 PY in dabigatran patients and rivaroxaban patients, respectively. The corresponding HR was 0.82 (95% CI 0.70 to 0.97, p=0.02).

After 4802 dabigatran patients were propensity-score matched to 4802 apixaban patients event rates per 100 PY for stroke were 4.6 in dabigatran patients and 3.6 in apixaban patients. The HR for stroke for dabigatran vs. apixaban treatment was 1.26 (95% CI 0.66 to 2.39,

p=0.49). For major bleeding, event rates per 100 PY were 16.9 in dabigatran patients and 12.4 in apixaban patients. The HR was 1.37 (95% CI 0.97 to 1.94, p=0.07).

Dabigatran users were observed to have a statistically significant lower risk of major bleeding compared to rivaroxaban users and no difference compared to apixaban users. Neither cohort was observed to have a significant difference in stroke risk. Results of this study may better inform clinical decisions in management of NOAC usage for NVAF patients within the United States.

1160-0202 Early dabigatran treatment after transient ischemic attack and minor ischemic stroke does not result in hemorrhagic transformation (Canadian Pradaxa Acute Stroke Safety Study [CPASS]).

This was a prospective, multi-centre registry designed to demonstrate the feasibility and safety of initiating dabigatran therapy within 14 days of TIA or minor stroke in AF patients.

Early dabigatran treatment did not precipitate symptomatic haemorrhagic transformation after minor stroke. Asymptomatic haemorrhagic transformation was associated with larger baseline infarct volumes. Early recurrent ischaemic events may be clinically more important. This observation does reassure current practice patterns are safe, but conclusive evidence will require a larger sample size.

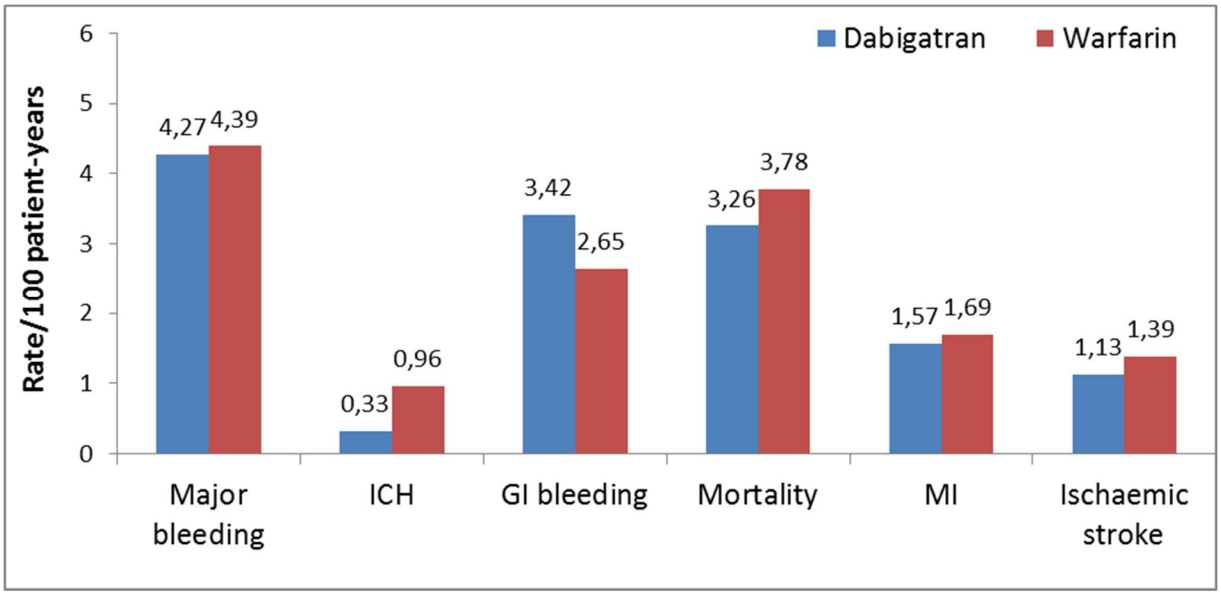
Selected study results from non-interventional studies from independent sources

In the following sections, investigator initiated studies with high relevance in BI's view are described in further detail.

Cardiovascular, bleeding, and mortality risks in elderly Medicare patients treated with dabigatran or warfarin for nonvalvular atrial fibrillation [P14-15648]

This is a retrospective, propensity score matched analysis of US Medicare claims database (October 2010 – December 2012). The study included new users of Pradaxa (n=67 207) or warfarin (n=67 2017), aged ≥65 years. The results show a non-significant lower major bleeding rate of 4.27/100 PY for Pradaxa compared to 4.39/100 PY for warfarin with an adjusted HR of 0.97 (P=0.50). The rate of ICH is significantly lower with 0.33/100PY for Pradaxa compared to 0.96 /100PY for warfarin with an adjusted HR of 0.34 (P<0.001). The rate of GI bleeding is however significantly increased with a rate of 3.42 / 100PY for Pradaxa and a rate of 2.65/100PY for warfarin. These results closely mirror the results generated for the dose of 150mg b.i.d. in the MAH clinical trial programme for SPAF patients. The differences between dabigatran and warfarin for other endpoints such as ischemic stroke (IS, aHR: 0.80, significant decrease), MI (aHR: 0.92, non-significant decrease, refer to section "Myocardial infarction") and mortality (aHR: 0.86, significant decrease) are also comparable to the results seen in RE-LY for DE 150 mg b.i.d. Of note is that in the US only the 150 mg b.i.d. and the 75 mg b.i.d. dose for patients with severe renal impairment are approved (SVII.Figure 1).

SVII.Figure 1 Results from a non-interventional study published by Graham et al. assessing the safety and effectiveness of dabigatran vs. warfarin



Results from this trial triggered the CCDS update to version 19 (dated 19 Dec 2017) and are included in the CCDS section "Clinical trials". The EU-SmPC was updated accordingly.

Comparative stroke, bleeding, and mortality risks in older Medicare patients treated with oral anticoagulants for nonvalvular atrial fibrillation. Graham DJ, Baro E, Zhang R, Liao J, Wernecke M, Reichman ME, Hu M, Illoh O, Wei Y, Goulding MR, Chillarige Y, Southworth MR, MaCurdy TE, Kelman JA [P19-00642].

The objective of the study was to investigate the safety and effectiveness of commonly marketed oral anticoagulants. In this retrospective new-user cohort study patients with NVAF enrolled in US Medicare who initiated warfarin (n=183 318), or a standard dose of dabigatran (150 mg twice-daily; n=86 198), rivaroxaban (20 mg once-daily; n=106 389) or apixaban (5 mg twice-daily; n=73 039) between October 2010 and September 2015 were enrolled. Propensity score adjusted Cox proportional hazards regression was used to estimate adjusted HRs and 95% CIs for the outcomes of thromboembolic stroke, intracranial haemorrhage, major extracranial bleeding, and all-cause mortality, comparing each NOAC with warfarin, and with each other NOAC.

The study reported that compared to warfarin, each NOAC was associated with reduced risks of thromboembolic stroke (20%-29% reduction; P=0.002 [dabigatran], P<0.001 [rivaroxaban, apixaban]), intracranial haemorrhage (35%-62% reduction; P<0.001 [each NOAC]), and mortality (19%-34% reduction; P<0.001 [each NOAC]). The NOACs had similar risk for thromboembolic stroke but rivaroxaban was associated with increased risks of intracranial haemorrhage (vs. dabigatran: HR=1.71; 95% CI 1.35-2.17), major extracranial bleeding (vs. dabigatran: HR=1.32, 95% CI 1.21-1.45; vs. apixaban: HR=2.70, 95% CI 2.38-3.05), and death (vs. dabigatran: HR=1.12, 95% CI 1.01-1.24; vs. apixaban: HR=1.23, 95% CI 1.09-1.38). Dabigatran was associated with reduced risk of intracranial haemorrhage (HR=0.70;

95% CI 0.53-0.94) and increased risk of major extracranial bleeding (HR=2.04; 95% CI 1.78-2.32) compared with apixaban.

The authors conclude that among patients treated with standard dose NOAC for NVAF and warfarin users with similar baseline characteristics, dabigatran, rivaroxaban, and apixaban were associated with a more favourable benefit-harm profile than warfarin. Among NOAC users, dabigatran and apixaban were associated with a more favourable benefit-harm profile than rivaroxaban.

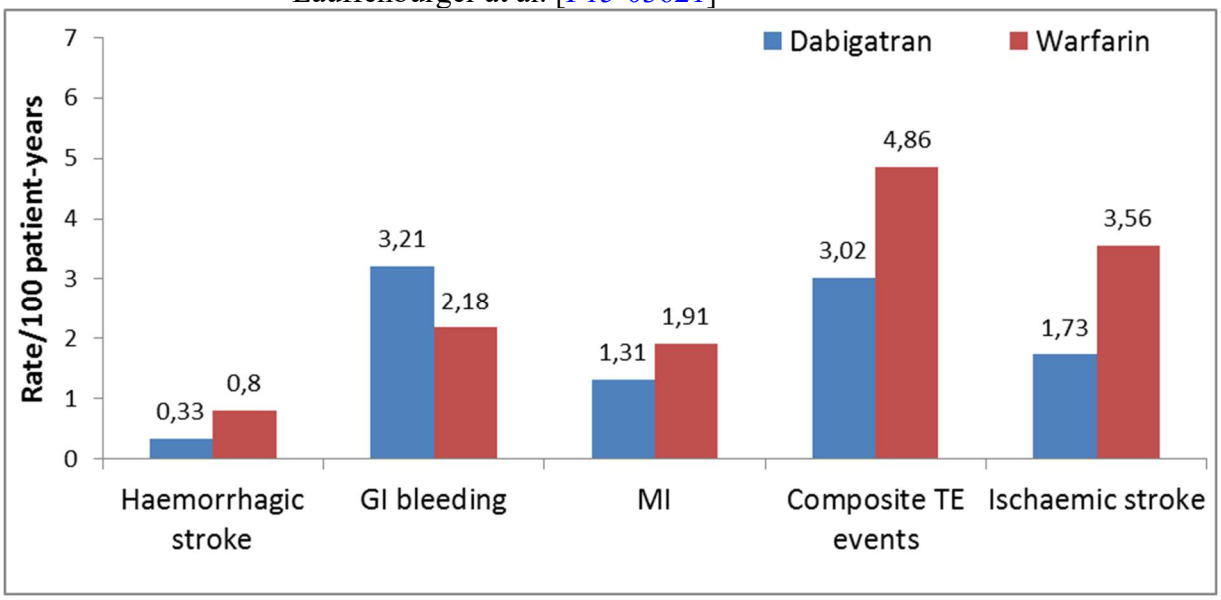
In summary, this publication on real world evidence of antithrombotic treatment with Pradaxa did not change the favourable benefit-risk profile of Pradaxa, and in fact confirmed the favourable benefit-risk profile also in comparison to other NOACs.

Effectiveness and Safety of Dabigatran and Warfarin in Real-World US Patients with Non-Valvular Atrial Fibrillation: a Restrospective Cohort Study [P15-03621]

This is a retrospective, propensity score weighted analysis of Truven Health Market Scan and Medicare databases (2009-2012). The study included new users of Pradaxa (n=21 070) and warfarin (n=43 865). The GI bleeding rate was with 3.21/100 PY higher for Pradaxa-treated patients compared to 2.18/100PY in warfarin treated patients. The HR was significantly higher for Pradaxa treated patients (adjusted HR: 1.11; 95% CI: 1.02 – 1.22). The hemorrhagic stroke rate was significantly reduced for Pradaxa treated patients (0.33/100PY) as compared to warfarin treated patients (0.8/100PY) with a adjusted HR of 0.51 (95%CI: 0.4 – 0.65). Of note is that in the US, only the 150 mg BI and the 75mg b.i.d. dose for patients with severe renal impairment is approved (see figure below).

In this study the frequency of ICH is lower and the frequency for GI bleeding higher than for warfarin. The other endpoints show a similar picture as seen in clinical trials, namely a lower rate of ischaemic stroke (aHR: 0.91, 95% CI: 0.81 – 1.02, non-significant decrease) and a composite of thromboembolic events (aHR: 0.86, 95% CI: 0.79 – 0.93, significant decrease) in dabigatran vs. warfarin treated patients. The MI rate is in this trial also lower for Pradaxa as compared to warfarin (aHR: 0.88, 95% CI 0.77 – 0.99, see section “Myocardial infarction”), which is the opposite to what has been observed in the RE-LY clinical trial.

SVII.Figure 2 Results from a non-interventional retrospective study published by Lauffenburger at al. [P15-03621]

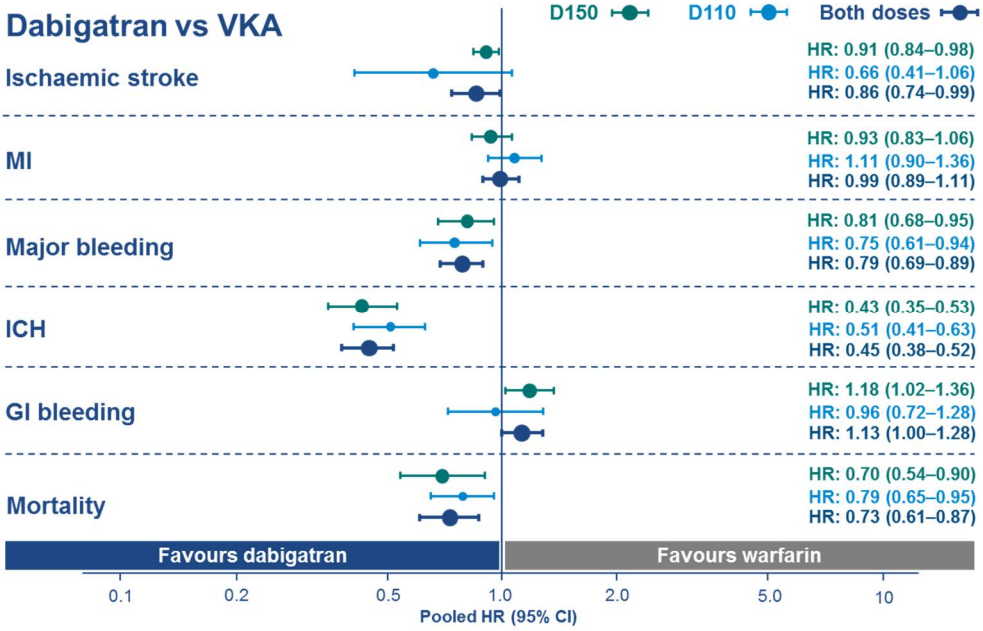


Dabigatran in real-world atrial fibrillation: Meta-analysis of observational comparison studies with vitamin K antagonists [P16-09188]

Although meta-analyses are prone for significant personal biases, may be methodologically not adequately designed, may cumulate results from poorly designed studies and have therefore to be interpreted with caution, they can give (if run appropriately) a cumulative overview of the research field and identify the overall measure of a treatment effect by the combination of several independent study results. The present meta-analysis compares the safety of dabigatran with warfarin including 20 observational studies covering more than 700 000 patients. 11 studies included only new users of dabigatran or warfarin, 7 studies included a mix of new and experienced users and 2 studies included only experienced users. 210 279 patients were treated with dabigatran, 501 019 patients were treated with warfarin. The HR for major bleeding in comparison to VKA was for Pradaxa 150 mg b.i.d. 0.81 (95%CI: 0.68 – 0.95) and for Pradaxa 110 mg b.i.d. 0.75 (95%CI: 0.61 – 0.94) with the pooled HR for Pradaxa being 0.79 (95% CI: 0.69 – 0.89) (SVII.Figure 3). A marked reduction in ICH was confirmed in this meta-analysis with a HR of 0.51 (95% CI: 0.41 – 0.63) for 110mg b.i.d., 0.43 (95% CI: 0.35 – 0.53) for 150mg b.i.d. and with the pooled HR for Pradaxa being 0.45 (95% CI: 0.38 – 0.52). GI bleeding was found to be increased for Pradaxa 150mg b.i.d. (HR: 1.18, 95% CI 1.02 – 1.36, significant increase), decreased for Pradaxa 110mg b.i.d. (HR. 0.96, 95% CI 0.72 – 1.28, non-significant decrease) with a pooled increased HR for Pradaxa being 1.13 (95% CI 1.00 – 1.28). These results closely mirror the results generated for the dose of 110mg b.i.d. and 150mg b.i.d. in the MAH clinical trial programme for SPAF patients. The differences between dabigatran and warfarin for other endpoints such as ischemic stroke (IS, HR 150mg b.i.d: 0.91, 95% CI 0.84 – 0.98; HR 110mg b.i.d: 0.66, 95% CI 0.41 – 1.06; pooled results HR 0.86, 95% CI 0.74 – 0.99), MI (HR 150mg b.i.d: 0.93, 95% CI 0.83 – 1.06; HR 110mg b.i.d: 1.11, 95% CI 0.90 – 1.36; pooled results HR 0.99, 95% CI 0.89 – 1.11) refer to section “Myocardial infarction”) and mortality (HR 150mg b.i.d: 0.70, 95% CI 0.54 – 0.90; HR 110mg b.i.d: 0.79, 95% CI 0.65 – 0.95;

pooled results HR: 0.73, 95% CI 0.61 – 0.87) are also comparable to the results seen in RE-LY (see figure below).

SVII.Figure 3 20 retrospective studies including 210 279 patients on dabigatran and 501 019 on VKA. Not all studies assessed all outcomes. Pooled estimates calculated by random-effects meta-analysis; circles scaled to weighting in analysis [P16-09188]



Overall, the results of this study are in agreement with previous studies that demonstrate improved safety outcomes, e.g. major bleeding, haemorrhagic stroke etc, and similar efficacy outcomes, e.g. ischaemic stroke, in NVAF patients treated with dabigatran compared to warfarin.

IIS 1160-0210: Safety and Efficacy of Minimally Interrupted Dabigatran vs. Uninterrupted Warfarin in Adults Undergoing Atrial Fibrillation Catheter Ablation: The ABRIDGE-J Randomized Clinical Trial

This study was conducted at 28 centres in Japan and compared the safety and efficacy of minimally interrupted dabigatran vs. uninterrupted warfarin in NVAF catheter ablation candidates. 499 patients were treated and 442 underwent ablation (dabigatran=220, warfarin=222). Appropriate dose anticoagulation was administered 4 weeks pre- and at least 3 months post-ablation in all patients. Dabigatran was interrupted before catheter ablation (holding of 1–2 doses) and resumed after ablation. Primary endpoints were the incidence of embolism during the peri-operative period, and the existence of atrial thrombus just before the ablation. The main secondary endpoint was the incidence of major bleeding events until 3 months post-ablation.

Before ablation, there was 1 cerebral infarction and 1 thrombus in the left atrium in the warfarin group, but none in the interrupted dabigatran group. After ablation, the incidence of

major bleeding events was significantly lower with dabigatran (1.4±0.8%, 95% CI 0.4%-4.2%) vs. warfarin (5.0±1.5%, 95% CI 2.8%–8.8%) (p=.03). There were 0 and 1 (0.5%) thromboembolic events after ablation in the dabigatran and warfarin groups, respectively.

In patients undergoing ablation for NVAF, anticoagulation with minimally-interrupted dabigatran did not increase thromboembolic events and was associated with fewer bleeding complications than uninterrupted warfarin.

Characterising the risk of major bleeding in patients with Non-Valvular Atrial Fibrillation: noninterventional study of patients taking Direct Oral Anticoagulants in the EU

This was a pharmacoepidemiological study using longitudinal data collected in 8 electronic health care databases from 6 EU countries to characterise the use of DOACs (dabigatran, rivaroxaban, apixaban) as well as the risk of major bleeding in a real-world setting to help establish the effectiveness of existing and future risk minimisation measures.

The objectives and conclusions for each objective are summarised below:

Objective 1: assess the risk of major bleeding associated with use of DOACs when compared to other OACs in patients with NVAF overall and in relevant clinical and demographical subgroups in a real-life setting. Conclusion: Compared to other OACs, apixaban was not associated with an increased risk of GI bleeding in all data sources and seemed to be associated with the lowest risk of major bleeding events compared to dabigatran and rivaroxaban.

Objective 2: assess the utilisation of DOACs in the EU for treatment of NVAF, including the characterisation of new DOAC users in NVAF patients. Conclusion: The overall incidence of new DOAC users increased during the study period, with the highest increase for apixaban. Cross national drug utilisation studies with a standard protocol may help to compare drug use and identify sources of variation enabling health care decisions.

Objective 3: assess prescribers' compliance with SmPC recommendations for each DOAC. *Conclusion: Contraindications, Special Warnings and Precautions, and potential DDIs were present in a substantial number of new DOAC users. Differences found between the databases might be related to 'true' differences in prescription behaviour but could partially relate to discrepancies in database characteristics.*

The availability of results from this study triggered an EMA Article 5(3) procedure for DOACs including Pradaxa.

PFP Australia

The dabigatran etexilate PFP in Australia was completed in 2013. The results are summarised below. In Australia, the dabigatran etexilate PFP was initiated to allow Australian physicians a controlled, structured, early experience with dabigatran etexilate in the newly approved indication "Prevention of stroke and systemic embolism in patients with NVAF and at least

one additional risk factor for stroke". The PFP commenced on 31 May 2011 and patient enrolment in the programme was closed on 14 Oct 2011.

A total of 28 057 patients were enrolled in the Australian PFP. As of 31 Aug 2013 the cumulative patient exposure to dabigatran etexilate in the PFP was 48 809 PY. By 30 Nov 2013, 3418 enrolled patients reported at least 1 adverse reaction to BI. The data from these 3418 patients were compared to those from 52 423 case reports received from ROW, and also with data from the RE-LY clinical trial.

Reporting rates per 10 000 PY for serious/fatal bleeding, serious/fatal MI and serious/fatal stroke showed higher rates for the PFP than for ROW. This likely reflects the stimulated reporting situation of the PFP, as opposed to the spontaneous reporting from ROW. Another factor may be found in the differences in the patient populations, which showed the PFP population to be on average older and (according to reported concomitant medication) possibly at a higher CV risk than the ROW population. A comparison with data from the RELY clinical trial showed reporting rates to be lower for the PFP for most events. The reporting rate for fatal MI was similar to that seen in RE-LY; the reporting rate was slightly higher for fatal stroke. The advanced age of the PFP population may have played a role in both. For fatal stroke the small absolute number of reports from the PFP must also be taken into consideration.

In summary, observations suggest that differences in patient population and the specific stimulated reporting conditions of the PFP explain the differences seen in various reporting rates when Australian data are compared to ROW. The benefit-risk ratio for Pradaxa is unchanged and favourable.

Post-marketing data

The SMQ Haemorrhage terms (excl laboratory terms) was used to retrieve cumulative post-marketing cases (including non-interventional studies) reporting bleeding events up to 28 Feb 2022. A characterisation of the risk based on post-marketing data is presented below (data source: Pradaxa PBRER with DLP 18 Mar 2022 [s00104884-01], section 16.4.1.4).

At DLP, there were 57 807 post-marketing case reports for Pradaxa in the BI GSP which included at least 1 haemorrhagic ADR from the SMQ. This represents 42.4% of the total post-marketing cases for Pradaxa (n=136 320). Included in these cases were 70 974 individual haemorrhagic events (serious and non-serious), distributed among 330 different PTs.

Of these 57 807 cases, 51 072 (88.4%) were spontaneous reports, 6735 (11.6%) were solicited.

A total of 42 153 serious AEs were reported from the SMQ 'Haemorrhage', representing 59.4% of all 70 974 events from the SMQ. This includes 5877 AEs associated with a fatal outcome from the SMQ, representing 8.3% of all events from the SMQ. Another 28 821 events were non-serious events, representing 40.6% of all events from the SMQ.

Grouping all AEs irrespective of seriousness to anatomical regions reveals the following distribution:

- GI tract (including oral cavity): 29 454 AEs (41.5%)
- Intracranial (including spinal): 8195 AEs (11.6%)
- Urogenital tract: 6625 AEs (9.3%)
- Others: 26 700 AEs (37.6%)

The distribution of AEs with respect to anatomical location has remained consistent over time, with the GI tract being the system most commonly affected.

Of the 57 807 post-marketing haemorrhagic cases received during the reporting interval, information on patient age (ranging from <45 to ≥100 years) was reported in 40 588 (70.2%) cases while age was not reported in 17 219 (29.8%) cases. Age ≥65 to ≥100 years was reported in 35 670 cases (61.7%) of all 57 807 cases, which comprises 87.8 % of cases in which age was reported (n=40 588).

Information on patient weight was available in 16 204 (28%) of the 57 807 post-marketing haemorrhagic cases retrieved by the SMQ, and is not considered sufficient to draw sound conclusions.

TTO of the haemorrhagic events was reported in 22 137 (38.2%) of 57 807 cases retrieved by the SMQ. Of these 22 137 cases, 4185 (18.9%) reported events that occurred within the first 10 days of treatment. This may represent a post-marketing reporting bias, as clinical trial data have shown that haemorrhagic events occur fairly steadily over time, though the data is not truly interpretable as this information was only available in less than 40% of all reports.

Of the 57 807 cases retrieved for this SMQ, 28 315 (48.9%) contained information on concomitant diseases. The most commonly represented diseases are typical of the aged patient population with AF.

The types and the distribution of concomitant medications are typical of standard of care for a patient population with AF.

Post-marketing cases with bleeding and renal failure

From these 57 807 bleeding cases (SMQ Haemorrhage; see above) a search was performed to identify all ICSRs where a patient clearly experienced the haemorrhagic event under treatment with Pradaxa (onset date – therapy start date equal to or greater than zero; multiple therapy dates were not considered) and where the temporal relationship between the renal function value and the onset of the haemorrhage can be clearly determined.

With this algorithm, BI identified 2415 cumulative ICSRs.

1715 of the 2415 cases contained sufficient information to establish that both measurement of renal function values and start date of Pradaxa therapy took place before the start of the

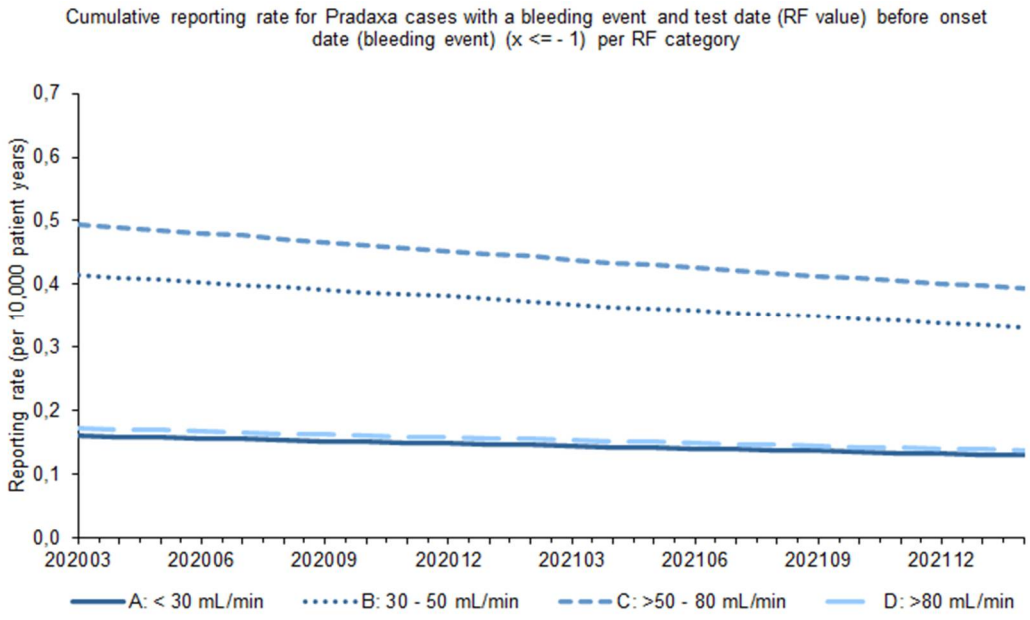
bleeding event. These 1715 cases are the basis for further evaluation presented below; the well-known limitations of spontaneous reporting need to be considered though.

Of the 1715 cases, 224 patients had documented RF values below 30 mL/min, 573 patients between 30 and 50 mL/min, 681 patients between 50 and 80 mL/min, and 237 patients above 80 mL/min at any time prior to the onset of bleeding event. In cases with more than 1 data set available, only the minimal (worst) reported renal function value per patient was taken for the classification (following a conservative approach).

Restricting the time gap between determination of RF and the onset of the bleeding event to a medically more sensible time frame (i.e. 7 days) led to a set of 466 cases. The distribution of these cases according to renal function revealed 88 patients with RF values <30 mL/min, 143 patients with 30 – 50 mL/min, 168 patients with >50 – 80 mL/min, and 67 patients with RF values >80 mL/min.

The RF test dates any time before bleeding (n=1715) were then translated into reporting rates in order to put the received number of cases with information on RF value per category over time into perspective with the growing post-marketing exposure. The figure below shows the reporting rates for Pradaxa cases with RF measured prior to bleeding event based on overall cumulative Pradaxa exposure.

SVII.Figure 4 Reporting rate for Pradaxa cases with renal function (RF) measured prior to bleeding event from March 2020 through February 2022



Data source: data on file, AR-CV-017 summary (2022 02)

For patients with mild and moderate renal insufficiency (categories C and B, respectively in the figure above), there is a continued trend towards lower reporting rates of such cases during the last years. For patients with severe renal insufficiency and normal renal function

(categories A and D in the figure above), the cumulative reporting rate is stable at a very low level of approximately 0.2 ICSRs / 10 000 PY).

Based on the post-marketing data presented, the risk minimisation activities initiated by BI are considered to be effective. While potential underreporting is a limitation of post-marketing data analysis, the overall reporting rate for patients with severe renal impairment experiencing a bleeding event has been approximately halved since the initiation of the risk minimisation activities.

Post-marketing cases of bleeding due to potential interactions with concomitant drugs

Interaction with anticoagulants or P-gp inhibitors

The table below shows the effect of concomitant medications which may pose an increased risk of haemorrhage due to PK or PD interaction when taken simultaneously with Pradaxa on the percentage of case reports involving any bleeding event (cumulative; DLP 28 Feb 2022). The case selection includes all post-marketing events, including events considered to be causally unrelated.

SVII.Table 31 Co-medications posing risk factors for haemorrhagic events

Co-medications	ICSRs with no bleeding [n (%)]	ICSRs with any bleeding [n (%)]	ICSRs with serious bleeding [n (%)]	ICSRs with fatal bleeding [n (%)]	All ICSRs [n (%)]
P-gp inhibitors[1] / no anticoagulants[2]	15 078 50.4%	14 835 49.6%	10 735 35.9%	1638 5.5%	29 913 100.0%
Anticoagulants / no P-gp inhibitors	5929 40.0%	8884 60.0%	6573 44.4%	988 6.7%	14 813 100.0%
P-gp inhibitors + anticoagulants	3083 37.8%	5068 62.2%	4046 49.6%	656 8.1%	8151 100.0%
All ICSRs / no P-gp inhibitors / no anticoagulants	78 513 57.6%	57 807 42.4%	33 975 24.9%	4860 3.6%	136 320 100.0%

[1] Drug class 'P-gp inhibitors' consisted of: amiodarone, clarithromycin, dronedarone, ketoconazole, nelfinavir, quinidine, reserpine, ritonavir, saquinavir, verapamil, tacrolimus, and cyclosporin.

[2] Drug class 'anticoagulants' included the following groups (WHO DD ATC 4 level): VKA, heparin group, other antithrombotic agents, and platelet aggregation inhibitors excl. heparin.

Data source: AR-CV-018 DIAR V01 (2022 02)

The concomitant administration of P-gp inhibitors appears to be accompanied by a modest increase in risk of haemorrhagic events, while the concomitant use of anticoagulants shows a larger PD interaction. The combined administration of Pradaxa with anticoagulants and P-gp inhibitors shows both influences. The cumulative percentage for the various case selections appears stable.

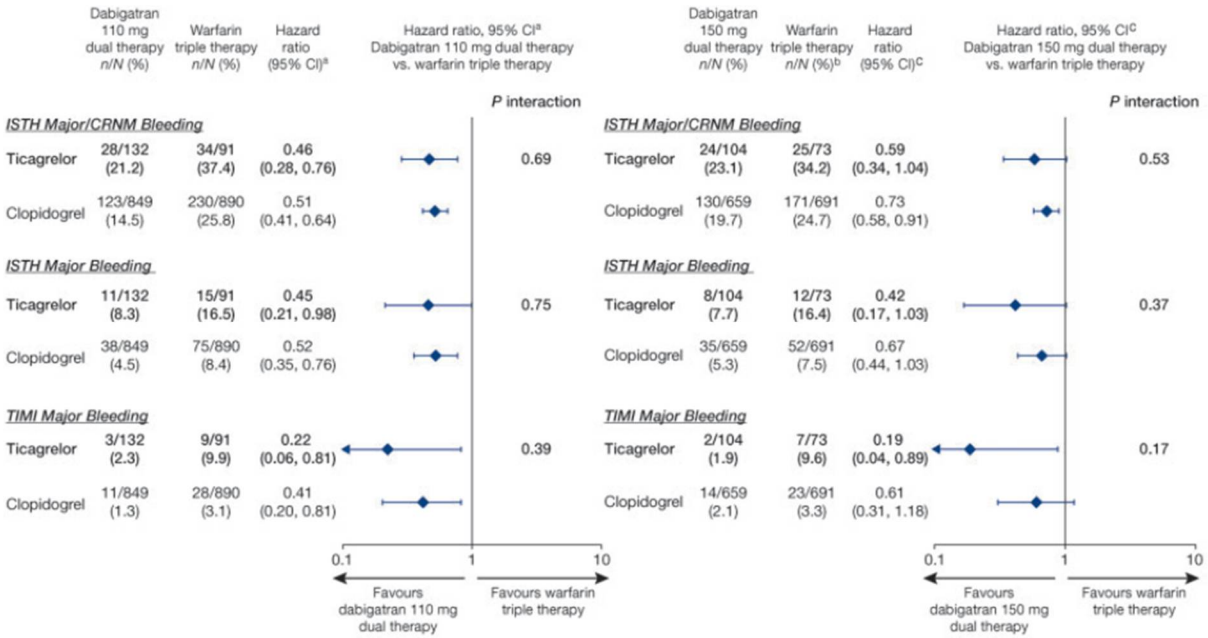
Dual anti-thrombotic therapy with ticagrelor or clopidogrel

In 2019, Oldgren et al published a subgroup analysis from the RE-DUAL trial (1160-0186) evaluating the safety and efficacy of dabigatran dual vs. warfarin triple therapy in 2 pre-specified patient subgroups: one with PCI due to ACS or undergoing elective PCI) and one by antithrombotic treatment with ticagrelor or clopidogrel [P19-01595]. The summary below focuses on the latter, comparing outcomes in those treated with ticagrelor vs those treated with clopidogrel.

The RE-DUAL PCI trial primary endpoint was time to first ISTH major or clinically relevant non-major bleeding event. Further safety endpoints included major bleeding events according to ISTH and TIMI definitions; and efficacy outcomes including the composite of death or thromboembolic events (MI, stroke, or systemic embolism), or unplanned revascularisation (PCI/ coronary artery bypass graft), MI and all-cause death.

In the group of patients treated with ticagrelor, the study treatment-independent incidence of the first ISTH major or clinically relevant non-major bleeding event was 26.3%, and in those treated with clopidogrel 20.1%; multivariable adjusted HR 1.35, 95% CI 1.05–1.72. Across the subgroups of patients with ticagrelor or clopidogrel, the risks of experiencing the primary outcome of ISTH major or clinically relevant non-major bleeding, as well as ISTH major bleeding events alone, and TIMI major bleeding events, were consistently reduced with dabigatran 110mg dual therapy and dabigatran 150 mg dual therapy vs. warfarin triple therapy. All interaction P-values were non-significant (SVII.Figure 5).

SVII.Figure 5 Bleeding events by treatment with ticagrelor or clopidogrel



Note: 58 patients who received ticagrelor + clopidogrel are included in the ticagrelor subgroup; 93 patients who received neither clopidogrel nor ticagrelor are included in the clopidogrel subgroup. The choice of ticagrelor or clopidogrel was at the discretion of the investigator, these groups are not directly comparable due to allocation bias.

[a]From Cox proportional hazard model stratified by age (elderly vs. non-elderly).

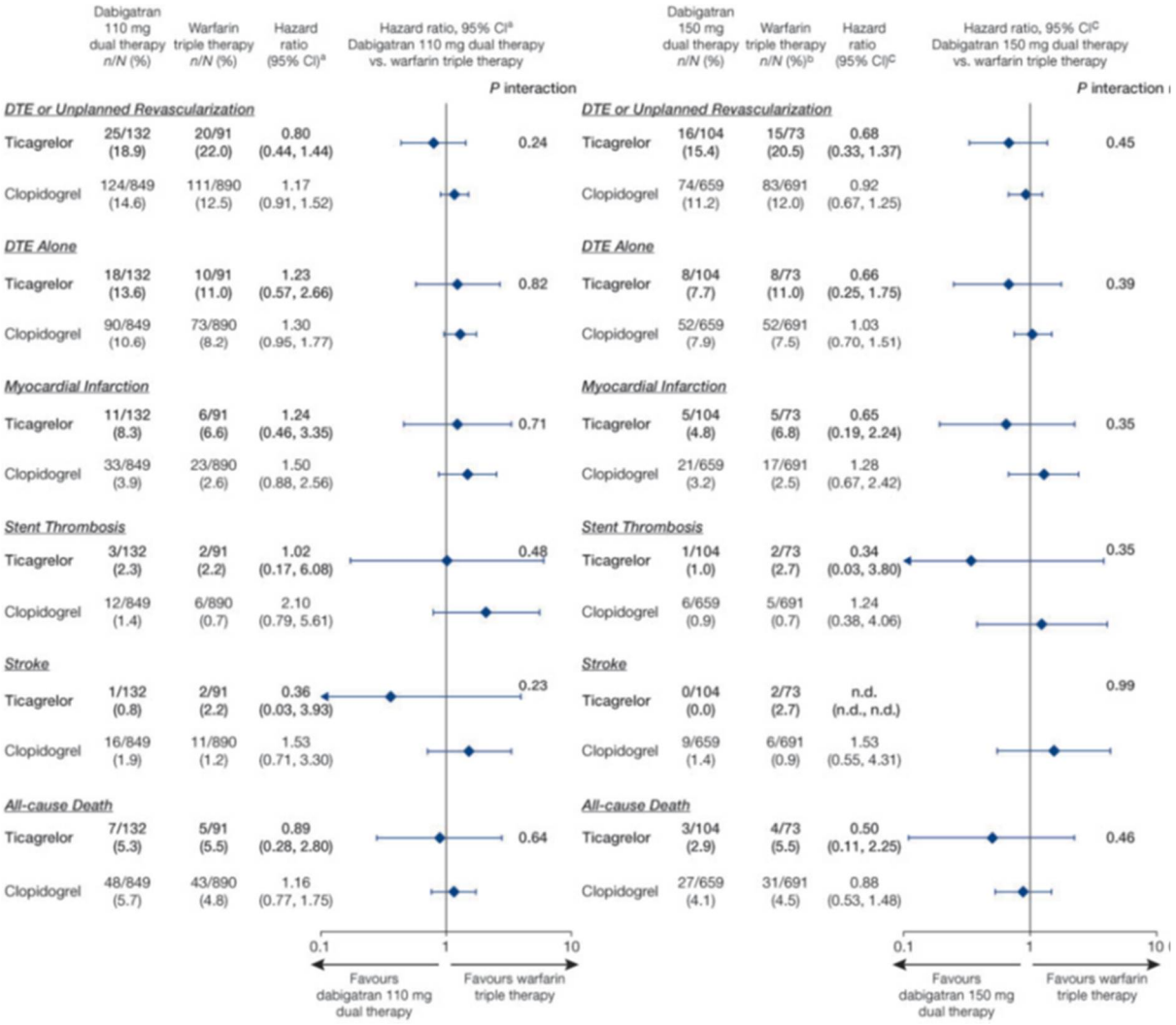
[b]For the comparison with dabigatran 150 mg dual therapy, elderly patients outside the USA were excluded.

[c]From unstratified Cox proportional hazard model. ACS, acute coronary syndrome; CI, confidence interval;

CRNM, clinically relevant non-major; ISTH, International Society on Thrombosis and Haemostasis; PCI, percutaneous coronary intervention; TIMI, thrombolysis in myocardial infarction.

The study treatment independent incidence of death, thromboembolic events, or unplanned revascularisation was 18.7% in those treated with ticagrelor and 12.9% in those treated with clopidogrel; multivariable adjusted HR 1.34, 95% CI 1.00–1.82. Minor variations were observed for the composite endpoint of death, thromboembolic events, or unplanned revascularisation, for dabigatran 110mg or 150mg dual therapy vs. warfarin triple across subgroups of treated with ticagrelor or clopidogrel but all interaction P-values were non-significant. Numerical differences in the composite of death or thromboembolic events and the individual thromboembolic endpoints were also observed for those patients treated with ticagrelor or clopidogrel, but all interaction P-values were non-significant (SVII.Figure 6).

SVII.Figure 6 Death, thromboembolic events, and unplanned revascularisation by treatment with ticagrelor or clopidogrel



Note: The choice of ticagrelor or clopidogrel was at the discretion of the investigator, these groups are not directly comparable due to allocation bias.

[a]From Cox proportional hazard model stratified by age (elderly vs. non-elderly).

bFor the comparison with dabigatran 150 mg dual therapy, elderly patients outside the USA were excluded.

[c]From unstratified Cox proportional hazard model.

CI, confidence interval; DTE, death or thromboembolic event (myocardial infarction, stroke, or systemic embolism); HR, hazard ratio; n.d., not done (one treatment group had zero events and HR is not given).

The vast majority of the study patients were treated with clopidogrel, but 12% of the patients received ticagrelor as part of their antithrombotic regimen. In this study, the majority of patients treated with ticagrelor (73%) had an ACS at index event, in line with contemporary guidelines recommending ticagrelor in preference to clopidogrel on top of aspirin after an ACS episode. Patients treated with ticagrelor had a higher bleeding risk than the patients who the physician treated with clopidogrel. Patients treated with ticagrelor at investigator's discretion were also associated with higher risk of the composite of death, thromboembolic

events, or unplanned revascularisation, of borderline statistical significance, than patients receiving clopidogrel in this study.

Despite the higher bleeding risk observed in patients treated with ticagrelor, the benefits of both dabigatran 110 mg and 150 mg dual therapy compared with warfarin triple therapy were consistent across the ticagrelor and clopidogrel subgroups.

Post-marketing data on interactions (cumulative, health authority and spontaneous cases only)

Until the DLP of this reference period, BI received cumulatively 83 ICSRs with concomitant use of ticagrelor in the GSP; 53 of the 83 cases report overt haemorrhagic events. In 43 of these cases, ASA was also reported as co-medication and in 2 cases enoxaparin was reported as co-medication. The data did not show any deviating safety.

SVII.3.1.1.4 Risk factors and risk groups

The risk of haemorrhages with Pradaxa increases with declining kidney function. Kidney function diminishes with age. Therefore, the elimination of dabigatran may be reduced, and dabigatran blood levels may be increased, in elderly patients and in patient with reduced kidney function. As a consequence, the risk of bleeding is increased in these patients. The highest rates occur in the very elderly (age >75 years) with poor kidney function.

Indication: pVTEp

The rate of MBEs increases with moderate renal impairment (CrCl of 30 to 50 mL/min) in the dabigatran etexilate 220 mg and enoxaparin treatment groups compared with the dabigatran etexilate 150 mg treatment group. The elimination of dabigatran may be reduced and exposure to dabigatran increased in elderly patients, particularly during the post-operative period. Further details are given in the following tables.

SVII.Table 32 Number (%) of patients with MBEs for the active controlled trials 1160-0019, 1160-0024, 1160-0025, 1160-0048, and 1160-0064 by CrCl and age category

	Dabigatran etexilate 150 mg MBE/patients			Dabigatran etexilate 220 mg MBE/patients			Enoxaparin[1] MBE /patients		
	n	N	%	n	N	%	n	N	%
CrCl [mL/min]									
<30	0	7	0.0	0	12	0.0	1	14	7.1
30 – 50	0	185	0.0	8	239	3.3	10	279	3.6
>50 – 80	14	1011	1.4	17	1227	1.4	20	1434	1.4
>80	14	1464	1.0	26	2127	1.2	25	2300	1.1
Value not reported	1	70	1.4	1	87	1.1	0	84	0.0
Age [years]									
<65	10	1193	0.8	19	1686	1.1	12	1845	0.7
65 – 75	13	1116	1.2	16	1448	1.1	25	1653	1.5
>75	6	428	1.4	17	558	3.0	19	613	3.1

umber of events, n = total number of patients in category, % = number of patients with MBEs
CrCl rate based on MDRD: >80 mL/min no renal impairment, >50-80 mL/min mild renal impairment, 30-50 mL/min moderate renal impairment, <30 mL/min severe renal impairment
[1] Trial 1160-0024: 30 mg b.i.d. enoxaparin, remaining trials: 40 mg b.i.d. enoxaparin
Data source: data on file: RMP update tables 2010, tables 13.11 and 13.12

SVII.Table 33 Number (%) of patients with MBEs for the active controlled trials 1160-0019, 1160-0024, 1160-0025, 1160-0048, and 1160-0064 by age category further divided by CrCl

Age [years]	CrCl [mL/min]	Dabigatran etexilate 150 mg MBE/patients			Dabigatran etexilate 220 mg MBE/patients			Enoxaparin[1] MBE/patients		
		n	N	%	n	N	%	n	N	%
<65	<30	0	0	0.0	0	1	0.0	0	1	0.0
	30 – 50	0	2	0.0	0	9	0.0	1	10	10.0
	>50 – 80	2	193	1.0	2	244	0.8	2	277	0.7
	>80	8	966	0.8	17	1395	1.2	9	1514	0.6
65 – 75	<30	0	1	0.0	0	2	0.0	0	1	0.0
	30 – 50	0	63	0.0	2	83	2.4	2	88	2.3
	>50 – 80	6	572	1.0	7	663	1.1	9	824	1.1
	>80	6	453	1.3	7	664	1.1	14	713	2.0
>75	<30	0	6	0.0	0	9	0.0	1	12	8.3
	30 – 50	0	120	0.0	6	147	4.1	7	181	3.9
	>50 – 80	6	246	2.4	8	320	2.5	9	333	2.7
	>80	0	45	0.0	2	68	2.9	2	73	2.7

umber of events, n = total number of patients in category, % = number of patients with MBEs
CrCl rate based on MDRD: >80 mL/min no renal impairment, >50-80 mL/min mild renal impairment, 30-50 mL/min moderate renal impairment, <30 mL/min severe renal impairment
[1] Trial 1160-0024: 30 mg b.i.d. enoxaparin, remaining trials: 40 mg b.i.d. enoxaparin
Data source: data on file: RMP update tables 2010, Table 13.13

Indication: SPAF

The rate of MBEs increases with impaired RF independent of the treatment group and dabigatran etexilate dose. Further details are given in SVII.Table 34.

SVII.Table 34 Number of patients with MBEs for trial 1160-0026 (RE-LY) with yearly event rates

CrCl [mL/min]	Dabigatran etexilate 110 mg b.i.d.			Dabigatran etexilate 150 mg b.i.d.			Warfarin		
	N	PY	%/a	N	PY	%/a	N	PY	%/a
<30	0	28	0.0	7	53	13.3	0	53	0.0
30 – 50	120	2123	5.7	116	2201	5.3	112	1973	5.7
>50 – 80	154	5369	2.9	182	5456	3.3	206	5449	3.8
>80	57	3853	1.5	80	3825	2.1	94	3779	2.5

ımber of patients, %/a = yearly event rate
CrCl rate based on MDRD: >80 mL/min no renal impairment, >50-80 mL/min mild renal impairment, 30-50 mL/min moderate renal impairment, <30 mL/min severe renal impairment
Data source: RE-LY CTR [U09-3249-02], Table 15.3.2.2.2: 1, Figures 15.3.2.2.2:1 and 15.3.2.2.2:2

Indication: aVTEt

The rate of MBEs increases with impaired RF independent of the treatment group and dabigatran etexilate dose. Further details are given in the following tables.

The design of the studies included both a single dummy and a double dummy period. In the warfarin group, patients already on parenteral therapy at the time of randomisation were simultaneously given active warfarin just after randomisation for approximately 5 days. Once their INR was in the range of 2 to 3 they were to stop taking the parenteral therapy and continue on warfarin alone for the rest of the study.

In the dabigatran etexilate group, patients already on parenteral therapy at the time of randomisation were simultaneously given a placebo-warfarin just after randomisation for approximately 5 days. Once their sham INR was in the range of 2 to 3 they were to stop taking the parenteral therapy and immediately switch to dabigatran etexilate alone for the rest of the study.

This resulted in the fact that events could be counted in 3 possible ways, as described below:

- From the start of the single-dummy period for both treatment groups, referred to throughout as ‘start of any treatment’
- From the start of the double-dummy period for both treatment groups, referred to throughout as ‘start of double-dummy treatment’
- From the start of the single-dummy period for the warfarin treatment group, or from start of the double-dummy period for the dabigatran etexilate treatment group, referred to throughout as ‘start of active treatment’

SVII.Table 35 Number of patients stratified by CrCl experiencing MBEs during the treatment period for trials 1160-0053 (RE-COVER) and 1160-0046 (RE COVER II) (pooled data)

CrCl [mL/min]		1160-0053 + 1160-0046	
		Dabigatran etexilate 150 mg b.i.d.	Warfarin
<30	Patients, n (%)	8 (100.0)	11 (100.0)
	MBE (%)	0 (0.0)	0 (0.0)
30 – 50	Patients, n (%)	106 (100.0)	123 (100.0)
	MBE (%)	6 (5.7)	5 (4.1)
>50 – 80	Patients, n (%)	504 (100.0)	562 (100.0)
	MBE (%)	9 (1.8)	23 (4.1)
>80	Patients, n (%)	1811 (100.0)	1837 (100.0)
	MBE (%)	9 (0.5)	23 (1.3)

Data source: [U12-2617-01], Table 4.5.1.9.1.1

SVII.Table 36 Number (%) of patients experiencing a major bleeding event during double dummy period by age and CrCl (mL/min) for trials 1160-0053 (RE-COVER) and 1160-0046 (RE COVER II) (pooled data)

Age [years]	CrCl [mL/min]	Dabigatran etexilate 150 mg		Warfarin	
		N	%	N	%
<65	<30	0	0.00	0	0.00
	30 - <50	0	0.00	1	12.50
	>50 – 80	3	1.97	2	1.26
	≥80	8	0.51	16	1.06
65 – 75	<30	0	0.00	0	0.00
	30 - <50	2	5.71	1	4.17
	>50 – 80	2	0.88	8	3.16
	≥80	1	0.44	2	0.88
>75	<30	0	0.00	0	0.00
	30 - <50	4	5.97	3	3.66
	>50 – 80	4	3.23	6	4.84
	≥80	0	0.00	1	2.08

CrCl rate based on MDRD: >80 mL/min no renal impairment, >50-80 mL/min mild renal impairment, 30-50 mL/min moderate renal impairment, <30 mL/min severe renal impairment
Data source: Addendum to SCS aVTEt/sVTEp (updated), Table 8

Indication: sVTEp

The rate of MBEs increases with impaired RF independent of the treatment group and dabigatran etexilate dose. Further details are given in the following tables.

SVII.Table 37 Number of patients stratified by CrCl experiencing MBEs during the treatment period for trials 1160-0047 (RE-MEDY) and 1160-0063 (RE-SONATE)

	1160-0047 (RE-MEDY)						**1160-0063 (RE-SONATE)**					
	Dabigatran etexilate 150 mg b.i.d. MBE/patients			**Warfarin MBE/patients**			**Dabigatran etexilate 150 mg b.i.d. MBE/patients**			**Placebo MBE/patients**		
CrCl [mL/min]	n	N	%	n	N	%	n	N	%	n	N	%
<30	0	0	0.0	0	4	0.0	0	0	0.0	0	0	0.0
30 – 50	2	59	3.4	3	45	6.7	1	33	3.0	0	26	0.0
>50 – 80	3	328	0.9	8	289	2.8	1	153	0.7	0	155	0.0
>80	8	1031	0.8	14	1072	1.3	0	495	0.0	0	476	0.0

n = number of events, N = total number of patients in category, % = number of patients with MBEs
Data source: [U12-2617-01], tables 4.5.1.9.1.4 and 4.5.1.9.1.5

SVII.Table 38 Number (%) of patients experiencing a major bleeding event during the treatment period by age and CrCl (mL/min) for trials 1160-0047 (RE-MEDY) and 1160-0063 (RE-SONATE)

Age [years]	**CrCl [mL/min]**	**Dabigatran etexilate 150 mg**		**Warfarin**		**Placebo**	
		N	%	N	%	N	%
<65	<30	0	0.0	0	0.0	0	0.0
	30 – 50	1	14.3	0	0.0	0	0.0
	>50 – 80	0	0.0	2	2.1	0	0.0
	>80	3	0.2	12	1.3	0	0.0
65 – 75	<30	0	0.0	0	0.0	0	0.0
	30 – 50	1	3.7	0	0.0	0	0.0
	>50 – 80	4	1.6	1	0.7	0	0.0
	>80	5	2.2	2	1.4	0	0.0

SVII.Table 38 (cont'd) ''Number (%) of patients experiencing a major bleeding event during the treatment period by age and CrCl (mL/min) for trials 1160-0047 (RE-MEDY) and 1160-0063 (RE-SONATE)

Age [years]	CrCl [mL/min]	Dabigatran etexilate 150 mg		Warfarin		Placebo	
		N	%	N	%	N	%
>75	<30	0	0.0	0	0.0	0	0.0
	30 – 50	1	1.7	3	10.3	0	0.0
	>50 – 80	0	0.0	5	9.6	0	0.0
	>80	0	0.0	0	0.0	0	0.0

CrCl rate based on MDRD: >80 mL/min no renal impairment, >50-80 mL/min mild renal impairment, 30-50 mL/min moderate renal impairment, <30 mL/min severe renal impairment
Data source: Addendum to SCS aVTEt/sVTEp, Table 7

SVII.3.1.1.5 Preventability

Data concerning preventability of this reaction are not available for any of the indications.

SVII.3.1.1.6 Impact on the risk-benefit balance of the product

Severe haemorrhage (in particular severe GI or intracranial haemorrhage) is by far the most important risk of Pradaxa. This justifies that additional risk minimisation measures have only been implemented for haemorrhage. The increased risk of haemorrhage is clearly outbalanced by the decreased risk of systemic thromboembolic events.

SVII.3.1.1.7 Public health impact

Except for gastrointestinal haemorrhages, the bleeding rates of MBE, CRBE, any bleeding, and intracranial haemorrhage is lower in the dabigatran etexilate treatment groups compared to warfarin.

SVII.3.2 Presentation of the missing information

SVII.3.2.1 Missing information: Patients aged 0 to 2 years who were born prematurely

SVII.3.2.1.1 Evidence source

The source of evidence for this missing information is very limited because the concerned population (see Section SVII.3.2.1.2) was excluded from paediatric clinical trials.

SVII.3.2.1.2 Population in need for further characterisation

Patients with gestational age at birth <37 weeks or with body weight lower than the 3rd percentile (per WHO guidance).

SVII.3.2.1.3 Anticipated risk/consequence of the missing information

Due to the lack of experience in the patients described in Section SVII.3.2.1.2, the anticipated risk in this patient population is not known.

SVII.3.2.2 Missing information Paediatric patients with renal dysfunction (eGFR <50ml/min)

SVII.3.2.2.1 Evidence source

Dabigatran is eliminated primarily through the kidneys. Thus, at a given dose in patients with renal failure, dabigatran may accumulate. Adult clinical trial data show an increased risk of haemorrhage or bleeding in patients with severe renal failure treated with Pradaxa. Therefore, Pradaxa is contraindicated in adult patients with severe renal failure, and dose adaptations are needed in patients with moderate renal failure.

Paediatric patients with renal dysfunction (eGFR <50ml/min) were excluded from clinical trials, therefore there is no evidence of the safety of use of Pradaxa in this population.

SVII.3.2.2.2 Population in need for further characterisation

Paediatric patients with renal dysfunction defined as eGFR <50ml/min.

SVII.3.2.2.3 Anticipated risk/consequence of the missing information

Increased risk of haemorrhage.

SVII.4 REFERENCES

SVII.4.1 Published references

P09-11669 Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H, Diener HC, Joyner CD, Wallentin L, RE-LY Steering Committee and Investigators. Dabigatran vs. warfarin in patients with atrial fibrillation. N Engl J Med 2009; 361 (12): 1139-1151.

P10-03367 Haute Autorite de Sante, Commission de la Transparence. Pradaxa 75 mg, 110 mg capsule (dabigatran etexilate (as mesilate)) (Boehringer Ingelheim France) (B01AE07) (date of marketing authorization procedure europeenne centralised.: March 18, 2008): reason for application: Registration Safety Social and Communities (Opinion July 16, 2008).

P12-02756 Falck-Ytter Y, Francis CW, Johanson NA, Curley C, Dahl OE, Schulman S, Ortel TL, Pauker SG, Colwell CW. Prevention of VTE in orthopedic surgery patients: antithrombotic therapy and prevention of thrombosis, 9th

ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 141 (2) (Suppl), e278S - e325S (2012).

P13-08160 Ferreira J, Ezekowitz MD, Connolly SJ, Brueckmann M, Fraessdorf M, Reilly PA, Yusuf S, Wallentin L, RE-LY Investigators. Dabigatran compared with warfarin in patients with atrial fibrillation and symptomatic heart failure: a subgroup analysis of the RE-LY trial. European Journal of Heart Failure, Advance Access published July 9, 2013, doi: 10.1093/eurjhf/hft111 Eur J Heart Fail 2013. 15(9):1053-1061.

P13-09153 Schulman S, Eriksson H, Goldhaber SZ, Kakkar A, Kearon C, Mismetti P, Schellong S, Feuring M, Peter N, Friedman J. Safety of dabigatran versus warfarin for acute venous thromboembolism: pooled analyses of RE-COVER and RE-COVER II. ISTH 2013, 24th Cong of the International Society on Thrombosis and Haemostasis (ISTH) and 59th Ann Mtg of the Scientific and Standardization Committee (SSC), Amsterdam, 29 Jun – 4 Jul 2013 (Oral Presentation) 2013.

P13-10972 Lip G, Clemens A, Noack H, Ferreira J, Connolly S, Yusuf S. Guidance adherent dabigatran etexilate treatment versus warfarin in the RE-LY population: an analysis on the basis of the European label recommendations for dabigatran etexilate. ESC 2013, 35th Cong of the European Society of Cardiology (ESC), Amsterdam, 31 Aug – 4 Sep 2013 Eur Heart J 2013. 34(Suppl 1):791.

P13-11205 Marijon E, Heuzey JY le, Connolly S, Yang S, Pogue J, Brueckmann M, Eikelboom J, Themeles E, Ezekowitz M, Wallentin L, Yusuf S, RE-LY Investigators. Causes of death and influencing factors in patients with atrial fibrillation: a competing risk analysis from the Randomized Evaluation of Long-Term Anticoagulant Therapy study. Circulation, published online September 9, 2013,doi: 10.1161/CIRCULATIONAHA.112.000491 Circulation 2013. 128(20):2192-2201.

P13-12662 Reilly PA, Lehr T, Haertter S, Connolly SJ, Yusuf S, Eikelboom JW, Ezekowitz MD, Nehmiz G, Wang S, Wallentin L, RE-LY Investigators. The effect of dabigatran plasma concentrations and patient characteristics on the frequency of ischemic stroke and major bleeding in atrial fibrillation patients in the RE-LY trial. Journal of the American College of Cardiology, Accepted Manuscript, Available online 27 September 2013, doi: 10.1016/j.jacc.2013.07.104 J Am Coll Cardiol 2014. 63(4):321-328.

P13-16527 Hijazi Z, Hohnloser SH, Oldgren J, Andersson U, Connolly SJ, Eikelboom JW, et al. Efficacy and safety of dabigatran compared with warfarin in relation to baseline renal function in patients with atrial fibrillation: a RE-LY (randomized evaluation of long-term antocoagulation therapy) trial analysis. Circulation, published online December 9, 2013,

doi:10.1161/CIRCULATIONAHA.113.003628 Circulation 2014. 129(9):961-970.

P14-15648 Graham DJ, Reichman ME, Wernecke M, Zhang R, Southworth MR, Levenson M, Sheu TC, Mott K, Goulding MR, Houstoun M, MaCurdy TE, Worrall C, Kelman KA. Cardiovascular, bleeding, and mortality risks in elderly Medicare patients treated with dabigatran or warfarin for non-valvular atrial fibrillation. Circulation, published online October 30, 2014, doi: 10.1161/CIRCULATIONAHA.114.012061 Circulation 2015. 131(2):157-164.

P15-03621 Lauffenburger et al. Effectiveness and Safety of Dabigatran and Warfarin in Real-World US Patients with Non-Valvular Atrial Fibrillation: a Restrospective Cohort Study. J Am heart Assoc 2015;4:e001798.

P16-09188 Carmo J, Costa FM, Ferreira J, Mendes M. Dabigatran in real-world atrial fibrillation: meta-analysis of observational comparison studies with vitamin K antagonists. Thromb Haemost 116 (4), 754 – 763 (2016).

P17-09776 Cannon CP, Bhatt DL, Oldgren J, Lip GYH, Ellis SG, Kimura T, et al, REDUAL PCI Steering Committee and Investigators. Dual antithrombotic therapy with dabigatran after PCI in atrial fibrillation. New England Journal of Medicine, published on August 27, 2017, doi: 10.1056/NEJMoa1708454 N Engl J Med 2017. 377(16):1513-1524.

P17-03137 Calkins H, Willems S, Gerstenfeld EP, Verma A, Schilling R, Hohnloser SH, et al, RE-CIRCUIT Investigators. Uninterrupted dabigatran versus warfarin for ablation in atrial fibrillation. New England Journal of Medicine, published on March 19, 2017, doi: 10.1056/NEJMoa1701005; 2017. p. 1627-1636.

P19-00642 Graham DJ, Baro E, Zhang R, Liao J, Wernecke M, Reichman ME, et al. Comparative stroke, bleeding, and mortality risks in older Medicare patients treated with oral anticoagulants for nonvalvular atrial fibrillation. American Journal of Medicine, accepted manuscript, Published online: January 09, 2019, doi: 10.1016/j.amjmed.2018.12.023 Am J Med 2019.

P19-01595 Oldgren J, Steg PG, Hohnloser SH, Lip GYH, Kimura T, Nordaby M, et al, RE-DUAL PCI Steering Committee and Investigators. Dabigatran dual therapy with ticagrelor or clopidogrel after percutaneous coronary intervention in atrial fibrillation patients with or without acute coronary syndrome: a subgroup analysis from the RE-DUAL PCI trial. European Heart Journal, Published: 21 February 2019, doi: 0.1093/eurheartj/ehz059; 2019. P. 1553-1562.

P19-06030 Albisetti M, Brandao LR, Bomgaars L, Chalmers E, Luciani M, Mitchell LG, et al, DIVERSITY Trial Investigators. Efficacy and safety of dabigatran etexilate for treatment of venous thromboembolism in paediatric

patients - results of the DIVERSITY Trial. ISTH 2019, 27th Cong of the International Society on Thrombosis and Haemostasis (ISTH) and 65th Ann Mtg of the Scientific and Standardization Committee (SSC), Melbourne, 6 - 10 Jul 2019 (Oral Presentation) 2019.

P19-07958 Ferro JM, Coutinho JM, Dentali F, Kobayashi A, Alasheev A, Canhao P, et al, RE-SPECT CVT Study Group. Safety and efficacy of dabigatran etexilate vs dose-adjusted warfarin in patients with cerebral venous thrombosis: a randomized clinical trial. JAMA Neurology, Published online September 3, 2019, doi:10.1001/jamaneurol.2019.2764; 2019. p. 1457-1465.

P19-11322 Brandao L, Albisetti M, Halton J, Bomgaars L, Chalmers E, Mitchell L, et al. Safety of dabigatran etexilate for the secondary prevention of venous thromboembolism in children. Blood, December 5, 2019, doi:

P20-11143 Halton J, Brandao LR, Luciani M, Bomgaars L, Chalmers E, Mitchell LG, et al, DIVERSITY Trial Investigators. Dabigatran etexilate for the treatment of acute venous thromboembolism in children (DIVERSITY): a randomised, controlled, open-label, phase 2b/3, non-inferiority trial. Lancet Haematology, Published Online December 5, 2020, doi: 10.1016/S2352-3026(20)30368-9; 2021. p. e22-e33. 10.1182/blood.2019000998; 2020. P. 491-504.

R09-2242 Samama CM, Ravaud P, Parent F, Barre J, Mertl P, Mismetti P, et al. Epidemiology of venous thromboembolism after lower limb arthroplasty: the FOTO study. J Thromb Haemost 2007. 5:2360-2367.

SVII.4.2 Unpublished references

c01853156-02 Observational cohort study to evaluate the safety and efficacy of Pradaxa® (dabigatran etexilate) in patients with moderate renal impairment (creatinine clearance 30-50 mL/min) undergoing elective total hip replacement surgery or total knee replacement surgery. 1160-0084. 19 Mar 2015.

c01951554-12 GLORIA-AF: Global Registry on Long-Term Oral Anti-thrombotic Treatment in Patients with Atrial Fibrillation (Phase II/III – EU/EEA Member States). 1160-0136. 22 Oct 2014.

c01954741-02 An open label, non-comparative, pharmacokinetic and pharmacodynamic study to evaluate the effect of Dabigatran Etexilate on coagulation parameters including a calibrated thrombin time test in patients with moderate renal impairment (creatinine clearance 30-50 mL/min) undergoing primary unilateral elective total knee or hip replacement surgery. 1160-0086. 22 Apr 2014.

c01955897-02 GLORIA-AF: Global Registry on Long-Term Oral Anti-thrombotic Treatment in Patients with Atrial Fibrillation (Phase I). 1160-0114. 12 Jun 2014.

c02155743-03 Use of Pradaxa (Dabigatran Etexilate) for stroke prevention in patients with non valvular atrial fibrillation and mild to moderate renal impairment. 1160-0170. 03 Jun 2014.

c02161791-02 An exploratory study to investigate the pharmacokinetics and effects of DABIgatran etexilate in patients with stable severe RENAL disease: DabiRenal. 1160-0166, 19 Sep 2014.

c02248557-02 Relative bioavailability of dabigatran after administration of different dosage forms of multiple doses of 150 mg dabigatran etexilate (hard capsule, granules resolved in reconstitution solution, pellets on food) in healthy male volunteers (an open-label, randomised, multiple-dose, three-way crossover study). 1160-0194. 26 Sep 2014.

c02409758-01 Comparative effectiveness of oral anticoagulants: A cohort study (Phase 1 of the BI/BWH Pradaxa study program). 1160-0157. 20 Feb 2014.

c02921655-02 Amendment to CCDS and Master Sheet concerning new data based on targeted reviews of select data from the RE-LY study (1160-0026) and correction of errors concerning numbers of patients treated in clinical trials. 17 Nov 2014.

c03493519-01 The Comparative Safety and Effectiveness of Dabigatran and Warfarin Utilized in the Department of Defense (DoD) Non-Valvular Atrial Fibrillation Patient Population-An Administrative Database Analysis. 1160-0183. 09 Mar 2016.

c03541877-01 Observational cohort study to evaluate the safety and efficacy of switching from Lovenox® (enoxaparin) 40 mg to Pradaxa® (dabigatran etexilate) 220 mg in patients undergoing elective total hip or knee replacement surgery. 1160-0118. 06 Nov 2015.

c03697437-01 GLORIA – AF: Global Registry on Long-Term Oral Antithrombotic TReatment In PAtients with Atrial Fibrillation (Phase II/III – EU/EEA Member States) - EU Baseline Analysis for Phase II. 1160-0129. 23 May 2016.

c04596002-01 A prospective, open label study to evaluate the pharmacokinetics of dabigatran in non-valvular atrial fibrillation (NVAF) patients with severely impaired renal function on dabigatran etexilate 75 mg BID therapy. 1160-0173. 26 May 2016.

c05079154-04 Cohort study in prevention of venous thromboembolic events after orthopaedic surgery in patients treated with Pradaxa®: PETRA study. 1160-0102. 27 Jun 2014.

c08929115-01 Post-authorisation study to evaluate the effectiveness of the risk minimisation activities in the treatment of SPAF. 1160-0149. 12 Feb 2016.

c09069268-01 Single dose open-label PK/PD, safety and tolerability study of dabigatran etexilate mesilate given at the end of standard anticoagulant therapy in successive groups of children aged 2 years to less than 12 years followed by 1 year to less than 2 years. 1160-0089. 27 Jul 2016.

c09085437-01 Open-label, single dose, tolerability, pharmacokinetic/pharmacodynamics and safety study of dabigatran etexilate given at the end of standard anticoagulant therapy in children aged less than 1 year old. 1160-0105. 14 Jul 2016.

c13531195-01 A prospective Randomised, open label, blinded endpoint (PROBE) study to Evaluate DUAL antithrombotic therapy with dabigatran etexilate (110 mg and 150 mg b.i.d.) plus clopidogrel or ticagrelor vs. triple therapy strategy with warfarin (INR 2.0 – 3.0) plus clopidogrel or ticagrelor and aspirin in patients with non valvular atrial fibrillation (NVAF) that have undergone a percutaneous coronary intervention (PCI) with stenting (RE-DUAL PCI). 1160-0186. 13 Nov 2017.

c14372587-01 An observational study assessing the management of gastrointestinal and urogenital bleeding events in patients with non valvular atrial fibrillation treated with dabigatran etexilate. 1160-0162. 14 Dec 2016.

c14388942-01 Randomised Evaluation of dabigatran etexilate Compared to warfarIn in pulmonaRy vein ablation: assessment of an uninterrupted periproCedUral antIcoagulation sTrategy (The RE-CIRCUIT Trial). 1160-0204. 11 Apr 2017.

c16197989-01 The Comparative Safety and Effectiveness of Warfarin and Dabigatran Utilized in the Humana Non-Valvular Atrial Fibrillation Patient Population – A Retrospective Database Analysis. 1160-0192. 17 Jun 2019.

c19461930-01 1160-129 GLORIA AF end of p2 interim noninterventional CTR. 1160-0129. 30 Aug 2017.

c20654895-01 Non-interventional study describing patients' perception on anticoagulant treatment and treatment convenience when treated with Pradaxa or Vitamin K antagonist for stroke prophylaxis in atrial fibrillation. 1160-0261. 23 Oct 2018.

c21807097-02 A regulatory requirement non-interventional study to monitor the safety and effectiveness of Pradaxa (Dabigatran etexilate mesilate, 110 mg or 150 mg

b.i.d.) in Korean patients with non-valvular atrial fibrillation (SPARK: Safety study of Pradaxa in AF patients by Regulatory requirement of Korea). 1160-0139. 15 Jan 2018.

c22067736-01 The Comparative Safety and Effectiveness of Dabigatran, versus Rivaroxaban, and Apixaban Utilised in the Department of Defense (DoD) Non-Valvular Atrial Fibrillation Patient Population-A Retrospective Database Analysis. 1160-0274. 16 May 2018.

c24502871-01 RE-SPECT CVT: a randomised, open-label, exploratory trial with blinded endpoint adjudication (PROBE), comparing efficacy and safety of oral dabigatran etexilate versus oral warfarin in patients with cerebral venous and dural sinus thrombosis over a 24-week period. 1160-0248. 19 Mar 2019.

c25839310-01 Sequential Expansion of Comparative Effectiveness of Oral Anticoagulants: A Cohort Study (Phase 2 of the BI/BWH PRADAXA study program). 1160-0207. 10 Oct 2018.

c26496086-01 Open label, single arm safety prospective cohort study of dabigatran etexilate for secondary prevention of venous thromboembolism in children from 0 to less than 18 years. 1160-0108. 31 Jul 2019.

c26500834-01 GLORIA-AF: Global Registry Program on Long-Term Oral Anti-thrombotic Treatment in Patients with Atrial Fibrillation. 1160-0129, Phase III. 11 Jul 2019.

c26571231-01 Open-label, randomized, parallel-group, active-controlled, multi-centre, non-inferiority study of dabigatran etexilate versus standard of care for venous thromboembolism treatment in children from birth to less than 18 years of age: The DIVERSITY study. 1160-0106. 09 Aug 2019.

c28497947-01 GLORIA-AF: Global Registry on Long-Term Oral Antithrombotic Treatment in Patients with Atrial Fibrillation (Final Report of Phase III Results). 1160-0129. 17 Dec 2020.

c29754273-01 Open label, single arm safety prospective cohort study of dabigatran etexilate for secondary prevention of venous thromboembolism in children from 0 to less than 18 years. 1160-0108. 24 Apr 2020.

c29773859-01 Open-label, randomized, parallel-group, active-controlled, multi-centre, non-inferiority study of dabigatran etexilate versus standard of care for venous thromboembolism treatment in children from birth to less than 18 years of age: The DIVERSITY study. 1160-0106. 27 Apr 2020.

c31140776-01 GLORIA-AF: Global Registry on Long-Term Oral Antithrombotic Treatment in Patients with Atrial Fibrillation (Final Report of Phase III Results for EU/EEA Member States). 1160-0136. 08 Jan 2021.

c34109846-01 Clinical Overview Statement. GLORIA-AF: Global Registry on Long-Term Oral Antithrombotic Treatment in Patients with Atrial Fibrillation Final Phase III Results. 20 Jan 2020.

s00104884-01 Periodic Benefit-Risk Evaluation Report for Pradaxa (dabigatran etexilate), Reporting Period from 19 Mar 2021 to 18 Mar 2022. DD MMM YYYY.

U06-0269 Risk Management Plan for Dabigatran etexilate. 11 Jan 2007.

U06-1616 A Phase III, randomized, parallel-group, double-blind, active controlled study to investigate the efficacy and safety of two different dose regimens (75 mg Day 1 followed by 150 mg Day 2 completion, and 110 mg Day 1 followed by 220 mg Day 2 completion) of dabigatran etexilate administered orally (capsules), compared to enoxaparin 30 mg twice a day subcutaneous for 12–15 days in prevention of venous thromboembolism in patients with primary elective total knee replacement surgery – RE-MOBILIZE. 1160-0024. 30 Nov 2006.

U06-1704 Pharmacokinetics, pharmacodynamics, safety and tolerability of 150 mg dabigatran etexilate p.o. in patients with different degrees of renal impairment. 9 Nov 2006.

U07-3034 Summary of clinical safety (dabigatran etexilate, primary VTE prevention). 23 Jan 2007.

U07-3436-01 A randomised, parallel-group, double-blind, placebo controlled study to investigate the efficacy and safety of BIBR 1048 in prevention of venous thromboembolism in patients with primary elective total knee replacement surgery. 1160-0050. 05 Apr 2007.

U09-3249-02 Randomized Evaluation of Long term anticoagulant therapY (RELY®) comparing the efficacy and safety of two blinded doses of dabigatran etexilate with open label warfarin for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation: prospective, multi-centre, parallel-group, non-inferiority trial. RE-LY® STUDY. 1160-0026. 05 Jan 2011.

U11-1638-03 GLORIA-AF: Global Registry on Long-Term Oral Antithrombotic Treatment in Patients with Atrial Fibrillation (Phase II/III). 10 Jun 2013.

U11-2257-01 Open label, non randomized, multiple dose Phase I study to investigate the elimination, pharmacokinetics, pharmacodynamics and safety of dabigatran etexilate (Pradaxa®) under steady state conditions before, during and after haemodialysis in patients with End Stage Renal Disease (ESRD) undergoing regular haemodialysis. 1160-0121. 06 Sep 2011.

U12-1556-01 Observational cohort study to evaluate the safety and efficacy of Pradaxa® (dabigatran etexilate) for the prevention of venous thromboembolism in

patients undergoing elective total hip replacement surgery or total knee replacement surgery in a routine clinical setting. 1160-0085. 23 May 2012.

U12-2617-01 Summary of clinical safety. Treatment of acute DVT and/or PE and prevention of related death; and prevention of DVT and/or PE and related death. 10 Apr 2013.

U12-2653-01 SCS supportive appendix. Dabigatran etexilate, hard capsules 150 mg b.i.d. Appendices pertaining to 2.7.4. 15 Apr 2013.

U12-3378-01 Open-label safety and tolerability study of dabigatran etexilate given for 3 days at the end of standard anticoagulant therapy in children aged 12 years to less than 18 years. 1160-0088. 05 Jul 2012.

U13-3509-01 RELY-ABLE long term multi-center extension of dabigatran treatment. 1160-0071. 19 Jun 2013.

ABBREVIATIONS

ACS	Acute coronary syndrome
ADR	Adverse drug reaction
AE	Adverse event
AF	Atrial fibrillation
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
ASA	Acetyl salicylic acid
AST	Aspartate aminotransferase
AUC	Area under the curve
aVTEt/sVTEp	Treatment of DVT and PE, and prevention of recurrent DVT and PE in adults
b.i.d.	Bis in die, twice daily
BI	Boehringer Ingelheim
CAD	Coronary artery disease
CCDS	Company Core Data Sheet
CHA2DS2-VASc	Congestive heart failure, hypertension, age, diabetes mellitus,stroke, vascular disease, age, sex category, score to predict the risk of stroke
CHADS2	Congestive heart failure, hypertension, age, diabetes mellitus, stroke, score to predict the risk of stroke
CHF	Chronic heart failure
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CKD	Chronic kidney disease
CKD-EPI	Chronic kidney disease epidemiology collaboration
C_{max}	Maximum concentration
CRBE	Clinically relevant bleeding event
CrCl	Creatinine clearance
CRNMBE	Clinically relevant non-major bleeding event
CSR	Clinical study report
CTR	Clinical Trial Report
CV	Cardiovascular

DE	Dabigatran
DE-DAT	Dabigatran dual antithrombotic therapy (dabigatran + clopidogrel or ticagrelor)
DLP	Data lock point
DOAC	Direct oral anticoagulant
DoD	Department of Defense
dTT	Diluted thrombin time
DVT	Deep vein thrombosis
ECG	Electrocardiogram
ECT	Ecarin clotting time
ED	Emergency department
Edox	Edoxaban
EEA	European Economic Area
eGFR	Epidermal glomerular filtration rate
EMA	European Medicines Agency
ER	Emergency room
ESRD	End stage renal disease
EU	European Union
FDA	Food and Drug Administration
FOBT	Faecal occult blood test
FUM	Follow-up measure
GSP	Global safety platform
GFR	Glomerular filtration rate
GI	Gastrointestinal
GIS	Gastrointestinal symptoms
GVP	Good pharmacovigilance practice
GU	Urogenital
HAS-BLED	Hypertension, Abnormal liver/renal function, Stroke history, Bleeding history or predisposition, Labile INR, Elderly, Drug/alcohol usage
HCP	Healthcare professional
HPLC-MS/MS	High performance liquid chromatography – tandem mass spectrometry
HR	Hazard ratio

ICH	International Council on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICH	Intracranial haemorrhage
INR	International normalised ratio
ISTH	International Society on Thrombosis and Haemostasis,
LMWH	Low molecular weigh heparin
MAH	Marketing authorisation holder
MBE	Major bleeding event
MDRD	Modification of diet in renal disease
MedDRA	Medical Dictionary for Drug Regulatory Activities
MI	Myocardial infarction
N	Number of patients
NIS	Non-interventional study
NOAC	Novel oral anticoagulant
NVAF	Non-valvular atrial fibrillation
NYHA	New York Heart Association
OAC	Oral anticoagulants
PAC	Patient Alert Card
PBRER	Periodic Benefit-Risk Evaluation Report
PCI	Percutanoeous coronary intervention
PD	Pharmacodynamic
PE	Pulmonary embolism
PFP	Product Familiarisation Program
PG	Prescriber Guide
P-gp	P-glycoprotein
PK	Pharmacokinetic
PS	Propensity score
PSM	Propensity score matching
PT	Preferred term
pVTEp	Primary prevention of VTEs in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery
PY	Patient-years
q.d.	Quaque die, once daily

RF	Renal function
Riva	Rivaroxaban
RMM	Risk minimsation measure
RMP	Risk Management Plan
ROW	Rest of World
RR	Relative risk
SAE	Serious adverse event
SCS	Summary of Clinical Safety
SD	Standard deviation
SE	Systemic embolism
SEAP	Statistical and Epidemiological Analysis Plan
SmPC	Summary of Product Characteristics
SMQ	Standard MedDRA query
SOC	System organ class
SPAF	Prevention of stroke and systemic embolism in adult patients with NVAF, with one or more risk factors, such as prior stroke or TIA; age ≥ 75 years; heart failure (NYHA Class ≥ II); diabetes mellitus; hypertension
SSE	Stroke or systemic embolism
sVTEp	See aVTEt/sVTEp above
$t_{1/2}$	Terminal half-life
TAT	Triple antithrombotic therapy (warfarin + clopidogrel or ticagrelor)
THR	Total hip replacement
TIA	Transient ischaemic attack
TIMI	Thrombolysis in Myocardial Infarction
TKR	Total knee replacement
UK	United Kingdom
ULN	Upper limit of normal
US	United States
VKA	Vitamin K antagonist
vs.	versus
VTE	Venous thromboembolic event
WHO DD	World Health Organization Drug Dictionary

MODULE SVIII SUMMARY OF THE SAFETY CONCERNS

SVIII.Table 1 Summary of safety concerns

Important identified risks	Haemorrhage
Important potential risks	None
Missing information	Patients aged 0 to 2 years who were born prematurely[1] Paediatric patients with renal dysfunction (eGFR <50ml/min)[1]

[1]This safety concern is only valid in countries where the paediatric indication is approved.

SVIII.1 REFERENCES

Not applicable.

ABBREVIATIONS

Not applicable.

PART III PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

PART III.1 ROUTINE PHARMACOVIGILANCE ACTIVITIES

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires for the important identified risk 'Haemorrhage':
A questionnaire to collect standardised data to follow-up on serious haemorrhagic events is used for all spontaneous case reports where such a haemorrhagic event has been reported (Appendix 4). The questionnaire collects information on details of the reported bleeding event, such as the anatomic location, time of occurrence of the first signs or symptoms, outcome, medical history of bleeding events, alternative explanations, risk factors (e.g. liver diseases, injuries), renal impairment, treatment for bleeding, concomitant medication, action taken with Pradaxa, and reporter's causality.

Other forms of routine pharmacovigilance activities:
None.

PART III.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Part III.2.1 Study 1160.307 - category 3

Study short name and title
Safety of dabigatran etexilate for treatment of VTEs and prevention of recurrent VTE in paediatric patients from birth to less than 2 years of age: a European non-interventional cohort study based on new data collection.

Rationale and study objectives:
Conducted clinical trials evaluated limited numbers of young children with VTE. There exists a need for post-authorisation data collection to characterise the safety profile of dabigatran for treatment of VTE in children under 2 years of age.

Primary objective of this non-interventional study is to estimate the incidence of any bleeding events (major bleeding according to ISTH definition and minor bleeding events) among children under 2 years of age treated with dabigatran etexilate.

Secondary objectives are to:

- Describe baseline characteristics of children under 2 years of age administered dabigatran
- Estimate the incidence of recurrent VTE
- Estimate the frequency of AEs and SAEs

A further objective will be to estimate the incidence of post-thrombotic syndrome.

Study design:
This is a European non-interventional multi-centre cohort study based on new data collection. The study aims to enrol 50 paediatric patients under 2 years of age treated with dabigatran at approximately 30 study centres over a 2-year period. The time to evaluate the safety profile of dabigatran will be 3 months. Patients will be enrolled at paediatric hospitals/hospital departments and clinics. Safety outcomes will be estimated during the on-treatment period starting the day of cohort entry and ending at the time of disenrollment, death, discontinuation of the dabigatran treatment or switch to different anticoagulant, end of observation period (3 months), whichever comes first.

Study populations:
Patients under 2 years of age treated with dabigatran etexilate for VTE and for the prevention of recurrent VTE.

Milestones:

- Protocol submitted 22 Jun 2021
- Final study report estimated Q2 2025

PART III.3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

PIII.Table 1 Ongoing and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 – Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 – Required additional pharmacovigilance activities				
Ongoing				
None.				
Planned				
1160.307: Safety of dabigatran etexilate for treatment of VTE and prevention of recurrent VTE in paediatric patients from birth to less than 2 years of age: a European non-interventional cohort study based on new data collection.	Safety in patients under 2 years of age	Haemorrhage	Protocol Final study report	Submitted 22 Jun 2021 Estimated Q2 2025

PART III.4 REFERENCES

Not applicable.

ABBREVIATIONS

ADR	Adverse drug reaction
AE	Adverse event
HCP	Healthcare professional
ISTH	International Society on Thrombosis and Haemostasis
VTE	Venous thromboembolism

PART IV PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

This part is not applicable as there are no planned or ongoing post-authorisation efficacy studies imposed for Pradaxa.

PART IV.1 REFERENCES

Not applicable.

ABBREVIATIONS

Not applicable.

PART V RISK MINIMISATION MEASURES

RISK MINIMISATION PLAN

PART V.1 ROUTINE RISK MINIMISATION MEASURES

PV.Table 1 Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Important identified risks	
Haemorrhage	*Routine risk communication* SmPC Section 4.8 PL Section 4 *Routine risk minimisation activities recommending specific clinical measures to address the risk* *SmPC* • Section 4.2, where advice is given on estimating kidney function prior to treatment initiation and periodically as clinically indicated. This section also includes a description of patients at risk of haemorrhage • Section 4.3, where treatment is contraindicated in patient populations at risk • Section 4.4, where advice is given on patients at risk of haemorrhage. This section also provides information on the availability of the specific reversal agent Praxbind (idaruzicumab) for use when rapid reversal of anticoagulation is required • Section 4.5, which describes drug-drug interactions that might lead to an increased risk of haemorrhagic events • Section 4.9, where advice is given on management of overdose situations, including a reference to the specific reversal agent Praxbind (idaruzicumab) *PL* • Conditions and concomitant medications increasing the risk of bleeding are detailed in PL Sections 2 and 3
	Other risk minimisation measures beyond the Product Information Praxbind (idarucizumab) has been approved in adult patients as a specific reversal agent for rapid reversal of the anticoagulation effect of dabigatran case of emergency surgery or urgent procedures for situations of life-threatening or uncontrolled bleeding A paediatric investigation plan for idarucizumab has been completed. In paediatric patients for whom the specific reversal agent cannot be used, haemodialysis can remove dabigatran.

PV.Table 1 (cont'd) Description of routine risk minimisation measures by safety concern

Important potential risks	
None	
Missing information	
Patients aged 0 to 2 years who were born prematurely	*Routine risk communication* None. *Routine risk minimisation activities recommending specific clinical measures to address the risk* None. *Other risk minimisation measures beyond the Product Information* None.
Paediatric patients with renal dysfunction (eGFR <50ml/min)	*Routine risk communication* None *Routine risk minimisation activities recommending specific clinical measures to address the risk* *SmPC* Sections 4.2 and 4.4 *PL* Section 2 *Other risk minimisation measures beyond the Product Information* None

PART V.2 ADDITIONAL RISK MINIMISATION MEASURES

Part V.2.1 Risk of haemorrhage

Prescriber Guide for HCPs and Patient Alert Card for patients

Objectives
A PG is available for each approved indication. A separate PG is available for the paediatric indication.

In addition, a PAC that is valid for all indications is included in every package of Pradaxa as follows:

- Pradaxa capsules: combined paediatric/adult content

PACs used exclusively for the paediatric indication:

- Pradaxa coated granules: paediatric content only

Rationale for the additional risk minimisation activity
The Pradaxa PG and PAC were implemented to alert prescribers and patients, respectively, to the risk of haemorrhage when taking Pradaxa and to prevent the use of Pradaxa in patients with increased haemorrhage risks.

Target audience and planned distribution path
Target audience for the Pradaxa PG are physicians who prescribe Pradaxa. For the adult indications, these are cardiologists and general practitioners; prescribers are provided with the PG through customer facing functions (sales force, key account managers).

Paediatricians (e.g. paediatric haematologistis/oncologists, and emergency medicine physicians) will be provided with the PG through direct mailing. Additionally, for improvement of distribution, the Pradaxa PG will be distributed via digital media.

Target audience for the Pradaxa PAC are patients and, for the paediatric indication, caregivers, who receive Pradaxa prescriptions. Patients (and caregivers for the paediatric indication) receive the PAC at each prescription, since the PAC is included in every Pradaxa package.

Plans to evaluate the effectiveness of the interventions and criteria for success
For the evaluation of the effectiveness of the distribution of PG and PAC for the adult indications, study 1160.149 was performed. The objective of the study was to provide data on:

- Physicians' knowledge and recommendations to their patients on appropriate dosing and minimising the risk of bleeding when treated with Pradaxa
- Patients' understanding of the disease, bleeding signs, what to do in case of bleeding and how to deal with emergency situations

In summary, both PG and PAC were accepted and understood in the majority of prescribers and patients when received.

As a follow-up measure based on the results from study 1160.149, BI has implemented an action plan to improve distribution of the educational material. On 01 Jan 2020, the MAH initiated the switch in the EEA region from face-to-face distribution to the prescribing HCP through customer facing functions to digital availability of the PG and PAC.
All countries in the EMA region updated their local communication plan and implemented digital channels where HCPs and patients can download PG and PAC, respectively. Now

EAA countries utilise digital PG and PAC distribution. The digital switch of PG and PAC was finalised by the first half of 2021. Upon request, the HCP are still provided with hard copies of the PG and PAC. Monitoring of clicks and downloads (where available and allowed by local law) will be included in future PBRERs.

PART V.3 SUMMARY OF RISK MINIMISATION MEASURES

PV.Table 2 Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risks		
Haemorrhage	SmPC Sections 4.2, 4.3, 4.4, 4.5, 4.8, and 4.9 PL Sections 2, 3, and 4 Other risk minimisation measures: Praxbind (idarucizumab) has been approved in adult patients as a specific reversal agent for rapid reversal of the anticoagulation effect of dabigatran case of emergency surgery or urgent procedures for situations of life-threatening or uncontrolled bleeding. For paediatric patients, haemodialysis can remove dabigatran. Additional risk minimisation measures: Prescriber guide and patient alert card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up form Additional pharmacovigilance activities: Study 1160.307
Important potential risks		
None		
Missing information		
Patients aged 0 to 2 years who were born prematurely	No risk minimisation measures	Routine pharmacovigilance activities
Paediatric patients with renal dysfunction (eGFR <50ml/min)	SmPC Sections 4.2 and 4.4 PL Section 2	Routine pharmacovigilance activities

PART V.4 REFERENCES

Not applicable.

ABBREVIATIONS

BI	Boehringer Ingelheim
EEA	European Economic Area
HCP	Healthcare professional

MAH	Marketing authorisation holder
PBRER	Periodic Benefit-Risk Evaluation Report
PAC	Patient Alert Card
PG	Prescriber Guide
SmPC	Summary of Product Characteristics

PART VI SUMMARY OF THE RISK MANAGEMENT PLAN

SUMMARY OF RISK MANAGEMENT PLAN FOR PRADAXA (dabigatran etexilate)

This is a summary of the Risk Management Plan (RMP) for Pradaxa. The RMP details important risks of Pradaxa, how these risks can be minimised, and how more information will be obtained about Pradaxa's risks and uncertainties (missing information).

Pradaxa's Summary of Product Characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Pradaxa should be used.

This summary of the RMP for Pradaxa should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Pradaxa's RMP.

I. THE MEDICINE AND WHAT IT IS USED FOR

Pradaxa contains the active substance dabigatran and belongs to a group of medicines called anticoagulants. It works by blocking the activity of a substance in the body which is involved in blood clot formation.

Pradaxa is used in adults to (see SmPC for the full indications):

- Prevent the formation of blood clots in the veins after knee or hip replacement surgery
- Prevent blood clots in the brain (stroke) and other blood vessels in the body if you have a form of irregular heart rhythm called nonvalvular atrial fibrillation and at least one additional risk factor
- Treat blood clots in the veins of your legs and lungs and to prevent blood clots from re-occurring in the vein of your legs and lungs

Pradaxa is used in children from the time they are able to swallow to (see SmPC for the full indication):

- Treat blood clots and prevent blood clots from reoccurring

Further information about the evaluation of Pradaxa's benefits can be found in Pradaxa's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage.

II. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMISE OR FURTHER CHARACTERISE THE RISKS

Important risks of Pradaxa, together with measures to minimise such risks and the proposed studies for learning more about Pradaxa's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In the case of Pradaxa, these measures are supplemented with additional risk minimisation measures mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Pradaxa is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Pradaxa are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Pradaxa. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

List of important risks and missing information

Important identified risks	Haemorrhage
Important potential risks	None
Important missing information	Patients aged 0 to 2 years who were born prematurely[1]
	Paediatric patients with renal dysfunction (eGFR <50ml/min)[1]

[1]This safety concern is only valid in countries where the paediatric indication is approved.

II.B Summary of important risks

Important identified risk Haemorrhage	
Evidence for linking the risk to the medicine	Anticoagulation bears an inherent risk of haemorrhage. Based on clinical and post-marketing data, haemorrhage was defined as an important identified risk for Pradaxa. Dabigatran (the active substance of Pradaxa) is eliminated through the kidneys, and kidney function diminishes with increasing age. Therefore, the rates of haemorrhages depend on the dose and are related to renal (kidney) failure and age.
Risk factors and risk groups	The risk of haemorrhages with Pradaxa increases with declining kidney function. Kidney function diminishes with age. Therefore, the elimination of dabigatran may be reduced, and dabigatran blood levels may be increased, in elderly patients and in patient with reduced kidney function. As a consequence, the risk of bleeding is increased in these patients. The highest rates occur in the very elderly (age >75 years) with poor kidney function.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Sections 4.2, 4.3, 4.4, 4.5, 4.8, and 4.9 • PL Sections 2, 3, and 4 Other risk minimisation measures: • Praxbind (idarucizumab) has been approved in adult patients as a specific reversal agent for rapid reversal of the anticoagulation effect of dabigatran case of emergency surgery or urgent procedures for situations of life-threatening or uncontrolled bleeding. A paediatric investigation plan for idarucizumab has been completed. In paediatric patients for whom the specific reversal agent cannot be used, haemodialysis can remove dabigatran. Additional risk minimisation measures: • Prescriber guide and patient alert card
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Study 1160.307 See Section II.C of this summary for an overview of the post-authorisation development plan.

Missing information Patients aged 0 to 2 years who were born prematurely	
Risk minimisation measures	No risk minimisation measures

Missing information Paediatric patients with renal dysfunction (eGFR <50ml/min)	
Risk minimisation measures	Routine risk minimisation measures: • SmPC Sections 4.2 and 4.4 • PL Section 2

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

The following studies are conditions of the marketing authorisation:

There are no studies which are conditions of the marketing authorisation or specific obligation of Pradaxa.

II.C.2 Other studies in post-authorisation development plan

- Study 1160.307: Safety of dabigatran etexilate for treatment of VTE and prevention of recurrent VTE in paediatric patients from birth to less than 2 years of age: a European non-interventional cohort study based on new data collection

  Purpose of the study: Conducted clinical trials evaluated limited numbers of young children with VTE. There exists a need for post-authorisation data collection to characterise the safety profile of dabigatran for treatment of VTE in children under 2 years of age.

  The main objective of this non-interventional study is to estimate the incidence of any bleeding events (major bleeding according to ISTH definition and minor bleeding events) among children under 2 years of age treated with dabigatran etexilate.

ABBREVIATIONS

ADR	Adverse drug reaction
AF	Atrial fibrillation
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report

EU	European Union
GLORIA-AF	Global Registry on Long-Term Oral Antithrombotic Treatment In Patients with Atrial Fibrillation
PL	Patient leaflet
RMP	Risk Management Plan
SCAR	Severe cutaneous adverse reaction
SmPC	Summary of Product Characteristics

PART VII APPENDICES

PART VII TABLE OF CONTENTS

APPENDIX 4 SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Questionnaire: Bleeding Event Form Pradaxa - Version 8.1

Question ID	BI Questionnaire owner / TA	Questionnaire Name	Question category	Question
Q:BP01	Cardiovascular	Bleeding Event Form (Pradaxa)	Questionnaire	What was the gastrointestinal location of the reported bleeding? Gastrointestinal haemorrhage; Hematemesis: red blood or coffee grounds material Melena: black, tarry, foul-smelling stool; Hematochezia: bright red or maroon blood from rectum Occult GI bleeding: blood in stool in the absence of overt bleeding
Q:BP02	Cardiovascular	Bleeding Event Form (Pradaxa)	Questionnaire	What was the location of the reported bleeding? Intracranial haemorrhage Skinbleeding Blood in urine Genital haemorrhage Wound haemorrage /procedural site haemorrhage Other site (specify) No location identified
Q:BP03	Cardiovascular	Bleeding Event Form (Pradaxa)	Questionnaire	When did the first signs or symptoms of the reported bleeding event occur? Prior to start of treatment with Pradaxa, please specify: days/weeks. After start of treatment with Pradaxa, please specify: days/weeks. Not known
Q:BP04	Cardiovascular	Bleeding Event Form (Pradaxa)	Questionnaire	Does the patient have any episodes of bleeding in the medical history? If ”Yes” please specify.
Q:BP05	Cardiovascular	Bleeding Event Form (Pradaxa)	Questionnaire	Was there an alternative explanation, other than Pradaxa ®, for the bleeding event? If ”Yes” please specify.
Q:BP06	Cardiovascular	Bleeding Event Form (Pradaxa)	Questionnaire	Did the patient suffer from liver diseases that might have influenced the bleeding event? If ”Yes” please specify.
Q:BP07	Cardiovascular	Bleeding Event Form (Pradaxa)	Questionnaire	Did the patient suffer from an injury (e.g. fall, trauma, accident) that might have influenced the bleeding event? If ”Yes” please specify.

Questionnaire: Bleeding Event Form Pradaxa - Version 8.1

Q:BP08	Cardiovascular	Bleeding Event Form (Pradaxa)	Questionnaire	Did the patient suffer from renal impairment prior to or at the event onset of the bleeding event? Please specify: Renal function decreased prior to start with Pradaxa or renal function decreased prior to bleeding event.
Q:BP09	Cardiovascular	Bleeding Event Form (Pradaxa)	Questionnaire	Parameter Please provide date, value, and unit for - Creatinine - CrCl - GFR
Q:BP10	Cardiovascular	Bleeding Event Form (Pradaxa)	Questionnaire	Which treatment for the bleeding event was initiated? No treatment was initiated; Surgical procedure (please specify); blood transfusion (please specify; units; other drugs (please specify).

APPENDIX 6 DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES (IF APPLICABLE)

RISK OF HAEMORRHAGE

Adult and paediatric populations

Key messages of the additional risk minimisation measures

Physician educational material:

- The Summary of Product Characteristics
- Guide for healthcare professionals (prescriber guide) – separate document available for the paediatric indication
- **Guide for healthcare professionals (prescriber guide):**
    - Details of populations potentially at higher risk of bleeding
    - Information on medicinal products that are contraindicated or which should be used with caution due to an increased risk of bleeding and/or increased dabigatran exposure
    - Contraindication for patients with prosthetic heart valves requiring anticoagulant treatment
    - Recommendation for kidney function measurement
    - Recommendations for dose reduction in at risk populations
    - Management of overdose situations
    - The use of coagulation tests and their interpretation
    - That all patients should be provided with a Patient alert card and be counselled about:
        - Signs or symptoms of bleeding and when to seek attention from a health care provider
        - Importance of treatment compliance
        - Necessity to carry the Patient alert card with them at all times
        - The need to inform Health Care Professionals about all medicines they are currently taking
        - The need to inform Health Care Professionals that they are taking Pradaxa if they need to have any surgery or invasive procedure
        - An instruction how to take Pradaxa

The patient information pack:

- Patient information leaflet
- Patient alert card – available as follows:
    - Pradaxa capsules: combined paediatric/adult content
    - Pradaxa coated granules: paediatric content only

- **Patient guide (patient alert card)**
    - Signs or symptoms of bleeding and when to seek attention from a health care provider
    - Importance of treatment compliance
    - Necessity to carry the Patient alert card with them at all times
    - The need to inform Health Care Professionals about all medicines they are currently taking
    - The need to inform Health Care Professionals that they are taking Pradaxa if they need to have any surgery or invasive procedure