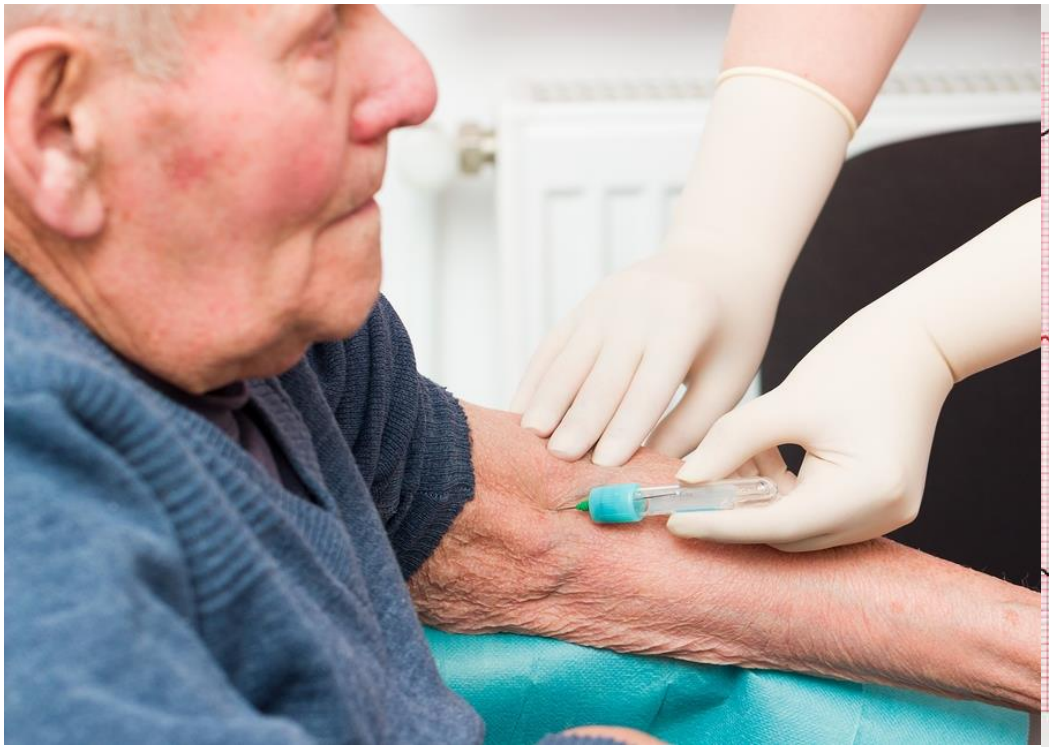
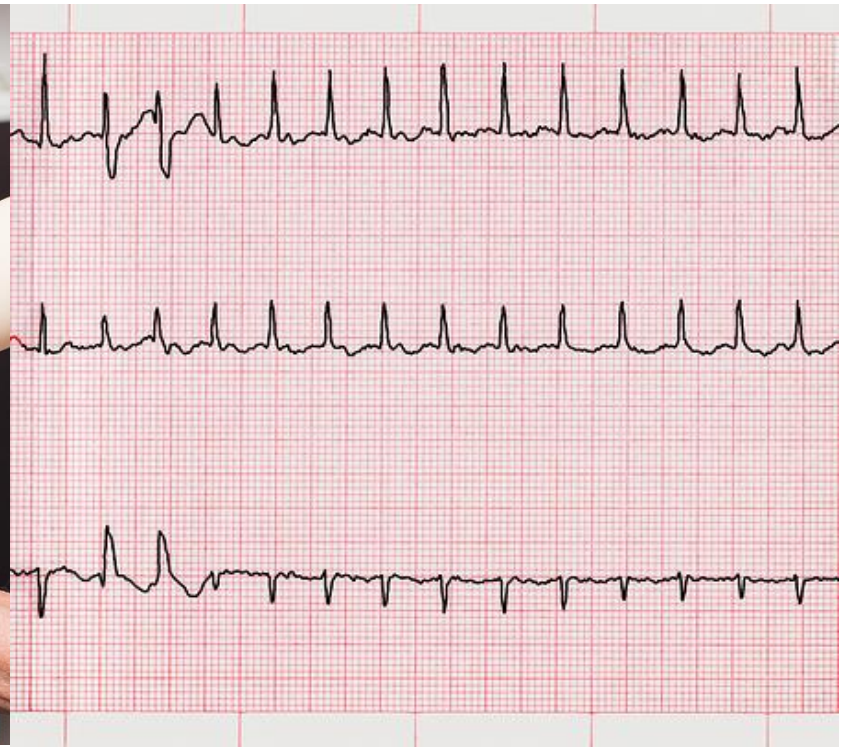
KCE REPORT 279

Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Centre

ANTICOAGULANTS IN NON-VALVULAR ATRIAL FIBRILLATION





KCE REPORT 279
HEALTH TECHNOLOGY ASSESSMENT

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ANTICOAGULANTS IN NON-VALVULAR ATRIAL FIBRILLATION

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2017 www.kce.fgov.be

COLOPHON

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Acknowledgements:	We thank the Southampton Health Technology Assessments Centre (SHTAC) for their commentary and advice on the chapter on cost-effectiveness. We thank Dominique Roberfroid (KCE) for calculating the pooled risk estimates per CHA2DS2-VASc stratum. We thank Carine Pochet (IMA) for running the analyses on Belgian data (IMA database).
Other reported interests:	Fees or other compensation for writing a publication or participating in its development: Rob Cook (Bazian will be paid a fee by the KCE to deliver the chapter 8 of this report) A grant, fees or funds for a member of staff or another form of compensation for the execution of research: Rob Cook (Bazian are paid to deliver a range of scientific research projects), Olivier Gurné (Yearly grant from Bayer for research in cardiology at Cliniques universitaires Saint-Luc) Consultancy or employment for a company, an association or an organisation that may gain or lose financially due to the results of this report: Olivier Gurné (consultancy for Boehringer and Pfizer), Lieven Annemans (evaluations in health economy) Payments to speak, training remuneration, subsidised travel or payment for participation at a conference: Marnix Goethals (participation to the BeHRA congress – inscription sponsorised), Olivier Gurné (participation to scientific meetings with Boehringer and Pfizer), Lieven Annemans (evaluations in health economy) Presidency or accountable function within an institution, association, department or other entity on which the results of this report could have an impact: Rob Cook (Bazian lead on a range of scientific research projects) Participation in scientific or experimental research as an initiator, principal investigator or researcher: Philippe Hainaut (Principal Investigator for most NOACs trials in VTE), Olivier Gurné (RELY and ARISTOTLE studies), Lieven Annemans (evaluations in health economy)

	Other possible interests that could lead to a potential or actual conflict of interest: Philippe Hainaut (Advisory boards NOACs pharmaceutical companies)
Layout:	Ine Verhulst, Joyce Grijseels

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Publication date:	9 januari 2017
Domain:	Health Technology Assessment (HTA)
MeSH:	atrial fibrillation; anticoagulants; secondary prevention; Belgium; cost-benefit analysis; Practice Patterns, Physicians'; Practice Guidelines as Topic
NLM Classification:	QV 193
Language:	English
Format:	Adobe® PDF™ (A4)
Legal depot:	D/2016/10.273/101
ISSN:	2466-6459

How to refer to this document?

Van Brabandt H, San Miguel L, Fairon N, Vaes B, Henrard S, Boshnakova A, Cook R, Davies R, Karnad A, Lovell A, Dubois C. Anticoagulants in non-valvular atrial fibrillation. Health Technology Assessment (HTA) Brussels: Belgian Health Care Knowledge Centre (KCE). 2016. KCE Reports 279. D/2016/10.273/101.

This document is available on the website of the Belgian Health Care Knowledge Centre.

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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
ACC	American College of Cardiology
ACE inhibitor	Angiotensin-Converting-Enzyme inhibitor
AF	Atrial Fibrillation
AHA	American Heart Association
AT II inhibitor	Angiotensin II receptor inhibitor
ATC	Anatomical Therapeutic Chemical
CEA	Cost-effectiveness analysis
CHD	Coronary Heart Disease
CUA	Cost-utility analysis
CVD	Cardiovascular Disease
DTI	Direct Thrombin Inhibitor
ECG	Electrocardiogram
ESC	European Society of Cardiology
FUP	Follow-up
FXaI	Factor Xa Inhibitor
GP	General Practitioner
HR	Hazard Rate
HR-QoI	Health-Related Quality of Life
HTA	Health Technology Assessment
ICER	Incremental cost-effectiveness ratio
ICPC-2	International Classification of Primary Care, 2nd edition
INAMI	Institut national d'assurance maladie-invalidité
INR	international normalised ratio
IQR	Interquartile range
LYG	Life years gained
NICE	The National Institute for Health and Care Excellence
NIHDI	National Institute for Health and Disability Insurance
NOAC	New Oral AntiCoagulant

NVAF	Non-valvular atrial fibrillation
OAC	Oral AntiCoagulant
PICO	Patient intervention comparator outcome
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QALY	Quality-adjusted life years
QoL	Quality of Life
RCT	Randomized Controlled Trial
Riziv	Rijksinstituut voor ziekte- en invaliditeitsverzekering
SIGN	Scottish Intercollegiate Guidelines Network
SR	Systematic Review
TIA	Transient Ischemic Attack
TTR	time in therapeutic range (of the international normalised ratio)
VKA	Vitamin K antagonist
WTP	Willingness to pay

SCIENTIFIC REPORT

1 AIMS

The present report is a rapid health technology assessment (HTA) of a new generation of oral anticoagulants. They are most often referred to as NOACs ("New Oral AntiCoagulants", "Novel Oral AntiCoagulants", "Non-vitamin-K Oral AntiCoagulants") but are also known as "Direct Oral Anticoagulants" (DOACs). Further in this report, we will use the acronym NOAC.

This HTA report includes:

1. A review on the clinical efficacy and safety of NOACs vs. vitamin K antagonists (VKAs) in patients with non-valvular atrial fibrillation (AF). Special attention is paid to stroke risk assessment in AF patients, as well as to the adherence of prescribers to practice guidelines in patients at the higher and lower end of the stroke-risk spectrum.
2. A systematic literature review and critical appraisal of international and Belgian economic evaluations of NOACs.
3. A description of anticoagulation practice in AF patients in Belgium. One part is devoted to a description of a subset of Flemish patients (Intego database) with a diagnosis of atrial fibrillation. A second part describes anticoagulation practice in Belgian patients treated with an anticoagulant, based on claims data (IMA – AIM database).

2 INTRODUCTION

New Oral AntiCoagulants are drugs used to prevent stroke and arterial thromboembolic events in patients with non-valvular AF. They are also available for use in the treatment and prevention of venous thromboembolic disease (venous thrombosis, pulmonary embolism), and in fact this was their first clinical indication. NOACs have been gradually introduced in Belgium for AF since August 2012. Presently 3 different NOACs are reimbursed: Eliquis (apixaban), Pradaxa (dabigatran), and Xarelto (rivaroxaban). They are increasingly replacing the older vitamin K antagonists (VKAs) [Marcoumar (phenprocoumon), Sintrom (acenocoumarol), and Marevan (warfarin)].

Between 2004 and 2015, the budget spent by the Belgian National Institute for Health and Disability Insurance (NIHDI, Riziv/Inami) for reimbursing anticoagulants has increased almost 60-fold from 1.6 to 95.3 million €. This amount does not taken into consideration savings related to the use of NOACs (no need for monitoring, adverse events) neither ristorno's negotiated with industry. This increased spending is due to an increasing number of patients treated with anticoagulants, and the introduction of the NOACS that cost per day almost ten times more than the VKAs. This observation has been the major motive to initiate the present Health Technology Assessment.

3 BACKGROUND

3.1 Antithrombotics

When a blood clot (thrombus) is formed within the circulatory system, it can block blood flow (thrombosis) and subsequently lead to disease such as ischemic stroke[a] or myocardial infarction. A thrombus that migrates within the circulatory system is called an embolus. Disease that results from an embolus blocking an artery is called an embolism. It is not always clear whether the blockage of an artery is caused by a thrombus or an embolus. Thromboembolic disease is a more general name that incorporates both pathophysiologic mechanisms in one single concept.

Antithrombotics are drugs used to prevent thrombosis in patients that are at increased risk of forming blood clots. Clot formation is the result of a complex interaction between the blood vessel wall, blood platelets and specific proteins (coagulation factors) that circulate within the blood. Antithrombotics derive their therapeutic effect through interaction with one or more of those elements.

There are two different kinds of antithrombotic drugs: anticoagulants and antiplatelets. Anticoagulants prevent clot formation predominantly through their action on coagulation proteins, whereas antiplatelet agents predominantly act upon platelets. Both groups of antithrombotics are available for clinical application in oral and parenteral formulations.

Aspirin (acetyl salicylic acid) is a typical antiplatelet drug. Its major indication is in the treatment and secondary prevention of acute coronary syndromes such as myocardial infarction, and peripheral artery disease.

Typical anticoagulants are coumarin (oral use), and heparin (parenteral use). These drugs are used for the treatment of venous thromboembolic disease (phlebothrombosis, pulmonary embolism) and for the prevention of thrombus formation in patients with atrial fibrillation or with a mechanical heart valve prosthesis. Whereas in venous thromboembolic disease, anticoagulation therapy is mostly temporary (3 to 6 months), in atrial fibrillation, it is mostly indicated for lifelong use.

[a] Stroke can also be induced by intracerebral bleeding in which case it is called haemorrhagic stroke.

3.2 Atrial fibrillation

Atrial fibrillation (AF) is a common heart rhythm disorder with a prevalence of 1.5-2.0% in the general population. It is characterised by a heartbeat that is irregular and most often too fast. It may occur in people with no particular heart problems, but it is also commonly seen in patients suffering from other conditions such as high blood pressure, ischemic heart disease, heart valve disease and heart failure. Depending on the underlying heart disease AF is divided into “valvular” and “non-valvular”. The term valvular AF is limited for use in AF related to rheumatic valvular disease (predominantly mitral stenosis) or prosthetic heart valves.[1]

The prevalence of AF increases with age. Less than 0.5% of people under the age of 50 suffer from AF, while 5 to 15% of over-eighty-year-olds have been diagnosed with AF.[2]

Some patients have no direct complaints when they develop AF, others complain of palpitations, being short of breath or of tiring easily. In some cases AF may lead to heart failure. The most dreaded complications of AF are thromboembolic events, particularly ischemic stroke. In AF, stroke is caused by blood clots that have formed in the left atrium coming loose and being carried along by the blood supplying the brain where they block an artery. This is most commonly seen in people over the age of 65 or in people suffering from an underlying heart condition. Therefore, these high-risk patients are treated with anticoagulants (“blood thinners”).[2]

3.3 Stroke risk assessment in atrial fibrillation

The risk for thromboembolic events in non-valvular AF is dependent on a number of risk factors. Major risk factors are prior stroke or thromboembolism, and older age (≥75 years). Non-major risk factors are heart failure (especially moderate to severe systolic LV dysfunction, defined arbitrarily as left ventricular ejection fraction ≤40%), hypertension, diabetes, female gender, age 65-74 years, and vascular disease (previous myocardial infarction, complex aortic plaque and peripheral artery disease).[3]

Several risk stratification tools have been described, among which the CHADS2 and the CHA2DS2-VASc scores which in recent years have been most studied. The CHADS2 score is cumulative on the basis of 5 clinical features: congestive heart failure (C), hypertension (H), age (A) ≥75 years, and diabetes mellitus (D) (all counted as 1 point), and a history of stroke or TIA (counted as 2 points) (Table 1).

Table 1 – Calculation of the CHADS2 and CHA2DS2-VASc risk stratification scores

	CHADS2	CHA2DS2-VASc
Congestive heart failure (especially moderate to severe systolic LV dysfunction, defined arbitrarily as left ventricular ejection fraction ≤40%)	1	1
Hypertension	1	1
Age >74 years	1	2
Diabetes mellitus	1	1
Stroke or TIA or thromboembolism in history	2	2
Vascular disease (previous myocardial infarction, complex aortic plaque and peripheral artery disease)		1
Age 65-74 years		1
Sex category (female)		1

Risk scores are obtained by adding the points (1 or 2) corresponding to each of the different risk factors. In women in whom “sex category” is the single risk factor, it is not taken into account for assessing risk.

Table 2 – Yearly risk of stroke stratified by CHADS2 score

$CHADS_2$ Score	No. of Patients (n = 1733)	No. of Strokes (n = 94)	NRAF Crude Stroke Rate per 100 Patient-Years	NRAF Adjusted Stroke Rate, (95% CI)†
0	120	2	1.2	1.9 (1.2-3.0)
1	463	17	2.8	2.8 (2.0-3.8)
2	523	23	3.6	4.0 (3.1-5.1)
3	337	25	6.4	5.9 (4.6-7.3)
4	220	19	8.0	8.5 (6.3-11.1)
5	65	6	7.7	12.5 (8.2-17.5)
6	5	2	44.0	18.2 (10.5-27.4)

Source: Gage et al.4 NRAF: National Registry of Atrial Fibrillation. In the « adjusted stroke rate », it is assumed that aspirin was not taken.

A more sensitive risk score, the CHA2DS2-VASc, has been introduced in 2009. It was originally known and developed as the "Birmingham 2009 schema and includes 3 additional non-major risk factors (female gender, age 65-74 years, vascular disease) (Table 1).[5] In women in whom "sex category" is the single risk factor, it is not taken into account for assessing risk.[6]

The CHA2DS2-VASc score has been validated in a cohort of patients extracted from the Euro Heart Survey.[5] This registry enrolled 5 333 patients, aged 66±14 years, with AF from 35 European countries, who were discharged from hospital between 2003 and 2004. The CHA2DS2-VASc score was validated in a cohort of 1084 patients that were not treated with an anticoagulant at discharge. The observed number of thromboembolic events by CHA2DS2-VASc score, observed during the first year after discharge fom hospital, is displayed in Table 3. As compared to the CHADS2 score, the CHA2DS2-VASc score better identifies individuals with a stroke risk that is close to zero. However, by increasing the sensitivity of the score, the number of false-postives inevitably increases as well.

Table 3 – Risk of thromboembolic events and ischemic stroke by CHA2DS2-VASc score

	Observed data in the CHA2DS2-VASc validation study (1)		Calculated data reported in EU and US guidelines (2)		Meta-analysis Asian studies		Meta-analysis Western studies	
Number:	1,084		7,329		289,089		119,396	
Era:	2003 - 2004		2000 - 2001		SR up to April 2015		SR up to April 2015	
CHA2DS2-VASc score	Number of events	TE event rate/year	Number of events	TE event rate/year	Number of events	Ischemic strokes/year	Number of events	Ischemic strokes/year
0	0	0	0	0	705	1.16 (0.52-1.80)	56	0.23 (0.03-0.42)
1	1	0.7	3	1.3	2389	**2.22 (0.84-3.59)**	128	**0.56 (0.08-1.03)**
2	3	1.9	15	2.2	3918	3.03 (1.12-4.94)	401	1.89 (1.12-2.59)
3	8	4.7	31	3.2				
4	4	2.3	38	4.0				
5	3	3.9	42	6.7				
6	2	4.5	36	9.8				
7	2	10.1	15	9.6				
8	1	14.2	3	6.7				
9	1	100	1	15.2				
Total	25		184					

Source: (1) Observed stroke rates in the Euro Heart Survey, used for the validation of the CHA2DS2-VASc score.[5] (2) Data reported in 2010 EU[3] and 2014 US[7] guidelines, by extrapolating data from the SPORTIF studies.[8] SR: systematic review. Asian and Western studies: data extracted from Joundi et al.(systematic review until April 2015). [9] Forest plots in the Appendix to this report.

CHA2DS2-VASc showed a modest improvement in predictive value against CHADS2.[5, 10] The c-statistic, representing a measure of the predictive ability of the test to correctly classify an individual into low (score=0), intermediate (score=1) or high (score>1) risk for thromboembolism, is 0.586 (0.477-0.695) for CHADS2 and 0.606 (0.513-0.699) for CHA2DS2-VASc.[5] The poor predictive value of these scores has been attributed to our incomplete understanding of the pathophysiological mechanisms underlying thromboembolism in AF.[11]

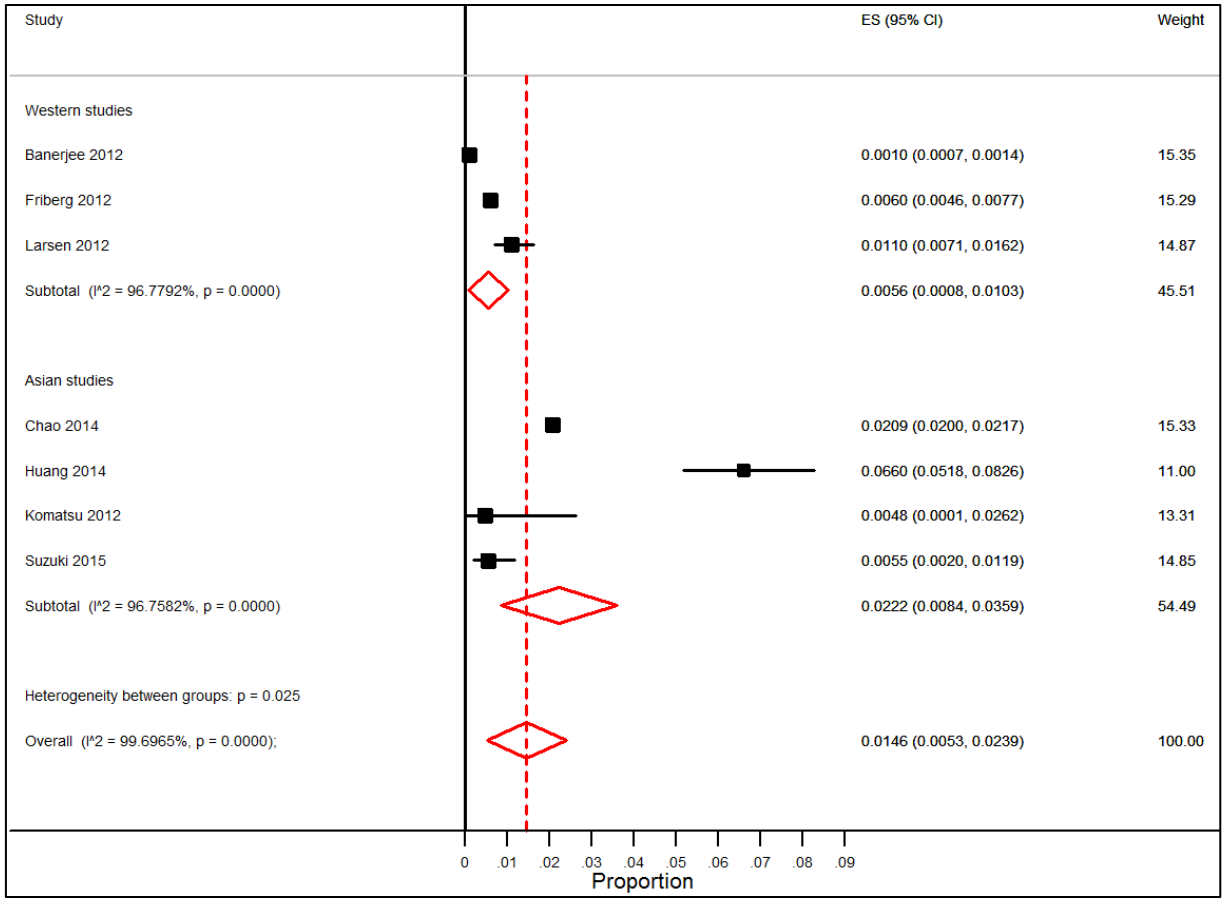
Among experts, there is considerable debate on the need for anticoagulation in patients with a CHA2DS2-VASc score=1 which is essentially due to the fact that the real risk of stroke for such patients is not known. Most data are extracted from observational (non-randomised) studies. Moreover, across registries definitions of thromboembolic events vary, and authors may decide to count strokes only, or to include all thromboembolic events (ischemic stroke, pulmonary embolism, peripheral embolism). Some registries include patients as soon as the are admitted to hospital because of a thromboembolic event, others only start counting events after discharge, thus avoiding selection bias. Another source of selection bias is that the thromboembolic risk is assessed in patients that are not taking an anticoagulant. However, most often it is not known why those patients were not anticoagulated. Furthermore, the observed rates may be no longer valid nowadays because stroke rates are decreasing over time.[7, 12, 13]

In a recently published meta-analysis, ischemic stroke risk was calculated in patients with a CHA2DS2-VASc score of 0, 1 and 2 respectively.[9] Ten studies met all inclusion criteria of the study. The summary estimate for the annual risk of ischemic stroke was 0.68% (95% CI: 0.12%–1.23%) for

CHA2DS2-VASc score=0, 1.61% (95% CI: 0%–3.23%) for CHA2DS2-VASc score=1, and 2.49% (95% CI 1.16%–3.83%) for CHA2DS2-VASc score of 2. There was substantial heterogeneity among studies, a.o. resulting from diversity of the ethnicitiy of the cohorts. The risk of stroke was particularly high in Asian studies. Therefore, we recalculated the meta-analysis using a technique described by Nyaga et al.[14] in which we considered Asian and Western studies separately. We used the command metaprop in Stata 12 (Statacorp, Texas) and applied a random effects model using the method of DerSimonian and Laird, with the estimate of heterogeneity being taken from the inverse-variance fixed-effect model. Confidence interval were computed with exact binomial (Clopper-Pearson) procedures. The resulting pooled estimate per stratum for patients with a CHA2DS2-VASc=1 score is shown in Figure 1 (data from CHA2DS2-VASc risk score 0 and 2 are provided in the Appendix to this report). Series that were published after Joundi's systematic review confirm the findings we extracted from the meta-analysis.[15-18] Using the worldwide stroke risk estimate [1.61% (95% CI: 0%–3.23%)] instead of data from Western countries [(0.56% 95% CI: 0.08%-1.03%)] may lead to overdiagnosis and overtreatment.

The consideration for studying Asian and Western populations separately here is not unique. For example Japanese patients were not enrolled in the global ROCKET AF trial[19] and instead, a separate phase 3 RCT (the J-ROCKET AF study) was conducted in Japan.[20] The reported reasons were differences in pharmacokinetics and the fact that lower anticoagulation targets are used in Japanese clinical practice.[20]

Figure 1 – Ischaemic stroke risk in patients with a CHA2DS2-VASc=1 score



Source: Original data extracted from Joundi et al.[9] This forest plot provides meta-analyses of Asian and Western studies separately. The Banerjee study[21] included 132,372 hospitalised Danish patients (1997-2008). Friberg et al.[22] included 182,678 hospitalised Swedish patients (2005-2008) and Larsen et al.[23] was based on a cohort of 1603 non-hospitalised individuals.

3.4 Stroke prevention in atrial fibrillation

Stroke prevention in patients with AF used to be realised with either oral anticoagulants or antiplatelet therapy. Whereas anticoagulants act upon the coagulation cascade, antiplatelets induce their effect by acting on blood platelets. Currently, two classes of oral anticoagulants are available for clinical use: the vitamin K antagonists (VKAs) and the Novel Oral AntiCoagulants (NOACs). The European Society of Cardiology (ESC) no longer recommends antiplatelets to be used for the prevention of stroke in AF.[17]

3.4.1 Vitamin K antagonists

For decades VKAs (in particular warfarin) have been the gold standard anticoagulant in the treatment of venous thromboembolic disease (deep venous thrombosis, pulmonary embolism) and for the prevention of cardiac thromboembolic disease (stroke, systemic embolism) in patients with atrial fibrillation.[24] They exert their action by inhibiting vitamin K which is required to activate several clotting factors. The action of VKAs is characterised by a long half-life.

In Belgium, 3 different VKAs are available for clinical use phenprocoumon (Marcoumar), acenocoumarol (Sintrom), warfarin (Marevan). Half-life is different across these agents: it is 8 hours for acenocoumarol, corresponding to an anticoagulant action for 48 hours following the last intake, it is 20 to 60 hours for warfarin corresponding to an anticoagulant action for 2 to 5 days following the last intake, and it is 140 to 160 hours for fenprocoumon which corresponds to an anticoagulant action for 1 to 2 weeks following the last intake (http://www.bcfi.be/nl/chapters/3?frag=1826).

The use of VKAs is complicated by their narrow therapeutic range and by a variety of food and drug interactions. Therefore, they require regular (monthly) laboratory monitoring and dose titration by means of the so-called international normalised ratio (INR) which should be kept between values 2 and 3.[25] The quality of VKA treatment is expressed as the “time in therapeutic range (TTR)”. Inadequate follow-up and dose titration may expose patients to periods of undertreatment and overtreatment: an INR <2.0 places patients with AF at risk for stroke, and an INR >3.0 increases the risk for bleeding. According to guidelines patients treated with a VKA should spend at least 70% of their time in the desired INR range of 2-3.[6, 26]

A systematic review included 6 RCTs (2 900 participants; mean age 69 years) in which adjusted-dose warfarin was compared with placebo or no treatment. One RCT was in secondary prevention, 5 in primary prevention. Two trials were double blinded. The average stroke rate was 4.5% per year for primary prevention and 12% per year for secondary prevention among patients assigned to the placebo or control groups. In a meta-analysis, warfarin was associated with a 64% (95% CI 49%-74%) reduction in stroke. The absolute risk reduction in all strokes was 2.7% per year for primary prevention and 8.4% per year for secondary prevention.[27] The increase of extracranial bleeding in the VKA group was small and less than a non-significant 0.3% per year. The risk of intracranial bleeding was very small: out of 2,900 patients enrolled in the trials, 6 intracranial bleedings occurred in the warfarin group versus 3 in the placebo or control group.[3, 27] Real world studies report reassuringly similar results.[27-29]

3.4.2 Antiplatelets

A meta-analysis of data from 7 trials in 3990 participants, comparing aspirin alone (ranging from 25 mg twice daily to up to 1300 mg/d) with placebo or no treatment, showed that aspirin was associated with a 19% (95>% CI -1% to 35%) reduced incidence of stroke. There was an absolute risk reduction of 0.8% per year for primary prevention trials and 2.5% per year for secondary prevention trials. When 3 additional RCT comparing other antiplatelet drug regimens were added to the meta-analysis, antiplatelet therapy reduced stroke by 22% (CI, 6% to 35%).[27]

A meta-analysis of 12 comparisons of adjusted-dose warfarin with antiplatelet therapy, warfarin was associated with a 37% (CI, 23% to 48%) reduction in strokes.[27] In a more recent systematic review an additional RCT[30] comparing aspirin with VKA in non-valvular AF was added.[31] Patients treated with a VKA had a lower risk of stroke (OR=0.557; 95% CI 0.411-0.753) and a lower risk of systemic embolism (OR=0.616; 95% CI 0.392–0.966). No significant difference in the rate of bleeding was noted (OR=1.497; 95% CI 0.730–3.070).[31]

Aspirin used to be considered a safer alternative than anticoagulants for the prevention of stroke in AF but in recent years it appeared that the bleeding

risk with aspirin is similar to that of anticoagulants. According to the AHA/ACC guidelines, aspirin may be considered in patients with non-valvular AF and a CHA2DS2-VASc score of 1, in whom no antithrombotic therapy or treatment with an oral anticoagulant may be considered as well.[7] In its most recent guideline, the ESC no longer recommends antiplatelets to be used for the prevention of stroke in AF.[17]

3.4.3 Combination therapy of anticoagulants and antiplatelets

The combination of AF and coronary heart disease is not uncommon in clinical practice. Approximately 15% of AF patients have a history of myocardial infarction and between 5–15% of AF patients will require stenting at some point in their lives.[17] Since anticoagulant therapy might be indicated in AF, and antiplatelet in myocardial infarction and related acute coronary syndromes, questions arise about the appropriateness and safety of such combination. An oral anticoagulant, and not combination therapy with antiplatelets, is recommended in AF patients with stable coronary artery disease. In patients treated for an acute coronary syndrome, and in those receiving a coronary stent, short-term triple combination therapy of oral anticoagulant, clopidogrel, and aspirin is recommended followed by a period of dual therapy (oral anticoagulant plus a single antiplatelet).[17] According to the validators of this report, there is no consensus among experts about these issues.

3.4.4 Novel Oral AntiCoagulants (NOACs)

Over the last decade, several alternative oral anticoagulants, other than VKAs, have been developed. They have a direct and reversible inhibitory effect on clotting factors. They are designated “novel oral anticoagulants”, or “non-vitamin K antagonist oral anticoagulants” with the abbreviation NOACs. Sometimes they are also referred to as DOACs, “direct oral anticoagulants”. There are two main types of NOACs: direct thrombin inhibitors (DTI - ximelagatran, dabigatran) and factor Xa inhibitors (FXaI - rivaroxaban, apixaban and edoxaban). Direct thrombin inhibitors (DTI) act via direct inhibition of thrombin. Factor Xa inhibitors (FXaI) are direct inhibitors of factor Xa. They disrupt both the intrinsic and the extrinsic coagulation pathways, preventing the formation of thrombin and subsequent clotting. Because the NOACs’ effect is determined solely by plasma concentration rather than by inhibition of clotting factor synthesis, they have a rapid onset of action. Furthermore, NOACs have more stable pharmacokinetic and pharmacodynamic characteristics than VKAs, making haemostasis monitoring and repetitive dosage adjustments unnecessary.

In Belgium, 4 NOACs are available for clinical use: apixaban (Eliquis), dabigatran (Pradaxa), rivaroxaban (Xarelto) and edoxaban (Lixiana). The elimination half-life of dabigatran is approximately 12–17h, of rivaroxaban 5-9h in the young and 11-13h in elderly, of apixaban 12h and of edoxaban 10-14h.[1] Cessation of administration results in a relatively rapid return to baseline physiology. Routine measurement of the anticoagulant effect of the NOACs is not necessary. However, because of the rapidly fading anticoagulant effect, strict therapy compliance by the patient is critical.[1]

Severe renal insufficiency (creatinine clearance <15 mL/min) is a contraindication for NOAC prescription. Dabigatran and rivaroxaban have specific dose adjustments for patients with decreased renal function, and a reduced dose of apixaban is needed in selected patients meeting multiple criteria.[10] These limitations are to a large extent reflected in Belgian reimbursement conditions (Table 11).

The use of dabigatran in patients with mechanical heart valves is associated with increased rates of thromboembolic and bleeding complications, as compared with warfarin.[32] Therefore, NOACs are not used in patients with AF and a mechanical heart prosthesis. In those patients a VKA is the anticoagulant of choice.[6]

Since 2003, 21 RCTs comparing the use a NOAC versus a VKA in AF have been published, of which 11 are related to a direct Factor Xa inhibitor (apixaban, betrixaban, darexaban, edoxaban, rivaroxaban) and 9 to a direct thrombin inhibitor (dabigatran, ximelagatran, AZD0837). More details are provided in the Appendix to this report.

Relevant trials will be discussed in further detail in a separate chapter on the clinical effectiveness and safety of NOACs.

3.5 Bleeding risk induced by vitamin K antagonists

Anticoagulants carry a risk of inducing major bleeding, including intracranial bleeding. In the Swedish Atrial Fibrillation cohort study, 182,678 subjects with a diagnosis of AF admitted to hospital between 2005 and 2008, were prospectively followed for an average of 1.5 years (260 000 years at risk).[22] The overall major bleeding rate with warfarin was 1.9% per year. The risk for intracranial bleeding in patients with non-valvular AF treated with anticoagulants ranges from 0.3% to 0.6% per year.[27, 33, 34] In the general population, aged 70 years, this rate is estimated to be ±0.15% per year.[35] In a Swedish study, the annual rate of intracranial bleedings was 0.6% in warfarin-treated and untreated patients alike (Figure 2).[36]

A VKA's anticoagulant action can be reversed with vitamin K. Specific reversal agents for NOACs have only recently been developed (idarucizumab, andexanet) as discussed later in this report.[37, 38]

The HAS-BLED score (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly [>65 years], Drugs/alcohol concomitantly) was developed to estimate this risk in patients with AF treated with an anticoagulant. Scores on this scale range from 0 to 9.[39] Of note, guidelines recommend not to use the score to exclude patients from anticoagulation therapy, but to encourage physicians to act on correctable risk factors for bleeding such as uncontrolled blood pressure, or the concomitant use of aspirin or non-steroidal anti-inflammatory drugs.[3] Anticoagulation is contraindicated in patients in whom bleeding risk far exceeds the risk for ischemic stroke such as those with malignant hypertension, ongoing occult gastrointestinal bleeding, or recurrent spontaneous intracranial bleeding.[36]

The proportion of AF patients in whom anticoagulation is contra-indicated has been reported to be around 15%.[40] In a Belgian study, of 468 patients admitted to hospital with stroke and previously known with AF, 113 (24.1%) had a contraindication for an anticoagulant.[41]

The concept of "net clinical benefit" of anticoagulation has been introduced to estimate the real benefit a patient derives from treatment. It is the rate of ischemic strokes prevented by anticoagulation minus the rate of haemorrhagic strokes they induce. Obviously, this is especially relevant in patients at low risk of ischemic stroke, since this risk may be of a similar magnitute as the risk of haemorragic stroke. In a Swedish study, the investigators compared the risk for ischemic stroke in patients not taking an anticoagulant (n=90,706; 188,470 pt-years) with the risk of haemorrhagic strokes in patients treated with warfarin (n=63,306; 114,569 pt-yrs).[36] The net result favored warfarin treatment for all patients except for those with a CHA2DS2-VASc score=0. The authors also defined an adjusted net clinical benefit which puts a weight of 1.5 for intracranial heamorrhage to account for the generally more disastrous consequences of intracranial bleeding over thromboembolic stroke. This was negative in CHA2DS2-VASc=0, and zero in CHA2DS2-VASc=1 (Table 4).

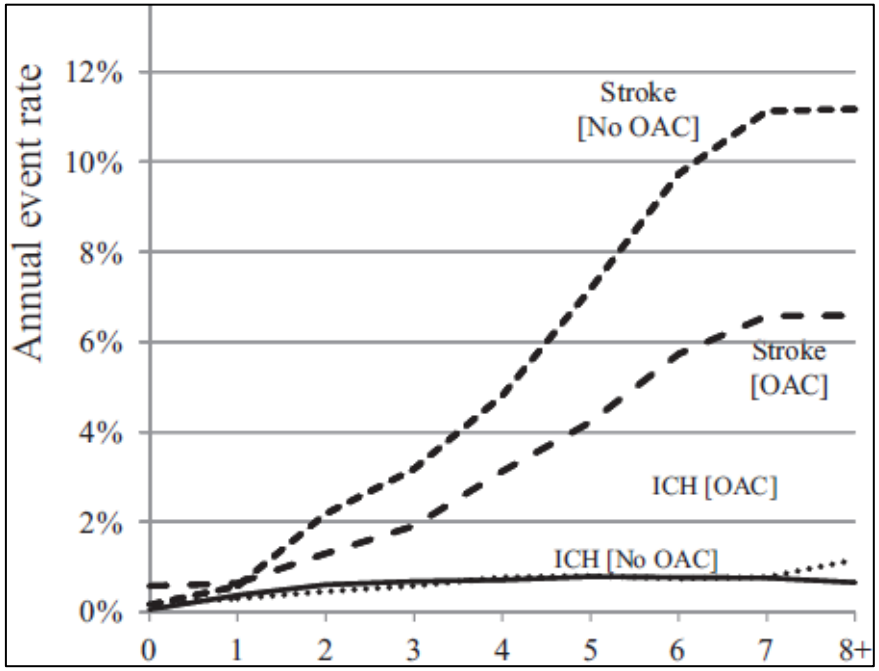
Table 4 – Net clinical benefit of warfarin

CHA2DS2-VASc score	Ischemic stroke off warfarin	Intracranial bleeding on warfarin	Net Clinical Benefit	Adjusted Net Clinical Benefit
0	0.2	0.2	0.0	-0.6
1	0.6	0.3	0.3	0.0
2	2.2	0.5	1.7	1.1

*Source: Friberg et al.[36] Ischemic stroke: yearly rate in patients off-warfarin. Intracranial bleeding (haemorrhagic stroke): yearly rate in patients on-warfarin. Net Clinical Benefit = (ischemic stroke – intracranial bleeding). Adjusted Net Clinical Benefit = [ischemic stroke – (1.5 * intracranial bleeding)].*

The net clinical benefit as a function of CHA2DS2-VASc score can be estimated from Figure 2. Ischemic stroke rates increase with increasing CHA2DS2-VASc scores from almost 0% to 12% per year in patients without anticoagulant and to 7% annually in patients with anticoagulant.[36]

Figure 2 – Relation between CHA2DS2-VASc score and ischemic/haemorrhagic stroke



Source: Friberg et al.[36] X-axis: CHA2DS2-VASc score. Stroke: ischemic stroke. OAC: anticoagulant. ICH: intracranial haemorrhage.

Similar findings were observed in a cohort study of 70,206 individuals with a diagnosis of AF in primary (n=29 568) or secondary care (n=40 638) in England (1998–2010).[15] In individuals with a CHA2DS2-VASc=1, the absolute risk of ischaemic stroke on warfarin was 0.4 (0.3 to 0.7) and 0.7 (0.6 to 0.8) without warfarin. The net clinical benefit of warfarin was positive but non-significant [0.1 (−0.2 to 0.4)].

Key points

- **Atrial fibrillation (AF) is a common heart rhythm disorder with a prevalence of 1.5-2.0% in the general population. Depending on the underlying heart disease, AF is divided into "valvular" and "non-valvular". The term valvular AF is limited for use in the context of rheumatic valvular disease or prosthetic heart valves. The present report is limited to non-valvular AF. This is the most common type of AF that can occur in the setting of different cardiac conditions, e.g. coronary artery disease or hypertension.**
- **The most dreaded complications of AF are thromboembolic events, particularly ischemic stroke. The risk of stroke in AF depends on a number of patient characteristics. Major risk factors are prior stroke or thromboembolism, and older age (≥75 years). Non-major risk factors are heart failure, hypertension, diabetes, female gender, age 65-74 years, and vascular disease.**
- **The yearly risk of stroke in AF ranges from 0% to more than 10%. This risk is estimated through the CHA2DS2-VASc score in which risk factors are attributed 1 or 2 points. With a CHA2DS2-VASc=0, the yearly stroke risk is close to zero, whereas a score ≥2 indicates a risk of 2% or more. In patients with a CHA2DS2-VASc=1, stroke risk is estimated to lie between 0.1 and 1.0%. The corresponding risk estimates may however not be very accurate since they are mostly based on data from hospitalised patients. With a worldwide decrease in stroke rates, the predicted stroke risk may nowadays be substantially lower than estimated.**
- **Anticoagulants reduce the risk of stroke in patients with AF by more than 60%. However, they also increase the risk of bleeding, particularly haemorrhagic stroke. The yearly risk of haemorrhagic stroke induced by anticoagulants ranges from 0.10 to 0.70% per year.**
- **Two classes of oral anticoagulants are available for clinical use: the vitamin K antagonists (VKAs) and the Novel Oral AntiCoagulants (NOACs). The present report discusses the clinical effectiveness and safety of oral anticoagulants in general with special emphasis on the incremental value of the NOACs versus VKAs.**

4 EFFICACY AND SAFETY OF NOACS

4.1 Search strategy

The PICO of interest and the criteria used for selection of publications is depicted in Table 5. The aim was to assess the comparative clinical effectiveness of NOACs versus vitamin K antagonists in patients with non-valvular atrial fibrillation for the primary and secondary prevention of stroke and systemic embolism. It was decided to focus on published systematic reviews.

Table 5 – PICO table and study selection criteria

Selection criteria	Inclusion criteria	Exclusion criteria
Population	Patients with non-valvular atrial fibrillation or atrial flutter	Mitral valve stenosis and mechanical valve prosthesis Studies limited to other indications for anticoagulants such as venous thrombo-embolic disease Peri-procedural use of anticoagulants (in the setting of surgical or non-invasive interventions)
Intervention	Anticoagulation treatment with one of the following novel anticoagulants (NOAC): • Apixaban • Dabigatran • Rivaroxaban • Edoxaban	Studies limited to specific clinical subgroups (e.g. renal failure, hepatic disease) of patients Studies on ximelagatran only were excluded from analysis Devices or technical interventions used for the prevention of stroke (e.g. Watchman)
Comparator	Anticoagulation treatment with one of the following vitamin K antagonists (VKA): • Phenprocoumon • Acenocoumarol • Warfarin	Anti-platelets such as aspirin, clopidogrel
Outcomes	Stroke and major bleeding	
Study design	Systematic reviews that provide a meta-analysis of benefit/harm of (at least) apixaban, dabigatran and rivaroxaban vs. VKA Phase 3 RCTs	Economic studies SRs based on sub-studies of RCTs, phase 2 RCTs, observational studies

First a search for systematic reviews was carried out in Medline (Ovid) on January 25, 2016 using the search string depicted in the Appendix to this report. Since a pre-assessment of the literature revealed that several SRs on the subject were published in recent years, and for the sake of efficiency, we started our search time window in January 1, 2014.This resulted in 242 hits. Only SRs of phase 3 RCTs of dabigatran, apixaban, rivaroxaban and/or edoxaban were considered. Ximelagatran was not considered of major interest since this molecule is no longer clinically used. Although the factor-Xa inhibitors (FXaI) (rivaroxaban, apixaban, edoxaban) and the direct thrombin inhibitor (DTI) (dabigatran) inhibit different coagulation factors, we

opted in our literature search for SRs that pooled all NOACs because published guidelines refer to these drugs as one class, and Belgian reimbursement rules also consider all NOACs as one single group. SRs could provide separate meta-analyses of DTI and FXaI NOACs, but at least a pooled meta-analysis of all NOACs was required. Economic studies and HTAs were excluded in the clinical part of the present report since they are addressed in a separate chapter.

Based on title and abstract, 11 publications were retrieved for full text evaluation. An additional search in Ovid's "In process and other non-indexed citations" resulted in 4 extra references that were considered for full text evaluation.

Similar searches were performed on January 25, 2016 in Embase. Starting the search time window in January 1, 2014, resulted in 656 hits. For the sake of efficiency, we changed the starting date in January 1, 2015 which resulted in 294 hits. Based on title and abstract, 3 additional publications that were not yet identified through Medline were retrieved.

Additional searches (search string: "anticoagulants AND atrial fibrillation") were performed in the databases of the Centre for Reviews and Dissemination which resulted in 100 hits, 5 of which were retrieved. A search in the Cochrane Library resulted in 25 hits, of which 1 was retrieved.[42] Reference lists of all accessed full-text articles were further searched for sources of potentially relevant information. This hand searching resulted in 2 additional selections.[43, 44]

After a first selection round based on title and abstract, 26 unique articles of potential interest were identified. Title, abstract and content were re-examined in a second round and reasons for exclusion are shown in the Appendix to this report. Five SRs were selected for full critical appraisal and application of the AMSTAR tool.[44-48] Among those, two studies were excluded: one[44] because it focused on mortality only, a second[46] because it did not incorporate the RCT on edoxaban. Although the AMSTAR score attributed to the SR of Ruff et al.[48] was low, we included this study for further analysis since it provided additional data on specific patient subgroups.

In conclusion, the evidence on the efficacy of NOACs in patients with non-valvular atrial fibrillation as reported in the present report was extracted from the remaining SRs[45, 47, 48] shown in the Appendix to this report.

A number of SRs that specifically reported on harms also emerged from our literature search. One focussed on efficacy and harms in the elderly,[49] two focussed on gastrointestinal bleeding,[50, 51] one on intracranial bleeding,[52] and one on major bleeding-related fatality.[53]

The search for SRs was supplemented with a search for RCTs published after January 1st 2014. Medline (Ovid) was searched on February 8, 2016 with the following search string: (exp Anticoagulants/ AND exp Atrial Fibrillation/) limited to (yr="2014-Current" and clinical trial,all). This resulted in 204 hits. Assessment of title and abstract, and excluding sub-studies of older phase 3 RCTs (RE-LY, ROCKET AF, ARISTOTLE, ENGAGE AF-TIMI 48), revealed no recent RCTs that compared a NOAC with a VKA for the prevention of stroke in patients with non-valvular atrial fibrillation. A similar search was performed in Embase but did not lead to new references.

4.2 Systematic Reviews

Among the SRs that we selected for data extraction, one[47] incorporated the 7 phase 3 studies mentioned earlier (appendix), one[45] did not consider the ximelagatran studies, and one[48] omitted the Japanese ROCKET study (Table 6). In a further chapter, these primary studies will be briefly presented.

Table 6 – RCTs represented in selected SRs

	SPORTIF III, 2003	SPORTIF V, 2005	RE-LY, 2009	ROCKET-AF, 2011	ARISTOTLE, 2011	J-ROCKET AF, 2012	ENGAGE AF, 2013
Providencia	√	√	√	√	√	√	√
Jia			√	√	√	√	√
Ruff			√	√	√		√

References: Jia et al.[45], Providencia et al.[47], Ruff et al.[48]

Providencia et al. included in their SR all phase 3 RCTs that investigated NOAC versus warfarin in patients with non-valvular AF.[47] Since ximelagatran – which is no longer commercially available - is the only direct thrombin inhibitor (DTI) besides dabigatran that has been tested in a phase 3 trial in AF patients, the authors included this drug in their meta-analysis to enable a more robust comparison between de two groups of NOACs (DTI versus FXaI).

Results favouring a better outcome with NOAC were also found for secondary endpoints: total mortality (RR = 0.90; 95%CI 0.86-0.95), cardiovascular mortality (RR = 0.88; 95%CI 0.83-0.94), and intracranial bleeding (RR = 0.49; 95%CI 0.37-0.63). No significant differences between the NOAC and warfarin were found concerning the incidence of ischemic stroke (RR = 0.97; 95%CI 0.83-1.14), myocardial infarction (RR = 1.01; 95%CI 0.83-1.24) and gastrointestinal bleeding (RR = 1.07; 95%CI 0.86-1.34).

Three sensitivity analysis were performed: the first excluding data from the SPORTIF III and V trials, since the drug was withdrawn from the market as a result of hepatotoxicity; the second excluded data from Japanese ROCKET AF study since, according to Japanese guidelines, patients above 70 years had a target international normalised ratio of 1.6 to 2.6, and therefore, different from the one used in other trials (2.0 to 3.0) - moreover, a lower dose of rivaroxaban (15 mg once-daily) was used; the third excluded data from all three studies. Similar results were obtained for all above-mentioned endpoints in the 3 different sensitivity analyses, when compared to those obtained using all included 7 RCTs. No significant differences between the two pharmacologic classes (DTI and FXaI) were observed.

In the SRs published by Jia et al.[45] and Ruff et al.[48] separate meta-analyses were performed for “high-dose NOAC” and “low-dose NOAC” vs. VKA. In the high-dose meta-analysis, dabigatran 150, rivaroxaban 20/15/10, apixaban 5/2.5, and edoxaban 60 were included. The low-dose, analysis include dabigatran 110 and edoxaban 30/15. The RR of NOAC vs. VKA for stroke or systemic embolism in the low-dose group was 1.03 (95%CI 0.84-1.27) and for major bleeding the RR was 0.63 (95%CI 0.36-1.04).[45, 48] Such subgroup meta-analysis by NOAC dose might be problematic. Only two of the RCTs followed a 1:1:1 design corresponding to patient groups receiving different NOAC doses.[54, 55] However, dose adjustment at entry in all studies was allowed depending on age, body weight, renal function or co-medication. No detailed outcome results have been published by adjusted NOAC dose.

4.3 Primary studies

In this paragraph, we briefly describe the primary studies included in the abovementioned SR. A summary of findings table for each RCT is provided in the Appendix to this report.

4.3.1 Ximelagatran

Ximelagatran has been studied versus warfarin in AF in two related phase 3 RCTs: the SPORTIF III and SPORTIF V studies.[56, 57] Later on, this drug has been withdrawn from the market due to liver toxicity.

4.3.1.1 SPORTIF III

In SPORTIF III, 3410 patients with AF and one or more stroke risk factors were randomised to open-label warfarin (adjusted-dose: INR 2·0–3·0) or ximelagatran (fixed-dose, 36 mg twice daily).[57] The primary endpoint was stroke or systemic embolism. Mean follow-up time was 17.4 months.
The primary event rate by intention to treat was 2.3% per year with warfarin and 1.6% per year with ximelagatran with an absolute risk reduction of 0.7%; 95% CI 0.1 to 1.4 and a relative risk reduction of 29%; 95% CI 6.5 to 52. Rates of disabling or fatal stroke, mortality, and major bleeding were similar between groups, but combined minor and major bleedings were lower with ximelagatran than with warfarin (29·% vs 25.8% per year). Raised serum alanine aminotransferase was more common with ximelagatran. Premature termination of study treatment happened in 246 (14%) patients in the warfarin group and 309 (18%) in the ximelagatran group. This was the result of study endpoints in 61 (4%) patients in the warfarin group and 52 (3%) in the ximelagatran group. 61 patients (4%) stopped warfarin because of adverse events compared with 132 (8%) on ximelagatran; this difference was mainly related to elevation of serum concentrations of transaminases in some patients treated with ximelagatran. A summary of findings table is provided in the Appendix to this report.

4.3.1.2 SPORTIF V

In SPORTIF V, 3922 patients with AF and one or more stroke risk factors were double-blinded randomised to warfarin (adjusted-dose: INR 2·0–3·0) or ximelagatran (fixed-dose, 36 mg twice daily).[56] This trial was based on the same protocol as SPORTIF III, except that anticoagulation was administered in a double-blinded manner.

The primary event rate with ximelagatran was 1.6% per year and with warfarin was 1.2% per year, corresponding to an absolute risk increase of 0.45% (95% CI: -0.13% to 1.03%) per year. There was no difference between treatment groups in rates of major bleeding, but total bleeding (major and minor) was lower with ximelagatran (37% vs 47% per year; 95% CI -14% to -6.0% per year). Serum alanine aminotransferase levels rose to greater than 3 times the upper limit of normal in 6.0% of patients treated with ximelagatran, usually within 6 months and typically declined whether or not treatment continued; however, one case of documented fatal liver disease and one other suggestive case occurred. A summary of findings table is provided in the Appendix to this report.

4.3.2 Dabigatran

Dabigatran has been studied versus warfarin in AF in one phase 3 RCT: the RE-LY trial.[54, 58]

In this non-inferiority trial, 18 113 patients who had AF and at least one risk factor for stroke were randomly assigned to receive in a blinded fashion fixed doses of dabigatran (110 mg or 150 mg twice daily) or, in an unblinded fashion, adjusted-dose warfarin (INR: 2-3). Patient were excluded from enrolment in case of severe renal failure.

The median duration of the follow-up period was 2.0 years. The primary outcome was stroke or systemic embolism.

Rates of the primary outcome were 1.69% per year in the warfarin group, as compared with 1.53% per year in the group that received 110 mg of dabigatran (relative risk with dabigatran, 0.91; 95%CI 0.74 to 1.11) and 1.11% per year in the group that received 150 mg of dabigatran (relative risk, 0.66; 95% CI, 0.53 to 0.82). In 2010 and 2014, the investigators published a correction for these percentages: 1.72, 1.54 and 1.12% respectively, leaving the relative risks almost unchanged. The rate of major bleeding was 3.36% per year in the warfarin group, as compared with 2.71%

per year in the group receiving 110 mg of dabigatran and 3.11% per year in the group receiving 150 mg of dabigatran. Corrections published in 2014 were 3.61, 2.92 and 3.40% respectively, again with no major changes in the relative risks.

The rate of haemorrhagic stroke was 0.38% per year in the warfarin group, as compared with 0.12% per year with 110 mg of dabigatran and 0.10% per year with 150 mg of dabigatran. The mortality rate was 4.13% per year in the warfarin group, as compared with 3.75% per year with 110 mg of dabigatran and 3.64% per year with 150 mg of dabigatran. A summary of findings table is provided in the Appendix to this report.

4.3.3 Rivaroxaban

Rivaroxaban has been studied versus warfarin in AF in two interrelated phase 3 RCT, the (global) ROCKET AF study[19] and the Japanese J-ROCKET AF study.[20]

4.3.3.1 ROCKET AF

In this non-inferiority trial, 14 264 patients who had AF and were at moderate-to-high risk of stroke (CHADS2 score of 2 or more) were randomly assigned to receive, in a blinded fashion, a fixed dose of rivaroxaban (20 mg or, depending on renal function, 15 mg daily) or, adjusted-dose warfarin (INR: 2-3). Patients were excluded from enrolment in case of severe renal failure.

A point-of-care device was used to generate encrypted INR values that were sent to an independent study monitor, who provided sites with either real INR values (for patients in the warfarin group in order to adjust the dose) or sham values (for patients in the rivaroxaban group receiving placebo warfarin). The median duration of the follow-up period was 707 days. The primary outcome was stroke or systemic embolism.

In the per protocol analysis, the primary end point occurred in 188 patients in the rivaroxaban group (1.7% per year) and in 241 in the warfarin group (2.2% per year) (hazard ratio in the rivaroxaban group, 0.79; 95% CI, 0.66 to 0.96). In the intention-to-treat analysis, the primary end point occurred in 269 patients in the rivaroxaban group (2.1% per year) and in 306 patients in the warfarin group (2.4% per year) (hazard ratio, 0.88; 95% CI, 0.74 to 1.03). Major bleeding occurred in 395 patients in the rivaroxaban group (3.6% per year) and in 386 in the warfarin group (3.4% per year) (hazard ratio, 1.04; 95% CI, 0.90 to 1.20), with significant reductions in intracranial bleeding (0.5% vs. 0.7%) A summary of findings table is provided in the Appendix to this report.

In December 2014, four years after completion of the ROCKET-AF trial, the US Food and Drug Administration (FDA) issued a recall notice for the device that was used for INR measurement in this study. This point-of-care device could provide an INR result that is lower than an automated, plasma-based laboratory INR in certain patients. In February 2016, five years after the publication of the results, the authors published information on this. They concluded that the possible malfunction of the device did not have any significant clinical effect on the primary efficacy and safety outcomes in the trial.[59]

4.3.3.2 J-ROCKET AF

J-ROCKET AF was a prospective, randomised, double-blind, non-inferiority phase III trial. 1 280 patients with non-valvular AF at high risk for stroke were randomized to receive 15 mg once-daily rivaroxaban or warfarin dose-adjusted according to Japanese guidelines. The primary objective was to determine non-inferiority of rivaroxaban against warfarin for the principal safety outcome of major and non-major clinically relevant bleeding, in the on-treatment safety population. The primary efficacy endpoint was the composite of stroke and systemic embolism.

The rate of the principal safety outcome was 18.04% per year in rivaroxaban-treated patients and 16.42% per year in warfarin-treated patients (HR 1.11; 95% CI 0.87–1.42), confirming non-inferiority. Intracranial bleeding rates were 0.8% with rivaroxaban and 1.6% with warfarin. In the ITT population analysis, the primary efficacy endpoint occurred at a rate of 2.38% per year and 2.91% per year in patients receiving rivaroxaban and warfarin, respectively (HR 0.82; 95% CI 0.46–1.45). In the on-treatment analysis, the primary efficacy endpoint occurred at a rate of 1.26% per year and 2.60% per year in patients receiving rivaroxaban and warfarin, respectively (HR 0.48; 95% CI 0.23–1.00). A summary of findings table is provided in the Appendix to this report.

4.3.4 Apixaban

Apixaban has been studied versus warfarin in AF in one phase 3 RCT: the ARISTOTLE study.[60]

In this randomised, double-blind trial, we compared apixaban (at a dose of 5 mg twice daily) with warfarin (target international normalized ratio, 2.0 to 3.0) in 18,201 patients with atrial fibrillation and at least one additional risk factor for stroke. Apixaban dose was reduced to 2.5-mg twice a day in a subset of patients with two or more of the following criteria: an age of at least 80 years, a body weight of no more than 60 kg, or a serum creatinine level of 1.5 mg/dL or more. Patients were excluded from enrolment in case of severe renal failure.
The median duration of the follow-up period was 1.8 years. The primary outcome was stroke or systemic embolism.

The rate of the primary outcome was 1.27% per year in the apixaban group, as compared with 1.60% per year in the warfarin group (hazard ratio with apixaban, 0.79; 95% CI, 0.66 to 0.95). The rate of major bleeding was 2.13% per year in the apixaban group, as compared with 3.09% per year in the warfarin group (hazard ratio, 0.69; 95% CI, 0.60 to 0.80), and the rates of death from any cause were 3.52% and 3.94%, respectively (hazard ratio, 0.89; 95% CI, 0.80 to 0.99). The rate of haemorrhagic stroke was 0.24% per year in the apixaban group, as compared with 0.47% per year in the warfarin group (hazard ratio, 0.51; 95% CI, 0.35 to 0.75), and the rate of ischemic or uncertain type of stroke was 0.97% per year in the apixaban group and 1.05% per year in the warfarin group (hazard ratio, 0.92; 95% CI, 0.74 to 1.13). A summary of findings table is provided in the Appendix to this report.

4.3.5 Edoxaban

Edoxaban has been studied versus warfarin in AF in one phase 3 RCT: the ENGAGE AF-TIMI 48 study.[55]

This is a randomised, double-blind, double-dummy trial comparing two once-daily regimens of edoxaban with warfarin in 21,105 patients with moderate-to-high-risk atrial fibrillation (median follow-up, 2.8 years). Patients were randomly assigned in a 1:1:1 ratio, to receive warfarin or high-dose (60 mg) or low-dose (30 mg) edoxaban. For patients in either group, the dose was halved if any of the following characteristics were present: creatinine clearance of 30 to 50 ml/min, body weight of 60 kg or less, or the concomitant use of verapamil or quinidine. Patients were excluded from enrolment in case of severe renal failure.

The primary efficacy endpoint was stroke or systemic embolism. Each edoxaban regimen was tested for non-inferiority to warfarin during the treatment period. The principal safety endpoint was major bleeding.
The rate of the primary endpoint during treatment was 1.50% per year with warfarin, as compared with 1.18% with high-dose edoxaban (hazard ratio, 0.79; 97.5% CI, 0.63 to 0.99) and 1.61% with low-dose edoxaban (hazard ratio, 1.07; 97.5% CI, 0.87 to 1.31). In the intention-to-treat analysis, hazard ratio for high-dose edoxaban versus warfarin was 0.87 (97.5% CI, 0.73 to 1.04) and 1.13 (97.5% CI, 0.96 to 1.34) with low-dose edoxaban versus warfarin. The yearly rate of major bleeding was 3.43% with warfarin versus 2.75% with high dose edoxaban (hazard ratio, 0.80; 95% CI, 0.71 to 0.91) and 1.61% with low-dose edoxaban (hazard ratio, 0.47; 95% CI, 0.41 to 0.55). A summary of findings table is provided in the Appendix to this report.

4.3.6 Summary table

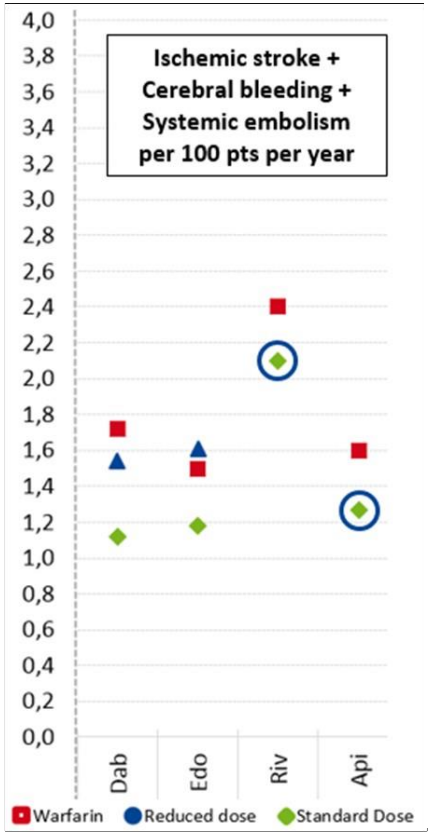
Table 7 summarises the relative and absolute risks (along with absolute risk differences) of major outcomes in the RCTs discussed above.

Table 7 – Absolute and relative risk for major outcomes in NOAC vs. VKA from pivotal RCTs

	Relative Risk (95% CI)				Absolute risk (% per year)											
	Stroke + SE	Ischemic stroke	Haemorrhagic stroke	Gastrointestinal bleeding	Stroke + SE			Ischemic stroke			Haem. stroke			GI bleeding		
					VKA	NOAC	Δ°	VKA	NOAC	Δ°	VKA	NOAC	Δ°	VKA	NOAC	Δ°
Dabigatran 110	0.89 (0.73–1.09)	1.11 (0.89-1.40)	0,31 (0,17-0,56)	1,10 (0,86-1,41)	1.7	1.5	-0.2	1.2	1.3	+0.1	0.38	0.12	-0.26	1.02	1.12	+0.10
Dabigatran 150	0.65 (0.52–0.81)	0.76 (0.60-0.98)	0,26 (0,14-0,49)	1,50 (1,19-1,89)		1.1	-0.6		0.9	-0.3	0.38	0.10	-0.28	1.02	1.51	+0.49
Rivaroxaban	0.88 (0.75-1.03)	0.94 (0.75-1.17)	0,67 (0,47-0,93)	1,54 (1,19-1,78)	2.4	2.1	-0.3	1.4	1.3	-0.1	0.70	0.50	-0.20	1.11	1.62	+0.51
Apixaban	0.78 (0.66-0.95)	0.92 (0.74-1.13)	0.51 (0.35-0.75)	0,89 (0,70-1,15)	1.6	1.3	-0.3	1.1	1.0	-0.1	0.47	0.24	-0.23	0.86	0.76	-0.10
Edoxaban 30	1.07 (0.87-1.31)	1.41 (1.19-1.67)	0,33 (0,22-0,50)	0,67 (0,53-0,83)	1.5	1.6	+0.1	1.3	1.8	+0.5	0.47	0.16	-0.31	1.23	0.82	-0.41
Edoxaban 60	0.79 (0.63-0.99)	1.00 (0.83-1.19)	0,54 (0,38-0,77)	1,23 (1,02-1,50)		1.2	-0.3		1.3	0.0	0.47	0.26	-0.21	1.23	1.51	+0.28

Data on dabigatran are extracted from Connolly et al.[54], rivaroxaban from Patel et al.[19], apixaban from Granger et al.[60] and edoxaban from Giugliano et al.[55] Data are extracted from the intention-to-treat population. Stroke + SE: Stroke and Systemic Embolism. Ischemic and haemorrhagic stroke are secondary endpoints in the trials and are included in "Stroke + SE". GI: gastrointestinal. °Δ = (NOAC-VKA). Definitions of outcomes may somewhat differ across trials.

Figure 3 – Primary outcome in RCTs, absolute incidence rate.



Source: Stroke risk + systemic embolism (SE) was the primary outcome in the pivotal RCTs, referred to in Table 7 ("Stroke" includes both ischemic and haemorrhagic stroke). In the dabigatran and edoxaban studies, one third of patients received the standard dose of the NOAC, one third the reduced dose and one third received warfarin. : In the RCTs on rivaroxaban and apixaban, only the combined analysis of standard and reduced doses was a predefined endpoint. In the rivaroxaban study 20.7% of patients received the reduced dose, in the apixaban study it was 4.7%.

4.4 Safety of NOACs

Ximelagatran was the first NOAC that has been studied in a phase 3 study versus warfarin in patients with AF.[56, 57] However, later on the drug was withdrawn from the market due to liver toxicity.

In RCTs, apixaban, dabigatran-110, and both doses of edoxaban had slightly lower rates of *major bleeding* in absolute terms (Table 7). It has been argued that the observed risk of major bleeding in the VKA arm of all NOAC trials is particularly high (between 3 and 4% per year) as compared to the usually expected 1 to 1.5%.[27, 61] The fact that 30 to 40% of participants of the RCTs used aspirin in combination with the anticoagulant may play a role here.

Specific reversal agents for NOACs have recently been developed (idarucizumab, andexanet).[37, 38] Idarucizumab (Praxbind) is available and reimbursed for use in Belgium (at a cost of €2 687) whereas andexanet is not yet reimbursed.

Some authors argued that the bleeding risk associated with dabigatran may be higher in real world than what was observed in the pivotal RCT. By December 2011 adverse drug event databases in Europe, Japan, and the US showed thousands of serious and fatal haemorrhages in patients taking dabigatran, particularly older patients.[62] An issue related to the bleeding risk of dabigatran merits attention. Internal Boehringer documents reportedly show that the company had produced extensive analyses indicating that bleeding risk may be reduced with little or no effect on the risk of ischaemic stroke. The company found that if the plasma levels of dabigatran were measured and the dose was adjusted accordingly major bleeds could be reduced by 30-40% compared with well controlled warfarin.[63] During internal email discussions about the potential merits of drug plasma monitoring one Boehringer employee said: "This may not be a onetime test and could result in a more complex message (regular monitoring) and a weaker value proposition.[63]

In all of the RCTs, NOACs were associated with a reduction in the risk of *haemorrhagic stroke* as compared with VKAs. In the NOAC arm of the trials, the yearly risk of haemorrhagic stroke ranged from 0.10 to 0.50%, whereas in the VKA arm it ranged from 0.38 to 0.70%. In absolute numbers, the risk difference for haemorrhagic stroke between the two drug classes was low, ranging from 0.20%[19] to 0.31%[55] per year. Of note, the risk of haemorrhagic

stroke observed in the pivotal NOAC RCTs was higher than in the older RCTs on VKA, in which it ranged from 0.3 to 0.6%.[27] The exact mechanism why NOACs apparently induce less intracranial bleeding then VKAs is not known.[52]

Although the risk of intracranial bleeding was reduced by the NOACs, the rate of *gastrointestinal bleeding* compared to VKA was significantly increased with some of them: rivaroxaban (RR: 1.54; 95% CI 1.19-1.78), edoxaban-60 (RR: 1.23; 95% CI 1.02-1.50) and dabigatran-150 (RR: 1.50; 95% CI 1.19-1.89). In a meta-analysis in which the authors got access to outcomes data in RCT participants older than 75 years, the increased risk for gastrointestinal bleeding with dabigatran-150 in the overall population further increased in the elderly (OR: 1.78; 95%CI: 1.35-2.35). They could not assess the risk for gastrointestinal bleeding with other NOACs because the crucial data were not disclosed.[49] In RCTs, at the standard dose, NOACs had on average an 0.25% higher absolute yearly risk of gastrointestinal bleeding than VKAs, whereas there was no significant difference at the reduced dose.[48]

In a recent retrospective cohort study in the US, the major bleeding risk was compared among newly anticoagulated AF patients initiating warfarin, apixaban, dabigatran or rivaroxaban. Only those initiated on apixaban had significantly lower major bleeding risk vs. those initiated on warfarin.[64]

In comparison with warfarin, the risk of *myocardial infarction* was significantly increased with dabigatran (RR: 1.38; 95% CI: 1.1–1.7) in the RE-LY trial and was associated with an absolute risk increase of 0.41%.[54, 65] No effect on myocardial infarction was observed (1.63% vs 1.69%) with anti-Xa drugs (pooled results of apixaban, edoxaban and rivaroxaban) as compared with warfarin.[65]

Dyspepsia was the main reason for premature dabigatran discontinuation in the RE-LY trial.[54] It was the only adverse effect that was significantly more common with dabigatran than with warfarin. It occurred in 5.8% of patients in the warfarin group, and in 11.8% and 11.3% in the 110-mg and 150-mg dabigatran groups respectively. In the light of the experience with ximelagatran, liver function tests were strictly followed, but elevations in the serum enzyme levels of more than 3 times the upper limit of the normal range did not occur more frequently with dabigatran, at either dose, than with warfarin (±2%).

4.5 Risk of bias in pivotal RCTs

A critical analysis of the methodology used in the RCTs suggests that there is a substantial risk of bias in these trials in favour of NOACs over VKAs.

The trials were conducted in 40 to 50 different countries, with diverse standards of care such as China, Taiwan, India, Bulgaria, Ukrain, or the Philippines. Differences in standards of care are particularly important for patients allocated to warfarin in whom maintaining an appropriate INR level is critical.

Although one would expect appropriate TTR levels in the context of a clinical trial (at least 70%), it appeared that the quality of the INR control of patients in the VKA arm of the trials was remarkably poor in all trials, especially in ROCKET-AF in which a TTR of 55% was reported. Moreover, 30 to 40% of participants of the RCTs used aspirin in combination with the anticoagulant which may also have played a role in the fact that more bleedings were observed in the VKA arm of the trials. Previous studies have shown that the combination of aspirin and warfarin may double the risk of bleeding, corresponding to an absolute increase of 2%.[66-68] Post hoc analyses of the pivotal trials suggest that the TTR obtained in those trials did not affect the reported results.

The high drop-out rates, especially in ROCKET-AF (rivaroxaban, 23%), ARISTOTLE (apixaban, 25%) and ENGAGE (edoxaban, 34%) in both the NOAC and the VKA arm of these trials is problematic.

In the RE-LY trial (dabigatran), there was no blinding in patients allocated to warfarin. Moreover, corrections in the reported results of the RE-LY trial have been published on two different occasions. Although those new findings reportedly did not change the original conclusions, they raise questions about the data integrity of the study.

Four years after completion of the ROCKET-AF trial, it was revealed that the device that was used for INR measurement in this study could provide an abnormal low INR value. Accordingly, a falsely low reading could mean that patients had their warfarin dose unnecessarily increased, leading to a greater risk of bleeding.[69] In February 2016, five years after the publication of the ROCKET AF trial results, the authors published further information, concluding that the possible malfunction of the device did not have any significant clinical effect on the primary efficacy and safety outcomes in the trial.[59, 69]

4.6 International practice guidelines

Guidelines on atrial fibrillation, including recommendations on thromboembolic risk assessment and stroke prevention, have been formulated by major scientific institutions. The European Society of Cardiology (ESC) issued in 2012 a focused update of its AF guideline.[6] In 2014, the American Heart Association (AHA) and the American College of Cardiology (ACC) jointly issued an update of a previous AF guideline.[7] In August 2016, during the preparation of this report, a full update of the ESC was published.[17]

Both guidelines advocate the use of the CHA2DS2-VASc score for assessing stroke risk in non-valvular AF. There are no major differences in their recommendations with regard to the initiation of anticoagulation. In patients with a CHA2DS2-VASc=1, the ESC uses the wording “antithrombotic therapy should be considered” whereas the AHA/ACC are more conservative in using the wording “antithrombotic therapy may be considered”. In its most recent version, the ESC confirms that in women in whom the “sex category” is the single risk factor, gender is not taken into account for assessing risk. In comparison with the 2012 guideline, this is more explicitly expressed in 2016 by formulating recommendations in males and females separately (Table 8).

Table 8 – European guideline on the indication for anticoagulants by CHA2DS2-VASc score

European Society of Cardiology, 2016		
Stroke risk score	**Recommendation**	**Grade/Level**
CHA2DS2-VASc=0 (includes ♀ without other stroke risk factors)	no antiplatelet or anticoagulant therapy is recommended	IIIB
CHA2DS2-VASc=1 in ♂	oral anticoagulation therapy should be considered, considering individual characteristics and patient preferences	IIaB
CHA2DS2-VASc=2 in ♀	oral anticoagulation therapy should be considered, considering individual characteristics and patient preferences	IIaB
CHA2DS2-VASc >2 in ♂	oral anticoagulation therapy is recommended for all	IA
CHA2DS2-VASc > 3 in ♀	oral anticoagulation therapy is recommended for all	IA
VKA or NOAC?	NOAC is recommended in preference to VKA	IA

Source: Kirchhof et al.[17]

In contrast to the 2012 version, the ESC favours NOACs above VKAs its 2016 version. The AHA/ACC does not clearly formulate a preference on what type of anticoagulant to prescribe, although it stipulates that the level of evidence for VKAs (level A, i.e. evidence derived from multiple RCTs) is higher than for NOACs (level B, referring to the fact that for each of the NOACs only one RCT has been published).

Within the group of NOACs, none of the guidelines recommend one NOAC over another.[6]

EU guidelines stress that the rules for dose reduction that were used in the phase 3 RCTs should be followed in clinical practice.[17] A separate 40-pages Practical Guide on the use of NOACs has been published by the ESC (and co-authored by pharmaceutical industry) in 2013[70], and updated in 2015[1]. It recommends dose reductions for NOACs in case of concomitant use of certain other drugs, and in case of some clinical patient characteristics.

The conflicts of interest of guideline development groups, and the implication of industry in the production of these guidelines is worrying. The ESC guideline for the management of AF is a 90 pages report.[17] It is supplemented with a 47 pages on-line document listing declarations of interest reported by the Task Force members.[b] A Practical Guide on the use of NOACs, published by the ESC, is co-authored with advisors from NOAC manufacturers "to assure data accuracy and completeness".[1] Other authors have also criticised current international guidelines generously favouring NOACs over VKAs, and inadequately reporting the uncertainties surrounding the use of anticoagulants in patients at low risk of stroke.[15, 71-73]

Key points

- **Any of the 4 available NOACs have been studied in only one phase 3 RCT. These studies have been criticized in relation with a number of methodological issues.**
- **Compared to VKAs, NOACs are equivalent in terms of ischemic stroke prevention.**
- **NOACs have a somewhat lower risk of inducing haemorrhagic stroke. In absolute numbers, the risk difference for haemorrhagic stroke between the two drug classes in RCTs ranged from 0.20% to 0.31% per year, a statistically significant difference. All NOACs except apixaban are associated with a somewhat higher risk of gastrointestinal bleeding at their standard dose, ranging from 0.28% and 0.51% per year.**
- **The reversal of the action of VKAs can be accomplished by administring vitamin K at a low cost (10€). For dabigatran a reversal agent (idarucizumab) has become available in Belgium recently, at a high cost (€2 687). For the other NOACs, a reversal agent has been developed, but it is not yet commercialised in Belgium.**
- **International guidelines recommend anticoagulation therapy in patients with a CHA2DS2-VASc score ≥2 (♂) or ≥3 (♀). In patients with a score of 0 in men or 1 in women (with their gender as the only risk factor), anticoagulation is not indicated. There is no consensus on the effectiveness/safety of anticoagulation in patients with a score of 1 in men or 2 in women.**

b https://www.escardio.org/static_file/Escardio/Guidelines/DOI/DOI_Summary_2016_AFIB.pdf

5 REIMBURSEMENT OF ANTICOAGULANTS IN BELGIUM

NOACs have been reimbursed in Belgium since 2009. At first, reimbursement was for the prevention of venous thromboembolism after knee and hip surgery only. Later on, these drugs were also reimbursed in patients with atrial fibrillation (Table 9) for the prevention of stroke. Dose reductions have to be taken into consideration depending on age and renal function. NOACs are not reimbursed in patients with severe renal failure (creatinine clearance <15 ml/min).

Table 9 – Chronology of NOAC reimbursement for atrial fibrillation in Belgium

Drug		Manufacturer	Reimbursed since
PRADAXA	dabigatran	Boehringer-Ingelheim	1.8.2012
XARELTO	rivaroxaban	Janssen Pharmaceuticals (Johnson & Johnson) / Bayer	1.9.2012
ELIQUIS	apixaban	Bristol Myers Squibb	1.9.2013
LIXIANA	edoxaban	Daiichi-Sankyo	1.10.2016

Source: RIZIV – INAMI

Three NOACs were reimbursed in Belgium the moment this report was initiated: dabigatran (Pradaxa), rivaroxaban (Xarelto), and apixaban (Eliquis). A fourth NOAC, edoxaban (Lixiana), went through the administrative reimbursement procedure during the preparation of this report, and became reimbursed from October 1, 2016. A daily dose of a NOACs presently costs 10 times as much as a VKA: 2.85€ versus 0.28€ per day (2016 price; source: Riziv/Inami). These figures do not take secret refunds from industry to the Riziv/Inami (article 81/81bis) into consideration.

Reimbursement conditions are rather restrictive (Table 3) and in essence reflect the inclusion criteria for patients to be enrolled in the 2009 RE-LY trial.[54] No specific reimbursement rules apply for VKAs. As discussed in a later chapter, international guidelines refer to the CHA2DS2-VASc stroke risk score to identify patients that may benefit from anticoagulation treatment. They leave it to the discretion of the treating physician to prescribe either a VKA or a NOAC. The Belgian reimbursement indications do not always match a high CHA2DS2-VASc score and NOAC prescription in Belgium is biased towards VKAs (Table 10). For example, in a 60 years old diabetic patient with AF and hypertension, a physician has *de facto* no choice between a VKA and a NOAC since NOACs are not reimbursed in those patients.

Table 10 – Reimbursement indications for NOACs in atrial fibrillation in Belgium (May 1, 2016)

	<65 years	65-74 years	≥75 years
	Secondary prevention	Secondary prevention	No additional requirements
OR	EF<40%	EF<40%	
OR	Heart Failure NYHA ≥2	Heart Failure NYHA ≥2	
OR		Diabetes	
OR		Coronary artery disease	
OR		Hypertension	

Source: RIZIV – INAMI https://www.riziv.fgov.be/webprd/appl/pssp/ssp/cns2/pages/DemandFormStandard.asp). EF: left ventricular ejection fraction. Secondary prevention refers to the prevention of stroke or systemic embolism. NYHA: New York Heart Association functional classification which places patients with heart failure in one of four categories based on how much they are limited during physical activity.

Table 11 – Reimbursed NOAC doses and conditions in Belgium (Oct 1, 2016)

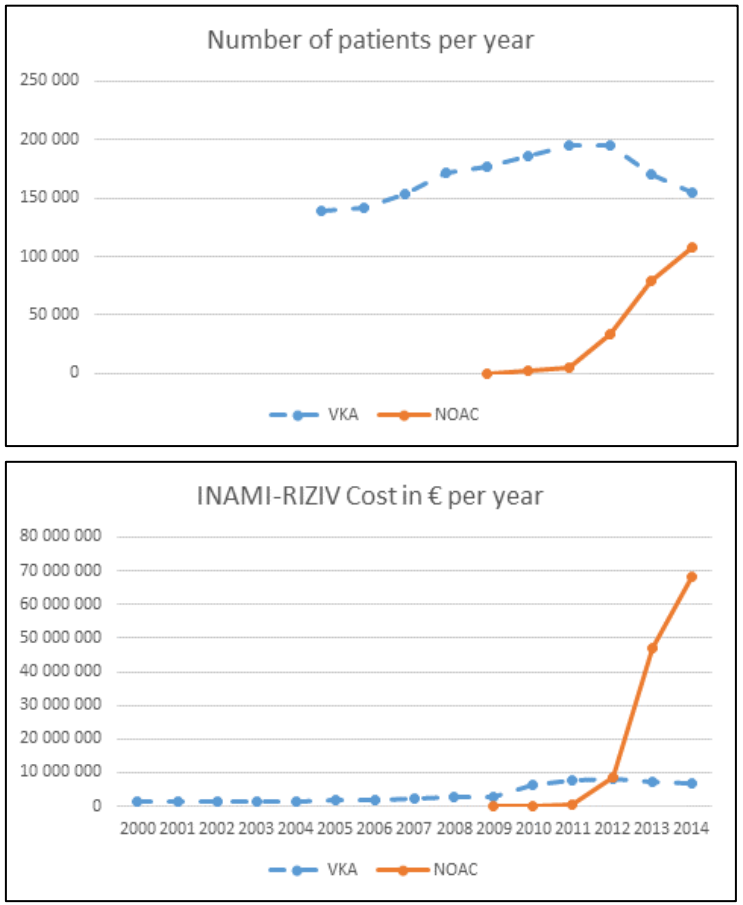
	Pradaxa (dabigatran)	Xarelto (rivaroxaban)	Eliquis (apixaban)	Lixiana (edoxaban)
Reimbursed doses in atrial fribrillation				
Standard daily dose	2 * 150 mg	1 * 20 mg	2 * 5 mg	1 * 60 mg
Contraindications	clearance <15 mL/min	clearance <15 mL/min	clearance <15 mL/min	clearance <15 mL/min
	>80 yrs. old			
	co-medication verapamil			
Reduced daily dose	2 * 110 mg	1 * 15 mg	2 * 2.5 mg	1 * 30 mg
In case of:	creatinine clearance 15-30 mL/min	creatinine clearance 15-50 mL/min	creatinine ≥1.5 mg/dL §	creatinine clearance 15-50 mL/min
			age ≥80 yrs. §	concomitant use ordronedarone, ciclosporine, erythromycine or ketoconazol;
			weight ≤60 kg §	weight ≤60 kg
Reimbursed doses in venous thromboembolic disease				
Standard daily dose postop.	2 * 110 mg (max. 35 days)	1 * 10 mg (max. 5 weeks)	2 * 2.5 mg (max. 38 days)	NA
Reduced daily dose postop.	2 * 75 mg (max. 35 days)			
Standard daily dose for treatment and sec.prev.	2 * 150 mg	initial 21 days: 2 * 15 mg; then 1 * 20 mg	Treatment: initial 7 days: 2 * 10 mg; then 2 * 5 mg for 6 months; then 2 * 2.5 mg for 6 months; total maximum: 12 months.	1 * 60 mg
Reduced daily dose for treatment and sec. prev.	2 * 110 mg			1 * 30 mg

§ ≥2 criteria have to be met. Source: RIZIV – INAMI; BCFI – CBIP.

A growing trend in the use of anticoagulants in Belgium has been noticed, already before NOACs entered the Belgian market in 2012. From 2004-2015 the number of patients taking an anticoagulant almost doubled, with an increasing proportion of NOACs vs. VKAs. During the same period, the Riziv/Inami yearly expenses for anticoagulants increased 60-fold from 1.6 to 95.3 million euros. We expect that in the years to come, yearly expenses for NOACs will reach 100 million euros. These reported expenses do not take into consideration the discounts that were negotiated with industry. According the RIZIV MORSE 2015 report[c], a refund equalling 29,1% of the total budget spent on ATC class B products was paid by industry.

[c] http://www.bemedtech.be/wp-content/themes/twentyeleven-child/pdf/info/20042016_1461141990_nl.pdf

Table 12 – Trend of Riziv – Inami expenses for anticoagulants in Belgium



Source: Farmanet/Pharmanet;Riziv – Inami. NOAC expenses represent official amounts and do not take into consideration discounts (which remain unknown to the public on the ground of commercial sensitivity). Data for 2015 are not yet completely available; extrapolating data from 11 months to 1 year results in expenses for VKAs of 6.1 million €, and for NOACs of 89.2 million €.

6 ADHERENCE TO ANTICOAGULATION GUIDELINES IN PRACTICE

In this chapter we briefly review to what extent physicians adhere to recommendations from guidelines, and in how far patients adhere to the prescriptions they received from their physicians. Medication compliance is defined as "the extent to which a patient acts in accordance with the prescribed interval, and dose of a medication." Persistence refers to the act of continuing the treatment for the prescribed duration.[74]

6.1 Physicians' adherence to guidelines

Despite an established association of AF with stroke, significant failure of guideline adherence in the prescription of oral anticoagulation in AF patients at high risk for stroke has been demonstrated in several large-scale studies.[75] It has also been reported that patients at the lowest risk of stroke are being prescribed anticoagulants, even though the bleeding risk induced by this treatment exceeds the benefit of stroke prevention.[72, 73]

6.1.1 Literature search

A systematic review of the literature has been undertaken on the July 18, 2016 in the following databases: (1) Medline using OvidSp, including *Epub Ahead of Print* and *In-Process & Other Non-Indexed Citations* (2) Embase using Embase.com and (3) Cochrane Database of Systematic Reviews using Wiley.

The search aimed to identify systematic reviews on inappropriate use of oral anticoagulants in patients with non-valvular AF. The search strategy included both relevant medical subject headings, free text terms and study design filter for systematic reviews. The study question and associated strategies for each database and search details can be found in the Appendix to this report. Once the search done, all the references files were imported in Endnote® software which performed a first deduplication. An Excel template was then used for keeping track of references inclusion and exclusion. Three formal systematic reviews were identified, all of them focusing on the underuse of anticoagulants in AF.[26, 40, 76] We found no systematic reviews reporting on the overuse of anticoagulants.

In addition, we looked for AF patient registries that reported anticoagulation use according to patients' risk profile in terms of CHADS2 or CHA2DS2-VASc scores. We identified those registries from references in publications retrieved through our general literature study on anticoagulation in AF. Below we briefly discuss data from large registries that initiated recruitment in 2008 or later. Some of them are still ongoing.

6.1.2 Systematic reviews

One systematic review identified 98 studies (1997-2008).[40] The proportion of patients with contraindications for oral anticoagulation therapy reportedly was not specified in most study populations. The authors found a prevalence of contraindications in around 15% of AF patients in the general literature and they chose a treatment level below 70% of the eligible population as the point at which they considered a population being under-treated. Of 54 studies that reported stroke risk levels and the percentage of patients treated, most showed underuse of oral anticoagulants for high-risk patients. Subjects with a CHADS2 score ≥2 were also undertreated, with 7 of 9 studies reporting treatment in less than 70% (range 39% to 92.3%) of patients. From 29 studies of patients with prior stroke or transient ischemic attack who should all have received oral anticoagulation according to guidelines, 25 studies reported undertreatment, with 21 reporting oral anticoagulation treatment levels below 60% (range 19% to 81.3%) of patients.

Another systematic review limited itself to data on undertreatment in Germany and identified 4 studies.[76] It concluded that approximately 50% of German patients are undertreated. The authors retrieved 87 publications on reasons for undertreatment of AF patients. They identified four major groups of causal factors: patient-related medical factors (former bleeding and bleeding risk, risk of falls, cancer, paroxysmal AF instead of chronic AF), general characteristics of patients (old age, non-adherence), physician-related factors (knowledge and cost–benefit), and other factors usually associated with the care (logistics, INR controls).

A third systematic review does not provide precise numbers but concludes that "most studies indicate suboptimal use of anticoagulants, despite the availability of NOACs". The authors refer to a UK study of warfarin use in AF patients from 430 general practices.[77] In the 12 351 low risk AF patients defined as a CHADS2 score of 0, 37.03% (4573/12 351) were on warfarin. Of those with a CHA2DS2-VASc score of 0, 26.56% (1492/5 618) were on warfarin.

6.1.3 AF patient registries

6.1.3.1 The PINNACLE registry

The National Cardiovascular Data Registry (NCDR)'s Practice Innovation and Clinical Excellence (PINNACLE) Registry was created in 2008 by the American College of Cardiology as a prospective office-based registry in the United States. Data from this registry have been used to evaluate oral anticoagulant prescription by cardiovascular specialists. Of 1 711 326 patients enrolled into the registry between 2008 and 2012, 359 315 (21.0%) had a diagnosis of AF. In the cohort of 10 995 patients with a CHADS2 score=0, a total of 2561 (23.3%) were prescribed an oral anticoagulant. Among those, 6 730 had a CHA2DS2-VASc score=0, of whom 1787 (26.6%) were prescribed an oral anticoagulant.[75]

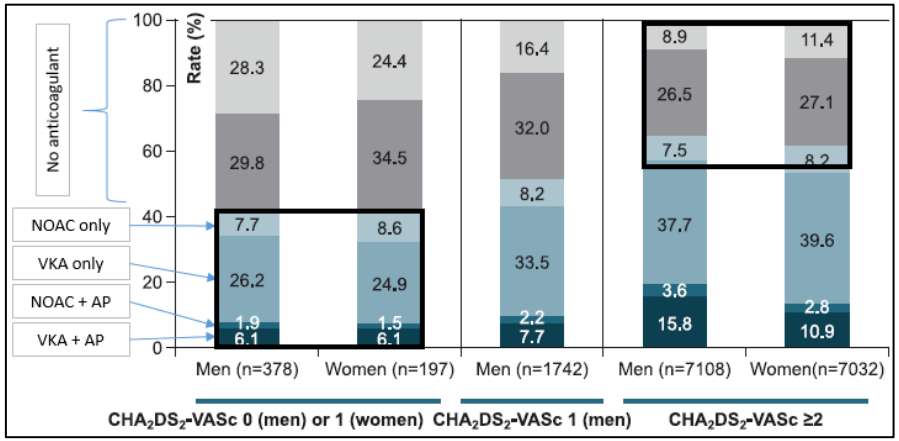
In another sub-study from the PINNACLE registry, oral anticoagulant prescription did not exceed 50%, even in highest-risk patients, including patients a CHA2DS2-VASc score exceeding 4.[78]

6.1.3.2 GARFIELD-AF registry

GARFIELD-AF is an ongoing, worldwide prospective registry of adults with recently diagnosed non-valvular AF. It consists of sequential cohorts of patients with newly diagnosed AF. Cohort 1 recruited patients in 2010-2011, cohort 2 in 2012-2013, cohort 3 in 2013-2014, cohort 4 in 2014-2015 and cohort 5 during the first half of 2015.[79]

Between March 2, 2010, and June 7, 2013, a total of 17 184 patients were enrolled at 858 randomly selected sites in 30 countries (63.1% in Europe).[79, 80] The main outcome measure was the use of anticoagulants (VKA or NOAC) for stroke prevention at AF diagnosis. Overall rate of anticoagulant use was 60% (49% VKA and 11% NOAC). 28% of patients received an antiplatelet alone, and 12% received no antithrombotic therapy. In patients at low risk (CHA2DS2-VASc=0 in men and =1 in women), 41.8% of men and 41.1% of women received an anticoagulant. In patients at high risk (CHA2DS2-VASc >1), 35.4% of men and 38.4% of women did not receive an anticoagulant (Figure 4).

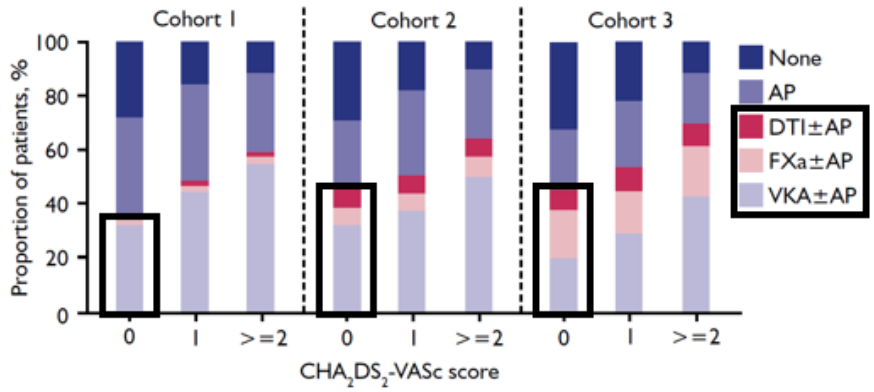
Figure 4 – Antithrombotic use in the GARFIELD registry by CHA2DS2-VASc score



Adapted from Lip et al.[80] AP: antiplatelet. Lower-left black box includes patients at low risk, treated with an anticoagulant (41.8% of men and 41.1% of women). Upper-right box includes patients at high risk, not receiving an anticoagulant (35.4% of men and 38.4% of women).

An analysis of consecutive GARFIELD cohorts allows to assess changes in anticoagulant prescription over time. Data were presented at the ESC Congress, London, 2015 in a poster presentation that is also available on line. Figure 5 is extracted from this poster, representing relative numbers only. It can be inferred from this figure that over time the percentage of AF patients that are treated with an anticoagulant increases over all risk categories. Over time, the proportion of anticoagulant patients treated with a NOAC increases.

Figure 5 – Antithrombotic use in GARFIELD by CHA2DS2-VASc score and cohort



		Cohort 1	Cohort 2	Cohort 3
score=0	VKA	32,2	32,2	19,8
	NOAC	2,0	13,0	25,4
	SUM	34,2	45,2	45,2
score=1	VKA	44,3	37,3	29,4
	NOAC	4,5	13,3	24,2
	SUM	48,8	50,6	53,6
score>1	VKA	54,9	49,9	42,9
	NOAC	4,4	14,4	26,8
	SUM	59,3	64,3	69,7

Adapted from TRI – Thrombosis Research Institute. http://www.tri-london.ac.uk/uploads/files/ESC%202015%20Treatment%20patterns%20poster.pdf. Left column: Black boxes include patients at low risk (CHA2DS2-VASc=0) that were treated with an anticoagulant. NOACs are represented here by DTI (direct thrombin inhibitors) and FXa (factor Xa inhibitors) and are depicted in different shades. Right column: proportion of patients treated with an anticoagulant by CHA2DS2-VASc risk score en by cohort (visual estimations from the left column chart).

A separate GARFIELD-AF poster represents the pattern of uptake of NOACS across Europe in the era between 2010 and 2014 in 17 475 newly diagnosed patients with non-valvular AF. The date of first commercial introduction across Europe ranged from August 2011 (Denmark, Sweden, Ukraine and UK) to June 2013 (Italy). Over all cohorts, NOAC use at baseline was highest in Belgium. Six months after NOACs became available, the proportion of patients on NOACs varied from 0.6% (UK) to 57.7% (Belgium). At 12 months, it ranged from 0.9% (UK) to 57.4% (Belgium). At 24 months, it varied from 2.1% (UK) to 59.9% (Belgium). It is not clear how many Belgian patients and centres are involved in GARFIELD-AF, neither if they are representative for all Belgian AF patients or cardiologist practices.

6.1.3.3 ORBIT-AF registry

The ORBIT-AF I registry enrolled over 10 000 all-comer outpatients with AF treated across the United States between June 2010 and August 2011. The registry largely predated the development of NOACS. Less than 10% of patients were on dabigatran, being the only approved NOAC in the US at that time.[81] In 2014, the registration of a new cohort of patients with newly diagnosed AF (ORBIT-AF II) was announced.[82] No data have been published yet on this second cohort.

Of 9957 evaluable patients in the ORBIT-AF I registry, 7563 (76.0%) received an oral anticoagulant at baseline. Across the spectrum of CHADS2 scores, rates of OAC increased from 52.5% among study subjects with a CHADS2=0 to 80.0% among those with a CHADS2 score >1.[83]

6.1.3.4 GLORIA-AF registry

The Global Registry on Long-Term Oral Antithrombotic Treatment in Patients with Atrial Fibrillation (GLORIA-AF) prospectively collected information on patients with newly diagnosed non-valvular AF. The baseline characteristics and initial antithrombotic management of the first 10 000 patients enrolled between November 2011 and February 2014 have been published.[84], [85] To be eligible for enrolment, patients had to have a CHA2DS2-VASc score of ≥1. Of the patients that entered the database, 32% were from Europe and 44% from North-America. CHA2DS2-VASc score was 1 in 14.5% and ≥2 in 85.5% of patients.

For Europe, 37.8% of patients were treated with a VKA and 52.4% with a NOAC. Antiplatelet treatment was given to 5.7% of patients, while 4.1% of patients did not receive any antithrombotic treatment (Table 13). Of patients with a CHA2DS2-VASc score=1, 83.3% were treated with an anticoagulant versus 91.1% of those with a CHA2DS2-VASc>1.

6.1.3.5 EORP-AF registry

The EURObservational Research Programme on Atrial Fibrillation (EORP-AF) Pilot Survey enrolled 3119 patients from February 2012 until March 2013.[86] It examined antithrombotic prescribing practice in 9 European countries amongst which Belgium, with particular focus on the patient risk factors determining oral anticoagulation and antiplatelet drug use. Oral anticoagulants were used in 80% of patients overall, most often VKAs (71.6%), with NOACs being used in 8.4%.Other antithrombotics (mostly antiplatelet therapy, especially aspirin) were used in one-third of patients, and no antithrombotic treatment in 4.8%. Of patients with a CHA2DS2-VASc score=0, 56.4% were receiving an oral anticoagulant (although some were because of cardioversion), while 16.8% received other antithrombotics (mostly aspirin). In contrast, of those with CHA2DS2-VASc=9, representing patients at highest stroke risk, only 66.7% received an oral anticoagulant, and 33.3% were treated with other antithrombotic drugs (mostly aspirin) although it is known that aspirin is minimally effective for stroke prevention and may not be any safer.[87]

At 1 year follow-up, oral anticoagulants were prescribed in 77.5% of registry patients. Persistence on VKA was 84%, on NOAC it was 86%.[88]

In a subset of 2634 patients, treatment was guideline adherent in 1602 (60.6%). Of the remaining 1032 patients, 458 (17.3%) were undertreated and 574 (21.7%) were overtreated according to current guidelines.[86] Overtreatment was largely determined by a high number of patients at high risk who were prescribed a combination of anticoagulants and aspirin (514; 19.5%). The absolute number of patients at low risk that were treated with an antithrombotic was 50, i.e. 66.6% of the low risk patients and 1.9% of the overall registry population. Multivariate predictors of undertreatment vs. guideline-adherent treatment included region (with undertreatment more likely in East and South Europe), lone AF, coronary artery disease, smoking, malignancy. Multivariate predictors of overtreatment vs. guideline-adherent treatment included persistent AF, coronary artery disease, peripheral vascular disease, and hypercholesterolemia. Women were less likely to be overtreated.

6.1.3.6 PREFER in AF registry

The PREFER in AF registry enrolled consecutive patients with AF from January 2012 to January 2013 in 461 centres in seven European countries (Austria, France, Germany, Italy, Spain, Switzerland, and the UK).[89] Patients were included if they were at least 18 years of age and had a history of AF documented within the preceding 12 months. Data from 7243 patients were published. Antithrombotic therapy was used by 82.3% of them.

In patients with a CHA2DS2-score=0, 199 of 318 (62.5%) received oral anticoagulation (Table 13). It was used in 70.1% of those with a CHA2DS2VASc score=1 (468 of 668 patients). Among patients with a CHA2DS2-VASc>1, 85.6% (4793 of 5600) received oral anticoagulants.

6.1.3.7 Summary of data from registries

Observational data indicate that compliance with the treatment guidelines for patients with the lowest and higher risk scores is suboptimal, including both over- and undertreatment. According to the abovementioned registries, more than half of patients at low risk (CHA2DS2-VASc=0) might be treated with an anticoagulant and hence, are overtreated according to current guidelines. In patients at high risk (CHA2DS2-VASc >1), up to 35% do not receive an anticoagulant and hence are undertreated.

Table 13 – Use of anticoagulants in patient registries by stroke risk

Registry	Country	Timeframe	Number of patients	% antico overall	% antico in CHADS2=0	% antico in CHA2DS2-VASc=0	% antico in CHA2DS2-VASc=1	% antico in CHADS2 >1	% antico in CHA2DS2-VASc >1
PINNACLE	US	2008 - 2012	±350000		23.2	26.6		±50	±50
GARFIELD	WW	2010 - 2013	17148	60		41.5°			63.1
ORBIT	US	2010 - 2011	9957	76	52.5			80	
GLORIA	WW	2011 - 2014	4703 (Europe)	90		§	83		91.1
EORP	EU	2012 - 2013	3119	80		56.4			66.7*
PREFER	EU	2012 - 2013	7243	82		62.5	70.1	85.6	86

*WW: worldwide.*CHA2DS2-VASc=9. °CHA2DS2-VASc=0 in men and 1 in women. §CHA2DS2-VASc=0 excluded from GLORIA.*

6.2 Physicians' adherence to appropriate dose prescription

Whereas the previous paragraphs focused on whether or not a physician prescribes an anticoagulant depending on a patient's risk of stroke, an important additional issue is whether a patient is prescribed the correct dose of an anticoagulant.

6.2.1 VKA dosing

For VKA prescription, correct dosing is monitored on average once a month through the international normalised ratio (INR). Dose adaptations should keep INR between values 2 and 3. The quality of VKA treatment is expressed as the "time in therapeutic range (TTR)". Obviously, the TTR reflects the physicians' as well as the patients' behaviour. According to guidelines patients treated with a VKA should spend at least 70% of their time in the desired INR range of 2-3.[6, 26] In a meta-analysis, pooled TTR was 59.1% (95% CI: 55.5-62.8%) and 64.3% (95% CI: 60.5-68.0%) for infrequent monitoring and frequent monitoring, respectively.[90] Significantly more time was spent in range in specialist care settings compared to usual care: +11.3% (95% CI: 0.1–21.7%). Naïve OAC users spent less time in range 56.5% (95% CI: 45.5–67.5%) than existing users 61.2% (95% CI: 57.2–65.2%). In a Belgian study on 604 patients (383 with AF) with an INR target of 2.5 and treated for at least 28 days, 52.7% of the INR values were within 0.5 INR units from target, and 68.2% within 0.75 INR units.[91]

6.2.2 NOAC dosing

Unlike VKAs, NOACs do not require haemostasis monitoring and repetitive dosage adjustments because of their more stable pharmacokinetic and pharmacodynamics profile. Each of the NOACs is available for AF patients in a standard and a reduced dose dose. Whereas severe renal failure (creatinine clearance <15 mL/min) is a contraindication for a NOAC, in patients with less advanced stages of renal failure, the reduced dose of the drug is prescribed. At initiation of the drug, the prescribing physician has to make a choice between the two doses, depending on renal function, the age, and in case of apixaban the weight of the patient (Table 11). Follow-up visits are indicated in patients on a NOAC every 3 to 6 months for checking adherence, side effects, co-medications and blood sampling (6 monthly).1

In 2014, an investigation on dabigatran by The BMJ caused a scientific media storm.[63], [92] The heart of the matter was that "Boehringer Ingelheim

failed to disclose that drug monitoring might reduce the risk of stroke and bleeding, which conflicted with the drugs "novel" no monitoring required status".[62] "The company found that if the plasma levels of the drug were measured and the dose was adjusted accordingly, major bleeds could be reduced by 30-40% compared with well controlled warfarin.[63] In a sub analysis of the RE-LY trail, it was found that both doses of dabigatran were associated with a more than 5-fold variation in plasma concentrations, and that individual benefit–risk might be improved by tailoring dabigatran dose.[93] In a separate publication the authors stipulated: "Of the new oral anticoagulants, RE-LY is the only trial that has published extensive data on this topic. It is likely that other anticoagulants will also exhibit variability in blood concentrations."[63, 94]

Recent data suggest that in real world practice, the lower dose of a given NOAC is prescribed more often than in was in the pivotal RCTs (Table 14).[95] This means that efficacy and safety results observed in those trials may not be applicable in real world conditions. Recent data from the REVISIT-US study showed that the reduced dose of apixaban was used about three times more often (15.5% versus 4.7%) in practice than in its pivotal RCT. "This may in part explain apixaban's less favourable ischemic stroke, and more favourable intracranial haemorrhage results vs. warfarin in this real-world analysis," researchers recently reported at the European Cardiac Arrhythmia Society Congress according to MedpageToday.d e A copy of the presentation was asked to C. Coleman (ccoleman@harthosp.org) on August 22, 2016, but so far our request remained unanswered.

Table 14 – Proportion of patients chronically prescribed a reduced dose of a NOAC

Reduced dose:	Dabigatran 110	Rivaroxaban 15	Apixaban 2.5
% reduced dose in RCT	49.7	20.7	4.7
% reduced dose in UK*	55.5	22.3	36.3
% reduced dose in Germany*	59.5	36.2	47.6
% reduced dose in France*	65.0	36.9	44.3
% reduced dose in Belgium§	58.1	44.1	23.7

*Sources: *Fay et al. (ESC Scientific Session, 2016. Poster P2597) in Eikelboom et al.[95] § cf. Chapter 11 of this report.*

For dabigatran, the 110 mg and 150 mg doses were approved by EMA. The FDA approved only the 150 mg twice daily dose and asked for a 75 mg twice daily dose to be developed for patients with severe renal impairment. This 75 mg dose was not tested in clinical trials and was chosen on the basis of pharmacodynamics and pharmacokinetic data.[63]

6.3 Patients' adherence to anticoagulant prescription

In previous studies where the efficacy of VKA was compared with aspirin, discontinuation rates on warfarin were not consistently higher than in the control arms of RCTs, although older patients were more likely to discontinue VKA.[96] In the Birmingham Atrial Fibrillation Trial of the Aged (BAFTA) study, 33% of patients randomised to warfarin discontinued therapy after a follow-up period of 2.7 years, compared to 24% of patients randomised to aspirin.[30, 96]

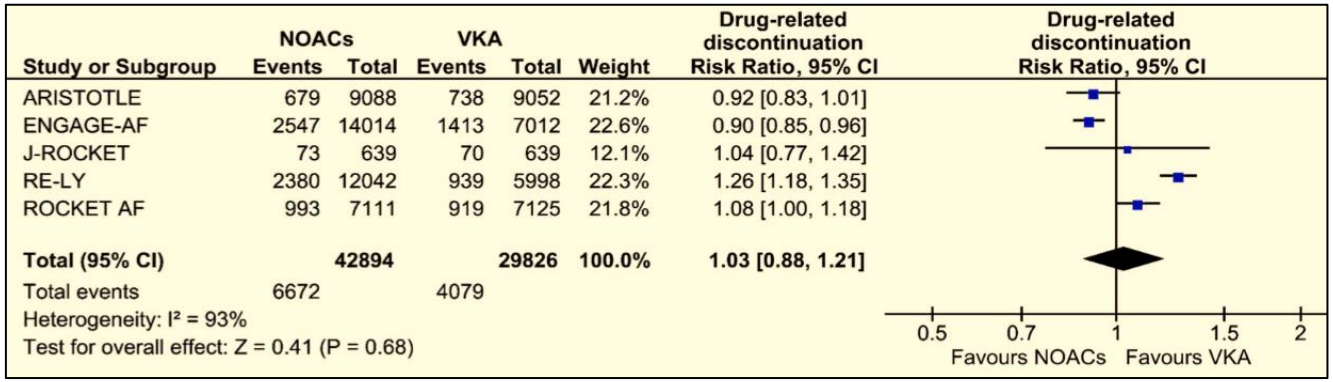
In a pooled analysis of data from the RCTs that compared VAK with NOACs, drug-related discontinuation rate was similar between NOACs and VKAs with a RR of 1.03 (95%CI 0.88-1.21).[97] There was however a large

d http://www.medpagetoday.com/cardiology/prevention/57483

e http://www.tctmd.com/show.aspx?id=134904&print=true

heterogeneity across studies (Figure 6). The RE-LY trial (dabigatran vs. VKA) was the only one of the RCTs in which patients in the VKA arm were not blinded.[54] Although a higher discontinuation rate might have been expected due to the inconvenience of regular blood testing needed for anticoagulation monitoring in the VKA group, this was not the case. Significantly more patients in the NOAC arm discontinued the drug (RR 1.26; 95%CI: 1.18-1.35). The rates of discontinuation for dabigatran 150 and warfarin were 15.5% versus 10.2% at 1 year, and 21.2% versus 16.6% at 2 years.

Figure 6 – Forest plot comparing the discontinuation risk in NOACs vs. VKAs



Source: Caldeira et al.[97] « Favours NOAC » indicates that compared to VKA users, less NOAC users discontinued treatment. "Favours VKA" indicates that more NOAC users than VKA users discontinued treatment.

Although the relative risk for discontinuation of the study drug in the VKA vs. the NOAC arms were comparable in the blinded RCTs, the absolute discontinuation rates were high in both arms in all studies. In the rivaroxaban ROCKET AF study, the proportions of patients who permanently stopped their assigned therapy before an end-point event were 23.7% in the rivaroxaban group and 22.2% in the warfarin group.[19] In the apixaban ARISTOTLE study, 25.3% of the patients in the apixaban group, and 27.5% of patients in the warfarin group discontinued the study drug before the end of the study.[60] In the apixaban ENGAGE study, permanent discontinuation rates were particularly high: 34,5% in the warfarin group, 34% in the apixaban-60 group, and 33.0% in the apixaban-30 group.[55]

Real world data from Germany indicate that persistence on oral anticoagulants at 1 year was better for NOACs than for VKAs with proportions of 63.6% and 79.2% respectively.[98] In a Swedish study, the overall persistence with any oral anticoagulant was high with 88.2 % at 1 year and 82.9% at 2 years. Multivariate analysis confirmed significantly higher persistence with warfarin and apixaban than with dabigatran or rivaroxaban.[99]

Key points

- **Worldwide, registries have shown the existence of a risk-treatment paradox, i.e. a substantial proportion of AF patients at high risk for stroke are not treated, and a substantial proportion of low risk patients are.**
- **A major advantage of NOACs over VKAs is that regular monitoring and dose adjustments are not needed. This may also have undesirable effects: it can reduce patient compliance, and it prevents the physician from assessing whether the appropriate dose (standard or reduced) of the NOAC is prescribed.**
- **Real world data show that the reduced dose of a given NOAC is prescribed more often than in was in the corresponding RCTs. The efficacy and safety outcomes derived from RCTs may therefore not be applicable in real world conditions.**
- **The discontinuation rates of both NOACs and VKAs in RCTs were high (25 - 35%) and similar for both classes.**

7 CLINICAL USE OF ANTICOAGULANTS IN NON-VALVULAR AF: DISCUSSION

7.1 Stroke risk associated with AF, versus bleeding risk associated with anticoagulants

Among thromboembolic events, ischemic stroke is the most dreaded complication in patients with non-valvular AF. In untreated patients with AF, the overall risk of stroke ranges from 0% to more than 10%.[4, 22, 27, 100] The risk of ischemic stroke depends on a number of clinical characteristics and is indirectly represented by the CHA2DS2-VASc score. Herein, previous stroke and age ≥75 years receive the highest weight and are given 2 points. Other risk factors (congestive heart failure, hypertension, diabetes, female gender, age 65-74 years, vascular disease) are attributed 1 point. These points are added and the higher the score, the higher the risk for thromboembolic events and ischemic stroke. Risk predictions in the CHA2DS2-VASc score are mostly based on data from hospitalised patients. With a worldwide decrease in stroke rates, this stroke risk may nowadays be substantially lower than estimated.[7]

Anticoagulants also increase the risk of major bleeding, including haemorrhagic stroke. This risk is estimated from previous VKA trials to range from 0.3% to 0.6% per year.[27, 33, 34] In more recent NOAC trials, the risk of haemorrhagic stroke in the VKA arm of the trials was higher (0.38 to 0.70%), whereas it was lower in the respective NOAC arms (0.10 to 0.50%) (Table [7]). In absolute numbers, the risk difference for haemorrhagic stroke between the two drug classes ranged from 0.20%[19] to 0.31%[55] per year. On the other hand, gastrointestinal bleeding occurs more often with NOACs, with the exception of apixaban. In absolute numbers, the risk difference for gastrointestinal bleeding between the two drug classes in RCTs ranged from 0.10%[54] to 0.51%[19] per year. There is no clear explanation for these difference.[52]

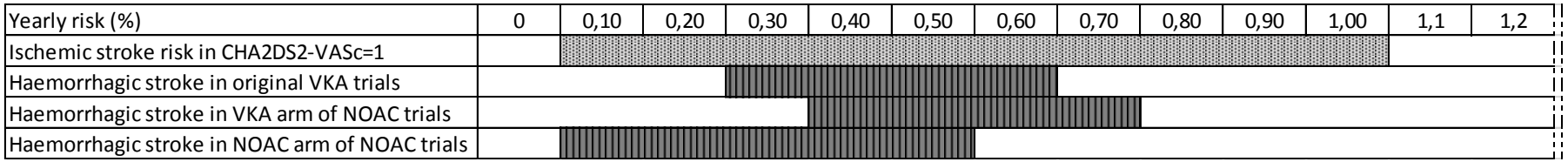
Factors that are related to bleeding risk are summarised in the HAS-BLED score (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly, Drugs/alcohol concomitantly). The score is not used to exclude patients from anticoagulation therapy but to encourage physicians to act on those risk factors for bleeding that can be

corrected".[3] In a large Swedish cohort, there was a positive association between CHA2DS2-VASc scores and the risk of bleeding in general, but not in relation to intracranial bleeding that showed relatively constant rates across CHA2DS2-VASc scores.[36]

International guidelines unanimously recommend anticoagulation therapy in patients with a CHA2DS2-VASc score ≥2 (♂) or ≥3 (♀), whereas in patients with a score of 0, such treatment is not indicated. The absolute stroke risk threshold above which anticoagulation is recommended in these guidelines has been lowered over the years. At the time the CHADS2 score was advocated, guidelines recommended anticoagulation in patients with a CHADS2 score≥1, using a 2% per year stroke risk threshold. With the application of the CHA2DS2-VASc score, this threshold has been implicitly lowered to a 1% risk per year.[73] There is no clear justification for this, since such threshold depends on patient preference and cannot be derived from trials.

There is considerable debate on the need for anticoagulation in patients with a CHA2DS2-VASc score=1 (♂) or 2 (in ♀), i.e. in those with only one risk factor (except female gender), since it is not certain that in these patients, the benefit of anticoagulation exceeds the risks. The absolute risk of stroke for any given CHA2DS2-VASc score is not exactly known and there are large differences in the estimates. This may be less important in patients at high risk in whom the risk of ischemic stroke due to AF largely exceeds that of haemorrhagic stroke induced by the anticoagulants. This is however less straightforward in patients with a CHA2DS2-VASc=1. In these patients, a systematic review of Western cohorts resulted in a pooled yearly risk of ischemic stroke of 0.56% (95%CI: 0.08 to 1.03%) (Figure 1). Given an overlapping range of risk of intracranial bleeding induced by anticoagulants, the benefit of anticoagulation in any given patient with with only one risk factor (except gender) does not necessarily exceed the harm. This concept is graphically displayed in Figure 7.

Figure 7 – Absolute risk of ischemic and haemorrhagic stroke, associated with oral anticoagulants, in CHA2DS2-VASc=1 patients



Sources: Ischemic stroke risk in CHA2DS2-VASc=1 patients extracted from Joundi et al.9 Rates are obtained from cohorts of hospitalised AF patients that were not anticoagulated. Stroke rates in contemporary cohorts may vary from these estimates. Haemorrhagic stroke in previous VKA trials (combined for all risk scores): systematic review of Hart et al.27 Data from pivotal NOAC trials are summarised in Table 7

Use of oral anticoagulants in real world conditions

In parallel with the strong recommendations formulated in the EU and US guidelines, several reports have focussed on the inappropriate use of anticoagulants in everyday practice. Especially the underuse of anticoagulation has been stressed by several authors, already before the NOAC era.

7.1.1 Undertreatment in high risk populations with a CHA2DS2-VASc risk score of ≥2 (♂) or ≥3 (♀)

Undertreatment can be defined as the practice in which patients who should be prescribed a given treatment, are not receiving it. It is hard to put forward the proportion of AF patients that should receive an anticoagulant, but this might be based on the prevalence of contraindications for anticoagulation in them. Previous studies reported contraindications in about 15% of patients.[40, 100] Hence, undertreatment can be suspected if less than 85% of a cohort of patients with an indication for anticoagulation are not treated.

Traditionally, undertreatment is explained by physicians being reluctant to prescribe anticoagulants in elderly because of their old age per se, or because they are more prone to be involved in falls.[10] Undertreatment can also result from patients refusing treatment, or inappropriately stopping it. Furthermore, a gap in the evidence base may also have a role since elderly people (85+) are poorly represented in RCTs. Recent observational data from The Netherlands however show that the bleeding risk with a VKA only mildly increases after the age of 80 years, while there is a sharp increase in the risk of thrombosis in this age group.[101] The study does however not provide details on elderly AF patients in whom it was decided not to start an anticoagulant, e.g. because of age, frailty, mobility problems, fall risk, or dementia.[102]

In a systematic review, from 29 studies of patients with prior stroke who should all have received oral anticoagulation according to guidelines, 21 reported oral anticoagulation treatment levels below 60% (range 19% to 81.3%) of patients. Subjects with a CHADS2 score ≥2 were also undertreated, with 7 of 9 studies reporting treatment in less than 70% (range 39% to 92.3%) of patients.[40] Data from more recent registries showed proportions of high risk patients treated with an anticoagulant ranging from 50% to 91%. In a Belgian study by Flemish general practitioners, 49.7 % of patients with AF at high risk (CHADS2 ≥ 2) of stroke were started an anticoagulant within the first six months after diagnosis.[103]

7.1.2 Overtreatment in low risk populations with a CHA2DS2-VASc risk score of 0 (or 1 in ♀ with no additional risk factors)

Recent international registries indicate that 27% to 63% of patients with a CHA2DS2-VASc=0 are treated with an anticoagulant.

In the abovementioned Belgian study by Flemish general practitioners, 51% of patients with a CHADS2 score=0 (n=285), and 58% of those with a CHA2DS2-VASc=0 (n=19) received an anticoagulant.[103] Since the absolute number of patients involved, these data should be taken cautiously.

7.1.3 Anticoagulation in patients with a CHA2DS2-VASc risk score of 1 (♂) or 2 (♀)

Patients with a CHA2DS2-VASc score=1 are positioned in a grey zone in which it is not fully clear whether the benefit from anticoagulation exceeds their potential harms, especially with respect to the most pertinent outcomes: ischemic versus haemorrhagic stroke.[16, 72, 73] From recent European registries, it appears that many of them are treated with an anticoagulant. In the GLORIA-AF registry (2011-2014), of patients with a CHA2DS2-VASc score=1, 83.3% were treated with an anticoagulant.[84] The PREFER in AF registry (2012-2013), anticoagulation was used in 70.1% of patients with a CHA2DS2-VASc score=1.[89]

7.1.4 Patients' adherence to anticoagulants

The absolute discontinuation rate of study drugs in the pivotal NOAC RCTs were particularly high in both arms in all studies and they were comparable for VKAs and NOACs. Given that fact that patients enrolled in RCTs are strictly followed, it might be that discontinuation rates in real-world settings are even higher.[96] Some real world studies have shown a better patient compliance with NOACs, others did not find clear differences as compared to VKAs.[98, 99]

Non-adherence might be less well tolerated for NOACs than for VKAs, because of their shorter half-life.[104] In the 2016 version of the US Clinical Performance and Quality Measures, it is stressed that missing even one dose of a NOAC can result in a period without protection from thromboembolism.[25]

7.2 New oral anticoagulants vs. vitamin K antagonists

7.2.1 Effect of NOACs versus VKAs on stroke

Based on RCTs, individual NOACs are equivalent to VKAs with respect to the reduction of "any stroke and systemic embolism", the primary endpoint in the non-inferiority RCTs that compared those two groups of agents.

Each NOAC has been studied against VKAs in patients with AF in only one RCT. In the RCTs on rivaroxaban and edoxaban, patients at low risk of stroke (CHADS2 score 0 or 1) were not included.[19, 55] No head to head comparisons of NOACs have been published so far. Cross-trial comparisons of different NOACs, and even meta-analyses of RCT data, may not be valid because of methodological differences across studies and heterogeneous baseline characteristics of participants across trials.[49]

Recent data indicate that in real world practice, the reduced dose of a given NOAC is prescribed more often than it was in the pivotal RCTs. Therefore, efficacy and safety results observed in those trials may not be obtained in real world practice.

7.2.2 Effect of NOACs versus VKAs on bleeding

In most studies, NOACs were associated with a slightly lower absolute risk of major bleeding than VKAs. An increased risk of gastrointestinal bleeding has been observed with dabigatran and rivaroxaban. In most studies, NOACs were associated with a small reduction in the absolute risk of haemorrhagic stroke, although the latter is already included in the primary endpoint of "any stroke and systemic embolism".

It has been argued that the lower risk of bleeding induced by NOACs versus VKAs may at least partly be related to a number of methodological limitations in the RCTs.

Major bleeding was reported in 1.6 to 2.9% of patients in the low NOAC dose subgroup of the trials, and in 2.1 to 3.6% in the high NOAC dose subgroup. In the VKA arms in these trials, major bleeding was observed in 3.1 to 3.6% (Table 7). On two different occasions, corrections in the reported results of the RE-LY trial have been published [105, 106] These corrections were related to additional primary efficacy and safety outcome events, detected during routine clinical site closure visits. They included 69 major bleedings, 1 stroke and 5 transient ischemic attacks. Although those new findings reportedly did not change the original conclusions, they raise questions about the data integrity of the study.[62]

Some additional particularities in the pivotal NOAC trials may at least partly explain the higher bleeding events observed in the VKA versus the NOAC patients. Thirty to 40% of participants of the RCTs used aspirin in combination with the anticoagulant. Previous studies have shown that the combination of aspirin and warfarin double the risk of bleeding, corresponding to an absolute increase of 2%.[66-68]

Furthermore, the quality of the anticoagulation therapy in the VKA arm of the trials was poorer than what could be expected from pivotal trials, with patients being in the therapeutic INR range only during a median of 55%[19] up to 68%[55] of the time. [107]Inappropriate dosing of VKA in the RCTs may have induced a higher than expected number of strokes due to VKA underdosing, or a higher number of bleedings due to VKA overdosing. All RCTs have been conducted in 40 to 50 different countries with different standards of care. In an analysis of the RE-LY trial, it was shown that local standards of care affected the benefits of NOACs. The trend towards increased mortality with warfarin in this trial was entirely due to investigator sites where INR monitoring was inferior.[66, 108-110]

In December 2014, four years after completion of the ROCKET-AF trial, the US Food and Drug Administration (FDA) issued a recall notice for the device that was used for INR measurement in this study. The authors concluded that the possible malfunction of the device did not have any significant clinical effect on the primary efficacy and safety outcomes in the trial.[59] However, several authors have criticised the fact that the manufacturer of rivaroxaban did not allow for an independent review of those data.[69]

7.2.3 Drug monitoring and compliance to treatment

From a clinical practice point of view, the major advantage of NOACs over VKAs is that regular monitoring and dose adjustments are not needed. The drugs are available in a standard and in a reduced dose from which the prescriber has to make a choice, based on age, body weight and/or renal function.

A lower need for office visits, and the associated costs, can therefore be expected to be lower in patients treated with a NOAC. For patients it may be important that lifelong monthly venous punctures are not needed if they are treated with a NOACs as opposed to a VKA. This element has been central in the successful marketing and widespread uptake of NOACs.[63] Nevertheless, although monitoring of haemostasis is not needed, follow-up of renal function is necessary. Follow-up visits are indicated every 3 to 6 months for checking drug adherence, side effects, co-medications and blood sampling (6 monthly). 1

The absence of intensive monitoring may make NOAC therapy for patients more acceptable than VKAs. However, in each of the RCTs, discontinuation of both warfarin and NOAC was particular high. For warfarin it ranged from 16.6%[54] to 34.5%[55] and for NOACs from 20.7%[54] to 34%[55]. The absence of monitoring could even have an opposite effect on compliance, since monitoring indirectly measures adherence with treatment.[10] A regular (mandatory) contact with the general practitioner may motivate patients to continue a therapy that is purely preventive and of which they feel no immediate effect.

Besides the absence of a need to monitor NOACs, there is - unlike the INR for VKAs - no option in clinical practice to assess therapeutic anticoagulation.6 NOACs come in two different dosages (Table 11) and the prescribing physician has to make a choice between two dosages (standard or reduced), but he has presently no means to check whether a patient is receiving the most appropriate dose, i.e. the dose with the largest net clinical benefit. A prescribing physician may be reluctant to prescribe the high dose of a NOAC in a given patient, and inappropriately opt for the reduced dose. This may lower the risk of bleeding, but may also make the treatment less effective. Except for dabigatran, the reduced dose of the NOACs have only been evaluated in small numbers of patients in the pivotal RCTs (Table 14).[95, 111]

In 2014, an analysis, performed by The BMJ, revealed that drug monitoring of dabigatran was possible in practice, and that this has been investigated by its manufacturer Boehringer Ingelheim.[63, 93] The company found that if the plasma levels of the drug were measured and the dose was adjusted accordingly, major bleeds could be reduced by 30-40% compared with well controlled warfarin. In the BMJ analysis, it is suggested that this critical information was not made public because it would weaken the central marketing message that monitoring is not needed for dabigatran. Hence, although NOAC drug monitoring is not advocated, it might be pertinent.

NOACs have also a lower half-live than VKAs which may be an advantage in case of bleeding or when surgery is needed. VKA's anticoagulant action can be reversed with vitamin K (at a cost of €10), and specific reversal agents for NOACs have recently been developed (idarucizumab, andexanet).[37, 38] Idarucizumab (Praxbind) is used at a dose of 5 gram, and comes at a RIZIV/INAMI cost of €2 687. Andexanet is not yet reimbursed. A disadvantage of a lower half-live is that it makes careful attention to dosing schedules an important aspect of maintaining protection against stroke. Two of the currently available NOACs in Belgium are twice-daily agents, further increasing the importance of strict adherence to prescription.

8 COST-EFFECTIVENESS OF NOACS

8.1 Introduction

This chapter offers an overview of published economic evaluations on novel oral anticoagulants (NOACs), compared with each other and to vitamin K antagonists (VKAs), for the prevention of stroke and systemic embolism in non-valvular atrial fibrillation (NVAF). The aim is to identify which are the most cost-effective options according to the literature and to offer a critical appraisal on the transferability of the results to the Belgian context.

8.2 Methods

8.2.1 Literature review

A systematic search was carried out between 25 April and 3 May 2016 to identify relevant primary economic evaluations or systematic reviews of economic evaluations.

The following bibliographic databases were searched: MEDLINE and Embase (via Embase.com), the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials (CENTRAL), the Database of Abstracts of Reviews of Effects (DARE), the Health Technology Assessment Database (HTA) and the NHS Economic Evaluation Database (EED) (via the Cochrane Library). The Health Technology Assessment Database (HTA) was also searched via the Centre for Reviews and Dissemination (CRD) search interface.

In addition to bibliographic databases, the grey literature was searched by looking at the websites of the UK National Institute for Health and Care Excellence (NICE) and fellow member organisations of the International Network of Agencies for Health Technology Assessment (INAHTA) to identify relevant health technology assessment reports or economic evaluations.

No language or date limits were set for the searches. A filter for economic evaluation studies was used for the MEDLINE and Embase search. Because relevant records were likely to have been indexed in different ways, or not indexed at all, the search strategy incorporated both indexing terms and free text words in the title or abstract.

The Embase search strategy was translated for the other databases and adapted to take into account the databases' size, coverage and available indexing terms. The search strategy was based on the Population, Interventions, Comparators and Outcomes (PICO) framework, as described below. Search strategies for Embase.com (includes both Embase and MEDLINE), Cochrane Library and CRD are listed in the Appendix to this report.

8.2.2 Selection process

The PICO along with the inclusion and exclusion criteria used for the selection of publications are shown in Table 15.

Table 15 – Selection criteria for economic evaluations

Selection criteria	Inclusion criteria	Exclusion criteria
A priori criteria		
Population	Patients with non-valvular atrial fibrillation or atrial flutter	Mitral valve stenosis and mechanical valve prosthesis Other indications for anticoagulants such as venous thromboembolic disease Peri-procedural use of anticoagulants (in the setting of surgical or non-invasive interventions)
Intervention	Anticoagulation treatment for the prevention of stroke and systemic embolism with one of the following novel anticoagulants (NOAC): • apixaban • dabigatran • rivaroxaban • edoxaban	Anticoagulant in combination with anti-platelet drug(s) Studies on Ximelagatran
Comparator	All NOACs listed under Intervention Anticoagulation treatment with one of the following vitamin K antagonists (VKA): • phenprocoumon • acenocoumarol • warfarin	Anti-platelet drugs (e.g. aspirin, clopidogrel) Devices or interventions used for the prevention of stroke (e.g. Watchman)
Outcomes	Incremental cost Incremental outcomes Incremental cost-effectiveness ratios	
Study design	Primary full economic evaluations (i.e. studies comparing at least two alternative treatments in terms of both costs and outcomes)*: • Cost-minimization analyses (CMA) • Cost-utility analyses (CUA, with results expressed as incremental cost per QALY gained) • Cost-effectiveness analyses (CEA, with results expressed as cost per life year gained) • Cost-benefit analyses (CBA, with a monetary valuation of health outcomes) Reviews of full economic evaluations (as a source of primary studies)	• Cost comparisons (not considering health outcomes) • Cost-outcome descriptions (not considering an alternative treatment) • Cost-consequence analyses (see note below)
Additional criteria (see below)		

Geography	• Western, Southern and Northern Europe • Canada • USA • Australia and New Zealand	• Eastern Europe • Rest of world
Type of Publication	Articles and reviews	Letters, news, conference proceedings and editorials

** Note: In cost-consequence analyses, both costs and outcomes of different alternatives are described. In such studies however, an incremental cost-effectiveness ratio (ICER) is not calculated or the results are expressed in disease-specific outcome (e.g. incremental cost per patient reduction of one point in the Activities of Daily Living – ADL scale). These studies are discarded as their results cannot be compared with those of other types of economic evaluations.*

The bibliographic database searches retrieved 1,429 potentially relevant studies, with a further 32 identified from grey literature searches. After eliminating duplicates, 1,355 records remained.

The selection of studies incorporated a three-stage sifting process: two rounds at title and abstract, then one round of sifting at full-text. First, their titles and abstracts were screened to exclude any clearly non-relevant studies using the PICO criteria (Table 15), leaving 172 relevant primary studies or reviews.

Because of the large number of studies it was decided to introduce an additional exclusion criteria based on country of study. To include those of most relevance to the Belgian healthcare system, we prioritised studies from Western, Southern and Northern Europe, USA, Canada, Australia and New Zealand. Using these extended selection criteria, a further 122 records were excluded at the second round of title and abstract screening (95 primary studies and 27 systematic reviews).

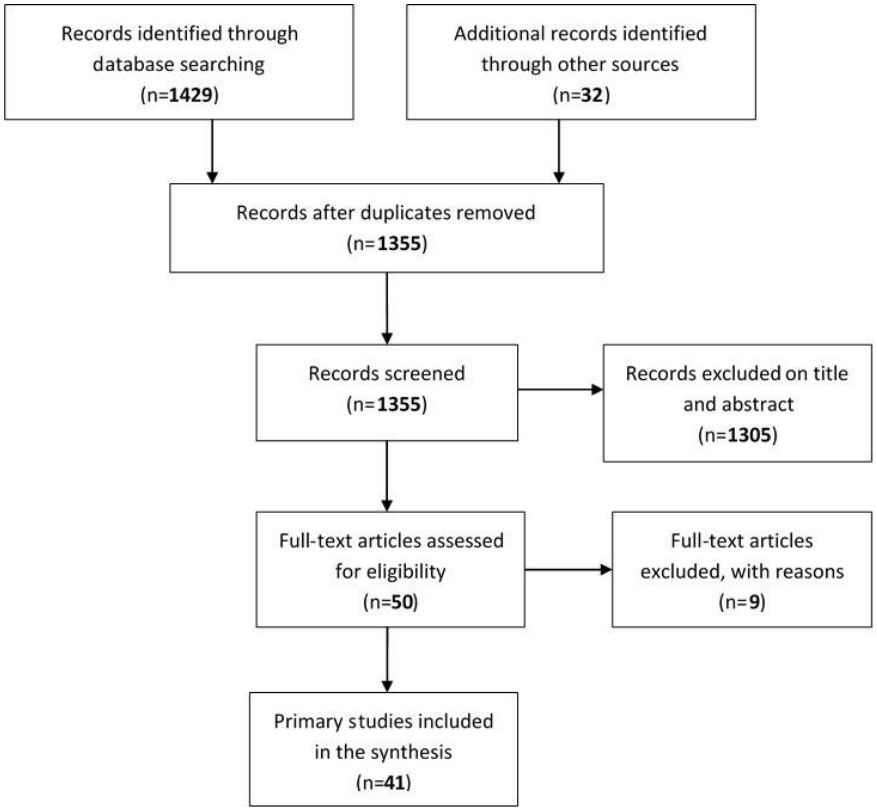
This left 50 studies for full text screening. At this stage, nine studies were excluded: three on study design, four on country, and two on comparator used. Therefore, 41 primary studies were included in the final analysis. Figure 1 describes a PRISMA flow chart of the selection process.

Reference lists of relevant reviews of economic evaluations published between 2011 and 2016 that were identified by our search were checked for additional references. This led to four additional studies being screened at full text stage – all NICE Health Technology Assessments [112-114]. These technology assessments are not included in our primary analysis because some information was redacted from the reports due to commercial sensitivity. However, their findings are described narratively in the results section.

All primary studies included in our review were critically appraised using The Scottish Intercollegiate Guidelines Network (SIGN) methodology checklist for economic studies (available at http://www.sign.ac.uk/methodology/checklists.html). The checklist evaluates the internal validity of each study by assessing whether:

- the study has a well-defined question
- the study design is well-justified
- the costs have been performed from a relevant viewpoint
- the appropriate and relevant outcomes have been measured
- discounting of future costs and outcomes has been performed appropriately
- assumptions have been made explicit and sensitivity analyses have been performed
- a decision rule has been made explicit
- the results provide relevant information to policy makers.

Figure 8 – PRISMA diagram



8.3 Results

8.3.1 Overview of economic evaluations

Table 16 provides an overview of the 41 studies included in the analysis (not including the NICE technology assessments).

Studies are from a total of 17 countries. Thirty three studies were performed in Europe. Within these, three studies focussed on Belgiuml[115-117]. Four studies were performed in the USA[118-121] and four in Canada[122-125]. No studies were identified from Australia or New Zealand.

All the studies dated from 2011 or later, with 24 published in 2014 or 2015, reflecting the recent increase in the NOAC literature.

Thirty-three of the 41 studies were deemed to be of 'high quality'. The remaining eight were judged to be of 'acceptable' quality according to the SIGN checklist.

Nineteen of the 41 studies compared a single NOAC to warfarin; 11 compared multiple NOACs to warfarin; four compared NOACs with other (non-warfarin) VKAs; and one compared NOACs to both warfarin and other VKAs. The remaining six studies compared NOACs to NOACs. To facilitate these different comparisons, the overview, costs, outcomes and ICER tables have been sub-grouped in the same manner.

Table 16 – Overview of economic evaluations

Author	Date	Country	Type of economic evaluation	Perspective	Time horizon	Drugs included in the model	Discount rate (per annum)	Quality rating
Single Comparisons: NOAC vs Warfarin								
Chevalier[127]	2014	France	CUA	Healthcare system	Lifetime	Dabigatran, Warfarin	4% both cost and health outcomes	Acceptable (+)
Davidson[128]	2013	Sweden	CEA/CUA	Societal	20 years	Dabigatran, Warfarin	3% both cost and health outcomes	High quality (++)
Dorian[129]	2014	UK	CEA/CUA	Healthcare system	Lifetime	Apixaban, Warfarin	3.5% both cost and health outcomes	High quality (++)
Freeman[122]	2011	USA	CUA	Healthcare payer	35 years or death	Dabigatran, Warfarin	3% both cost and health outcomes	High quality (++)
González-Juanatey[130]	2012	Spain	CEA/CUA	Healthcare system	Lifetime	Dabigatran, Warfarin	3% both cost and health outcomes	High quality (++)
Kamel[120]	2012	USA	CUA	Societal	20 years or death	Apixaban, Warfarin	3% both cost and health outcomes	High quality (++)
Kansal (b)[131]	2012	UK	CUA	Healthcare system	10 years	Dabigatran, Warfarin	3.5% both cost and health outcomes	High quality (++)
Kleintjens[117]	2013	Belgium	CEA/CUA	Healthcare payer	Lifetime	Rivaroxaban, Warfarin	3% cost and 1.5% health outcomes	High quality (++)
Krejczy[132]	2015	Germany	CUA	Healthcare system	20 years	Edoxaban, Warfarin	5% both cost and health outcomes	High quality (++)
Langkilde[133]	2012	Denmark	CUA	Healthcare payer	Lifetime	Dabigatran, Warfarin	2% both cost and health outcomes	High quality (++)
Lanitis (b)[134]	2014	Sweden	CEA/CUA	Societal	Lifetime	Apixaban, Warfarin	3% both cost and health outcomes	High quality (++)
Mensch[135]	2015	Germany	CUA	Healthcare system	35 years	Rivaroxaban, Warfarin	3% both cost and health outcomes	High quality (++)
Morais[136]	2014	Portugal	CEA/CUA	Healthcare system	Lifetime	Rivaroxaban, Warfarin	5% both cost and health outcomes	High quality (++)
Nshimyumukiza[123]	2013	Canada	CUA	Healthcare system	5 years	Dabigatran, Warfarin	3% both cost and health outcomes	Acceptable (+)

Pink[137]	2011	UK	CEA/CUA	Healthcare system	Lifetime	Dabigatran, Warfarin	3.5% both cost and health outcomes	High quality (++)
Rognoni (b)[138]	2014	Italy	CEA/CUA	Healthcare system	Lifetime	Edoxaban, Warfarin	3.5% both cost and health outcomes	Acceptable (+)
Shah[121]	2011	USA	CUA	Healthcare system	20 years	Dabigatran, Warfarin	3% both cost and health outcomes	High quality (++)
Sorensen[125]	2011	Canada	CEA/CUA	Healthcare system	Lifetime	Dabigatran, Warfarin	5% both cost and health outcomes	High quality (++)
Stevanović[139]	2014	Netherlands	CEA/CUA	Healthcare payer	Lifetime	Apixaban, Warfarin	4% cost & 1.5% health outcomes	High quality (++)
Multiple comparisons: NOAC vs. Warfarin								
Coyle[124]	2013	Canada	CUA	Healthcare payer	40 years	Apixaban, Dabigatran, Rivaroxaban, Warfarin	5% health outcomes. Cost adjusted to 2011	Acceptable (+)
Harrington[119]	2013	USA	CUA	Societal	30 years or death	Apixaban, Dabigatran, Rivaroxaban, Warfarin	3% both cost and health outcomes	High quality (++)
Janzic[140]	2014	Slovenia	CUA	Healthcare payer	Lifetime	Apixaban, Dabigatran, Rivaroxaban, Warfarin	3% both cost and health outcomes	High quality (++)
Kansal (a)[126]	2012	Canada	CEA/CUA	Healthcare payer	5 or 10 years	Dabigatran, Rivaroxaban, Warfarin	5% both cost and health outcomes	Acceptable (+)
Kongnakorn[116]	2014	Belgium	CEA/CUA	Healthcare payer	Lifetime	Apixaban, Dabigatran, Rivaroxaban, Warfarin	3% cost and 1.5% health outcomes	High quality (++)
Krejczy[141]	2014	Germany	CUA	Healthcare system	20 years	Apixaban, Dabigatran, Rivaroxaban, Warfarin	5% both cost and health outcomes	High quality (++)
Lanitis (a)[142]	2014	France	CEA/CUA	Healthcare payer	Lifetime	Apixaban, Dabigatran, Rivaroxaban, Warfarin	4% both cost and health outcomes	High quality (++)
Ravasio[143]	2014	Italy	CEA/CUA	Healthcare system	Lifetime	Apixaban, Dabigatran, Rivaroxaban, Warfarin	3% both cost and health outcomes	High quality (++)
Rognoni (a)[144]	2014	Italy	CEA/CUA	Healthcare system	Lifetime	Dabigatran, Warfarin	3.5% both cost and health outcomes	High quality (++)
Verhoef[145]	2014	UK and Netherlands	CUA	Healthcare system	Lifetime	Apixaban, Dabigatran, Rivaroxaban, Warfarin, Acenocoumarol, Phenprocoumon	UK: 3.5% both cost and health outcomes. Dutch: 4% cost and 1.5% health outcomes.	High quality (++)

Wisløff[146]	2014	Norway	CUA	Healthcare system	Lifetime	Apixaban, Dabigatran, Rivaroxaban, Warfarin	4% both cost and health outcomes	High quality (++)
NOAC vs. other VKA								
Barón[147]	2015	Spain	CEA/CUA	Healthcare system and societal	Not reported	Apixaban, Acenocoumarol	3.5% both cost and health outcomes	Acceptable (+)
Kourlaba[148]	2014	Greece	CEA/CUA	Healthcare payer	Lifetime	Rivaroxaban, Acenocoumarol	3.5% both cost and health outcomes	High quality (++)
Pletscher[149]	2013	Switzerland	CEA/CUA	Healthcare payer	Lifetime	Dabigatran, Phenprocoumon	2% both cost and health outcomes	Acceptable (+)
Wouters[118]	2013	Belgium	CUA	Healthcare payer	Lifetime	Dabigatran, Acenocoumarol, Phenprocoumon	3% cost & 1.5% health outcomes	Acceptable (+)
NOAC vs. Warfarin and other VKA								
Andrikopoulos[150]	2013	Greece	CUA	Healthcare payer	Lifetime	Dabigatran, Warfarin, Acenocoumarol	3.5% both cost and health outcomes	High quality (++)
NOAC vs. NOAC								
Athanasakis[151]	2015	Greece	CEA/CUA	Healthcare payer	Lifetime	Apixaban, Dabigatran, Rivaroxaban	3% both cost and health outcomes	High quality (++)
Canal Fontcuberta[152]	2015	Spain	CEA/CUA	Healthcare system and societal	Lifetime	Apixaban, Rivaroxaban	3.5% both cost and health outcomes	Acceptable (+)
Costa[54]	2015	Portugal	CEA/CUA	Healthcare system	Lifetime	Apixaban, Dabigatran, Rivaroxaban	5% both cost and health outcomes	High quality (++)
Lip[153]	2014	UK	CEA/CUA	Healthcare system	Lifetime	Apixaban, Dabigatran, Rivaroxaban	3.5% both cost and health outcomes	High quality (++)
Lip[154]	2015	UK	CEA/CUA	Healthcare system	Lifetime	Apixaban, Edoxaban	3.5% both cost and health outcomes	High quality (++)
Zheng[155]	2014	UK	CEA/CUA	Healthcare system	Lifetime	Apixaban, Dabigatran, Rivaroxaban	3.5% both cost and health outcomes	High quality (++)

8.3.2 Type of economic evaluation

All studies included cost utility analyses (CUAs in Table 16) and reported quality adjusted life years (QALYs) gained. In addition to this, 24 of the studies also incorporated cost effectiveness analyses (CEAs in Table 16) and reported life years (LYs) gained. All 41 studies were based on decision-trees and/or Markov models.

Nineteen studies appeared to be original models while 22 were adapted from one of five original models, as shown in Table 17.[116, 124, 128, 143, 152]

Most of the models used 6-week to 3-month cycle lengths to represent fixed and temporary health states (range 1 month to 1 year). The five core models all used similar health states: NVAF, ischaemic stroke, systemic embolism, myocardial infarction, intra-cranial haemorrhage, extra-cranial haemorrhage, minor or major bleeds and death. These health states were used in all 41 studies. Some studies also included transient states of the major health states, such as 'temporary', 'mild', 'moderate', 'severe' and 'fatal'.

These five original models have had a large influence on the literature. Typically, adaptations kept the core model consistent but replaced drug tariff inputs, resource valuations and population mortality rates with country specific sources.

The original articles by Dorian and Lip are from the same research group and based on the same model.[128, 152] The Dorian article compares just apixaban and warfarin, while the Lip article extends this via pair-wise indirect treatment comparisons to compare apixaban to dabigatran and rivaroxaban. Both are from the perspective of the UK's National Health Service. The model by Sorensen 2011[124] was the basis of adaptations in ten subsequent publications. The model is from a Canadian payer perspective, and compares dabigatran to warfarin.

There are a number of differences between the Sorenson and Dorian/Lip models. For example, different discount rates, the use of "real world" prescribing in the Sorenson article, the use of different costs and perspectives (UK vs. Canada), and different valuations of health states and treatment affects. Both the Sorenson and Dorian/Lip models were funded by their respective drug manufacturers, as were the RCTs from which treatment effects and outcomes were taken.

Table 17 – Adapted economic models

Adapted model	Adapted from		Country
Andrikopoulos 2013	Sorensen (Canada)	2011	Greece
Chevalier 2014			France
González-Juanatey 2012			Spain
Kansal 2012a			Canada
Kansal 2012b			UK
Langkilde 2012			Denmark
Pletscher 2013			Switzerland
Ravasio 2014			Italy
Wouters 2013			Belgium
Zheng 2014			UK
Barón 2015	Dorian 2014 (UK)		Spain
Lip 2015			UK
Lanitis 2014a			France
Lanitis 2014b			Sweden
Stevanović 2014			Netherlands
Athanasakis 2015	Lip 2014 (UK)		Greece
Costa 2015			Portugal
Lip 2015			UK
Lanitis 2014a			France
Stevanović 2014			Netherlands
Morais 2014	Kleintjens (Belgium)	2013	Portugal
Rognoni 2014b	Rognoni 2014a (Italy)		Italy

8.3.3 Time frame and discounting

Given the chronic nature of NVAF, most models reported a lifetime horizon. The precise definition of this varied from 5 to 35 years (or death, if sooner) based on a base-case population with NVAF aged between 63 and 75. One study defined 105 years as an age limit in their model.[117]

Because life time horizon is necessary for modelling this disease area, extrapolation of treatment outcomes from shorter-term trials was inevitably required. The ARISTOTLE trial on apixaban [60] had just 1.8 years follow up, RE-LY trial on dabigatran [54] 2 years, ENGAGE AF-TIMI 48 on edoxaban [55] 2.8 years, and ROCKET-AF on rivaroxaban [19] 1.93 years. The lack of detailed explanation on the specific methods used to perform such extrapolations, as well as on assumptions on treatment effect persistence over time represent a major potential weakness on all models. Some models avoided using a lifetime horizon in order to bypass longer term speculation. The shortest timeframe used was 5 years.[122]

Discount rates for costs and health outcomes ranged from 2 to 5% per annum; most included justification and followed their relevant country guidelines. While discount rates differences are ostensibly small, over the course of a lifetime horizon they can have a significant impact on the outcomes.

8.3.4 Perspective

The majority of the models were from a healthcare system perspective; 21 studies adopted this perspective. Fourteen were performed from a payer perspective and six from a societal, or healthcare system and societal perspective [118, 119, 127, 133, 146, 151]. Of the four that claimed to be performed from a societal perspective: Harrington included a cost estimate of the economic value of patient time for each visit[118], Davidson and Lanitis included social or community care costs[127, 133], while Kamel included only direct costs.[119].Of the two studies from both a healthcare system and societal perspective, both included costs of informal care to the dependent patient and home adaptations.[146, 151]

8.3.5 Population

All the studies modelled populations of patients with NVAF suitable for VKA treatment. In the majority of models, the populations were matched to those seen in the ARISTOTLE, RE-LY, ENGAGE AF-TIMI 48 or ROCKET-AF trials. Evaluations only included patients with a certain risk of stroke as defined by $CHADS_2$ scores ($CHADS_2$ scores are used to estimate stroke risk in NVAF patients, helping physicians to decide which antithrombotic therapy is most suitable). A handful of studies specifically required a mean $CHADS_2$ score of 2.1, reflecting mean scores in ARISTOTLE and RE-LY. The mean age of the population varied between studies and ranged from 63 to 75 years.

The key NOAC trials, which between them have influenced the populations used in most evaluations, are described below:

RE-LY[54] was an RCT of dabigatran vs warfarin. It randomised 18,113 patients with a mean CHADS2 score of 2.1. Participants either received dabigatran 110mg, dabigatran 150mg or adjusted-dose warfarin (goal INR 2.0-3.0). The mean time in therapeutic range (TTR) during the trial was 64%. The primary outcome of stroke or systematic embolism was 1.7% per year for warfarin, 1.5% for dabigatran 110mg and 1.1% for dabigatran 150mg. There was no difference in rates of major bleeding for patients on dabigatran 150mg and warfarin; bleeding was lower for patients on dabigatran 110mg. Follow up was for a median of two years.

ROCKET AF[19] was an RCT of 14,264 patients with mean CHADS2 score of 3.5. Participants were randomised to rivaroxaban 20mg or dose-adjusted warfarin (goal INR 2.0-3.0). Patients were on average older and sicker on ROCKET AF than on the other trials and mean TTR was consequently lower at 55%. Rates of stroke or systemic embolism were 2.1% per 100 patient years for rivaroxaban and 2.4% for warfarin. The annual rate of major bleeding was not different between the two groups. Median follow up was 1.93 years.

ARISTOTLE[60] was an RCT of 18,201 patients with a mean CHADS2 score of 2.1. They received either dose-adjusted warfarin or apixaban 5mg (reduced to 2.5mg for sicker patients). The mean TTR of warfarin patients in the trial was 62%. The Apixaban group saw 1.3% experience a stroke or systemic embolism, compared to 1.6% in the warfarin group. Major bleeding was also reduced in the apixaban group. Median treatment duration was 1.8 years.

ENGAGE AF-TIMI 48[55] was an RCT of 21,105 patients. Participants had a CHADS2 score of 2 or above, and were randomised to either dose-adjusted warfarin or edoxaban 60mg (30mg in sicker patients). The mean TTR was higher than in the other trials, at 68.4%. The annual rate of stroke or systemic embolism was 1.5% with warfarin vs 1.18% with high-dose edoxaban and 1.6% with low-dose edoxaban. Median follow up was 2.8 years.

8.3.6 Intervention and comparator

Intervention and comparators varied. Thirty-five studies evaluated the cost-effectiveness of NOACs (dabigatran, apixaban, rivaroxaban and edoxaban) with VKAs. Nineteen of these compared a single NOAC with warfarin, and 11 compared multiple NOACs with warfarin. Four studies focused on NOACs versus other VKAs, namely acenocoumarol and phenprocoumon.[117, 146-148] One study compared a NOAC (Dabigatran) with both warfarin and another VKA (Acenocoumarol).[149] Six studies assessed the cost-effectiveness of NOACs versus NOACs.[53, 150-154]

Dosing of the NOACs was similar throughout all 41 studies: apixaban (5mg twice daily); rivaroxaban (15-20mg once daily); edoxaban (30-60mg once daily).

Dabigatran had three possible dosage options which were used in the studies: dabigatran 110mg twice daily; dabigatran 150mg twice daily; dabigatran 150mg twice daily until the age of 80 then changed to 110mg twice daily, also defined as sequential dabigatran dosing. The latter dosage of dabigatran is the recommended dose for NVAF patients in the European Union.

8.3.7 Cost and outcome inputs

Cost and outcome inputs were derived from different sources, including published literature, publicly available tariffs, medical fee schedules and hospital data. Some assumptions were also made. For monitoring costs, some studies consulted experts for their opinion on the inputs that needed to be considered; for example, how to calculate the cost and number of physician visits and frequency of INR tests. The use of assumptions and expert opinion, while understandable, may unduly influence the outcomes of the models. For this reason most assumptions were tested in sensitivity analyses.

With regard to the outcomes and utility measures, QALYs and LYG were mostly obtained from the literature, including EQ-5D surveys, network meta-analyses and other published sources. Most studies extrapolated data on clinical effectiveness, such as event rates, relative risks and hazard ratios, from RCTs (most commonly RE-LY, ARISTOTLE, ENGAGE AF-TIMI 48 and ROCKET-AF trials), meta-analyses and network meta-analyses.

8.3.8 Industry sponsorship

Most of the studies were funded by grants from the pharmaceutical industry, predominately Pfizer, Bristol-Myers Squibb (BMS), Bayer and Boehringer Ingelheim (the manufacturers of the NOACs). Eight studies were funded by grants from non-industry institutions. A further eight studies did not report any funding. Twenty-three studies reported a conflict of interest. As widely acknowledged, conflicts of interest can introduce bias which has the potential to compromise the validity of the research.

8.3.9 Costs

Table 18 provides an overview of the total costs and monitoring costs reported. Total costs include not only the cost of the drug but also monitoring costs, treatment of complications and outpatient visits. Costs can be difficult to compare as perspective and standard medical practice vary between countries. Additionally, costs vary by currency and changes in exchange rates. Generally, all the studies took drug costs, acute event costs, long-term management costs and monitoring costs into account. Just one study did not consider long-term maintenance costs.[117]

VKAs differ from NOACs in that they require rigorous monitoring in order for patients to maintain an adequate International Normalised Ratio (INR). However, two studies did not report monitoring costs. [125, 130] Additionally, the way in which monitoring costs were reported differed study by study, and a range of assumptions were made in calculating them. This is understandable as variable components, such as the number of INR tests and physician visits, were taken into consideration when calculating the costs, and varied depending on the country and standard medical practice.

Patients on NOACs require renal functioning monitoring. However, only sixteen studies specifically mention any form of specific monitoring costs for NOACs.[53, 115, 116, 121, 127, 132, 133, 135, 139, 143, 146, 147, 150-153], and most of these do not describe whether costs included monitoring renal functioning. When the cost of renal monitoring was made explicit, details were often not forthcoming. Langkilde[132] offered the best description in this regard. The authors used estimates from publicly available data and tariffs from the Danish healthcare system. Renal tests were assumed to require one specific annual GP visit (though three in the first year), although the authors stated that in the real world, renal testing would likely occur during routine atrial fibrillation visits. Lip 2014[152] stated that dabigatran required annual renal monitoring in their model for patients with moderate to severe renal impairment, whereas this monitoring was not required for apixaban and rivaroxaban. Assumptions around costs were made from the UK's National Health Service. Lanitis[133] assumed an annual cost using a regional Swedish price tariff, but did not provide any details. Similarly, Baron[146] gave a monthly cost for renal monitoring using estimates from a Spanish Health System perspective, without describing any assumptions made.

8.3.9.1 Cost of adverse effects

Gastrointestinal bleeding is a common adverse effect with NOACs, and all included studies take into account extracranial bleeding in some manner – often mentioning gastrointestinal bleeding specifically. Dabigatran, rivaroxaban and edoxaban increase the chance of major gastrointestinal bleeding compared to warfarin, while apixaban reduces it. These differences are reflected in the anticoagulant's assigned transition probabilities towards the relevant extra-cranial haemorrhage (or similar) health state. However, not all costs associated with adverse effects are always considered. For example, dyspepsia is a side effect of dabigatran[54], and yet dyspepsia is not found in most models, which may lead to an underestimation of some NOAC costs. Although costs for treating dyspepsia, such as through proton pump inhibitors, were relatively low. Probabilities of discontinuation due to adverse effects were generally taken from the original clinical trial data.

8.3.9.2 NOACs versus VKAs

The total life-time costs for NOACs were greater than those for VKAs. Costs for both NOACs and warfarin varied between studies; some studies had to assume costs or extrapolate drug costs from other countries.

The way in which monitoring costs were calculated also differed, making cross country comparisons in this regard challenging. Calculations of monitoring costs assumed different tests and frequency of patient visits based on current practice in a country. Because of the variety of usual care across countries, applicability to the Belgian context is often limited.

A Canadian study[122] reported the lowest total mean costs per patient over their lifetime for both NOACs and VKAs out of all the studies: CAD $8,494 and $7,289 respectively. This could be partly explained by the fact that the authors used the lowest cost prices of drugs they could find in their cost reference list to estimate the cost of outpatient medications They also only included post-event costs for intracerebral haemorrhage and stroke. A US study[121] on the other hand, reported the highest total costs for both NOACs and VKAs, which were far greater than any other study at $381,700 and $378,500 for NOACs and VKAs respectively. The US authors took monthly costs of care for each complication into consideration as well as one-time costs per event for ischemic stroke, transient ischemic attack, intracranial haemorrhage and myocardial infarction. They also included routine costs of

established patient care visits which were conducted in months one and three post-event, then every three months for the next year, and every four months thereafter; these costs applied to all treatments.

8.3.9.3 NOACs versus NOACs

The costs of the NOACs varied between studies, and as such, it is not possible to conclude which NOAC is the most expensive. The range of total costs for apixaban was €9,600[139] to USD $381,700[119]. For dabigatran the total costs ranged from CAD $8,494[122] to USD $168,398 [119]. Rivaroxaban ranged from €6142 [135] to USD $78,738 [118]. Finally edoxaban ranged from €9732[139] to €21,052.[131]

Table 18 – Total costs and monitoring costs

Author/Date	Country	Comparison	Costs Included	Time Horizon	Total Mean Costs over Time Horizon	Annual Monitoring Costs	Source of Monitoring Costs
Single Comparisons: NOAC vs. Warfarin							
Chevalier 2014	France	Dabigatran (150/110mg BID sequential) vs. Warfarin (fluindione)	Drug costs, monitoring, event costs (inc. bleeds), follow-up costs, total costs	Lifetime	Dabigatran: €23 231. Warfarin (fluindione): €19 397	Annual INR monitoring (Euro): €1 608.48	French National Sickness Fund
Davidson 2013	Sweden	Dabigatran (150/110mg BID sequential) vs. Warfarin	Direct costs: drug costs, monitoring costs, event costs (inc. GI bleeding), total costs. Societal costs: admission costs, outpatient costs, and costs for social services	20 years	Dabigatran: €27 009 Warfarin: €24 797	Annual cost of warfarin and its monitoring: €776 (inc. one annual visit to doctor). Annual cost for dabigatran: €199 (inc. one annual visit to doctor)	Literature
Dorian 2014	UK	Apixaban (5mg BID) vs. Warfarin	Direct medical costs. Daily drug cost, warfarin monitoring, management costs, acute cost per episode (inc. GI bleeding). Maintenance cost per month.	Lifetime	Apixaban: £9 078 Warfarin: £6 920	Annual warfarin monitoring cost £248	UK sources and NHS reference costs
Freeman 2011	USA	Dabigatran (150mg BID or 110mg BID) vs. Warfarin	Daily cost of medication, cost of INR monitoring, cost of events (inc. GI bleeding). Indirect costs excluded.	35 years or death	Dabigatran (110mg): $164 576 Dabigatran (150mg): $168 398 Warfarin: $143 193	Annual monitoring costs: $84 Daily cost of INR laboratory tests: $6. As per the 14 INR costs per year. Dabigatran costs included patient	National Health Insurance medical care fee schedule

Author/Date	Country	Comparison	Costs Included	Time Horizon	Total Mean Costs over Time Horizon	Annual Monitoring Costs	Source of Monitoring Costs
Single Comparisons: NOAC vs. Warfarin							
						visits at 1 and 3 months, then every 3 months in first year and every 4 months thereafter	
González-Juanatey 2012	Spain	Dabigatran (150/110mg BID sequential) vs. Warfarin	Acute event costs (inc. GI bleeding), follow-up costs, drug costs (inc. with monitoring costs)	Lifetime	Dabigatran: €15 193 Warfarin: €10 343	INR annual monitoring: good control (70% of patients) - €382.83 per year; poor control (30% of patients) - €472.70.	Literature, Expert opinion
Kamel 2012	USA	Apixaban (5mg BID) vs. Warfarin	Daily drug costs, routine clinical monitoring, event costs (inc. GI bleeding), INR costs. Chronic costs of care for adverse events.	20 years or death	Apixaban: $381 700 Warfarin: $378 500	Exact value not reported. Included 14 INR tests for each 90-day period of warfarin treatment	National Health Insurance medical care fee schedule
Kansal(b) 2012	UK	Dabigatran (150/110mg BID sequential) vs. Warfarin	Drug costs and monitoring, event costs (inc GI bleeding), follow-up costs, total costs	10 years	Dabigatran: £19 645; Warfarin: £18 474	Annual INR monitoring for Warfarin = £414.90	NICE/NHS reference costs
Kleintjens 2013	Belgium	Rivaroxaban (20mg or 15mg daily) vs. Warfarin	Drug costs, consultation and INR monitoring costs, event costs (inc GI bleeding), total costs	Lifetime	Rivaroxaban: €18 695; Warfarin: €17 867	Annual monitoring costs for NOACs: €58 (inc. two GP visits); Annual warfarin monitoring costs: €672 (based on 15 GP visits and 15 INR tests)	Belgian KCE report
Krejczy 2015	Germany	Edoxaban (60mg BID or 30mg BID) vs. Warfarin	Total costs: event costs (inc GI bleeding), rehabilitation costs, hospitalization costs, monitoring costs and daily costs for drugs	20 years	Edoxaban (30mg): €21 052; Edoxaban (60mg): €20 157; Warfarin: €9 747	Annual Warfarin therapy: €153	Literature, National medical care fee schedule
Langkilde 2012	Denmark	Dabigatran (150/110mg	Drug costs and monitoring, event costs (inc GI bleeding), follow-up costs, total costs	Lifetime	Dabigatran: €18 752 Warfarin: €16 886	Annual monitoring for Warfarin = €975. Dabigatran = €211	Publicly available tariffs, assumptions

Author/Date	Country	Comparison	Costs Included	Time Horizon	Total Mean Costs over Time Horizon	Annual Monitoring Costs	Source of Monitoring Costs
Single Comparisons: NOAC vs. Warfarin							
		BID sequential) vs. Warfarin				in first year, then €17. Includes renal function tests	
Lanitis 2014b	Sweden	Apixaban (5mg BID) vs. Warfarin	Direct costs and indirect costs. Drug costs, monitoring costs (inc. renal), acute event costs (inc. GI bleeding), long-term costs	Lifetime	Total costs not reported	Annual average cost of INR monitoring: SEK 4,783 per patient (based on 16.66 INR tests)	Swedish HTA of Dabigatran
Mensch 2015	Germany	Rivaroxaban (20mg) vs. Warfarin	Direct costs only. Drug treatment costs; monitoring costs, event costs (inc GI bleeding), total costs	35 years	Rivaroxaban: €20 238 Warfarin: €9 464;	Annual warfarin monitoring costs: €100.88 (based on 13 INR tests)	Social Health Insurance medical care fee schedule
Morais 2014	Portugal	Rivaroxaban (20mg or 15mg daily) vs. Warfarin	Direct costs only. Drug acquisition, drug monitoring, event-related costs (inc GI bleeding), total costs	Lifetime	Rivaroxaban: €6 142; Warfarin: €6 061.	Annual monitoring costs in Euros (€). Rivaroxaban: €1260; Warfarin €3252	Population based cohort study
Nshimyumukiza 2013	Canada	Dabigatran (150mg BID) vs. Warfarin (standard dosing) or Warfarin (genetic guided dosing)	Drug costs, INR monitoring, one-time event treatment costs (inc GI bleeding), post event costs	5 years	Dabigatran (150mg): CAD $8 494 Warfarin (SD): CAD $7 289 Warfarin (GD): CAD $7 749	CAD ($): Annual mean INR monitoring (first year) SD-W $96.72; GT-W $60; INR monitoring (subsequent years) $48.36.	Assumption, Literature
Pink 2011	UK	Dabigatran (150/110mg BID sequential or 150mg BID or 110mg BID) vs. Warfarin	Drug costs, ward and procedure costs (which also included the cost of hospital drugs, such as proton pump inhibitors for dyspepsia), hospitalization costs (inc for GI bleeding), monitoring costs, total costs	Lifetime	Dabigatran (110mg): £10 529; Dabigatran (150mg): £9 850; Warfarin: £6 480.	Annual Warfarin - monitoring £198.39	Population based cohort study
Rognoni 2014(b)	Italy	Edoxaban (60mg BID) vs. Warfarin	Direct costs only. Total costs provided (drug costs,	Lifetime	Edoxaban: €20 337 Warfarin: €15 345;	Not reported	N/A

Author/Date	Country	Comparison	Costs Included	Time Horizon	Total Mean Costs over Time Horizon	Annual Monitoring Costs	Source of Monitoring Costs
Single Comparisons: NOAC vs. Warfarin							
			monitoring costs and adverse event costs inc. GI bleed)				
Shah 2011[f]	USA	Dabigatran (150mg BID or 110mg BID) vs. Warfarin	Annual cost of prophylaxis, cost of INR monitoring, patient visit, short and long-term event costs, inc. GI bleed	20 years	Dabigatran (150mg): $43 700. Dabigatran (110mg): $66 000. Warfarin: $12 500	Annual mean monitoring cost of Warfarin therapy: USD $545	National Insurance medical care fee schedule
Sorensen 2011	Canada	Dabigatran (150/110mg BID sequential or 150mg BID or 110mg BID) vs. Warfarin	Drug costs, monitoring costs for Warfarin, acute cost per episode (inc GI bleed), follow-up costs, total costs	Lifetime	Dabigatran: CAD $45 124 Warfarin: CAD $42 946.	Annual Warfarin INR monitoring cost (CAD) - within and outside of therapeutic range: $405.16	Population based cohort study
Stevanović 2014	Netherlands	Apixaban (5mg BID) vs. Warfarin	Direct medical costs. Daily drug cost, Warfarin monitoring, routine care, acute event life time cost, inc. bleeds, maintenance cost per month	Lifetime	Apixaban: €20 205 Warfarin: €18 353	Annual INR testing €224 and routine AF care per visit (number of visits not reported) €78.97	National medical care fee schedule
Multiple comparisons: NOACs vs. Warfarin							
Coyle 2013	Canada	Dabigatran (150mg or 110mg BID); Apixaban (5mg BID); Rivaroxaban (20mg) All vs. Warfarin	Drug cost (per annum), monitoring costs, clinical events (acute and long term, inc. bleeds), total costs	40 years	Dabigatran (150mg): $21 486 Dabigatran (110mg): $22,804 Apixaban: $21 966 Rivaroxaban: $22 016 Warfarin: $18,620	Annual INR monitoring: $240.69	Expert opinion, National medical care fee schedule
Harrington 2013	USA	Apixaban (5mg BID); Dabigatran (150mg BID); Rivaroxaban (20mg). All vs. Warfarin	Acute event costs (inc GI. bleeds), monitoring costs, economic value of patient time for visits, daily drug costs (including dyspepsia treatment), total costs	30 years or death	Rivaroxaban $78 738; Dabigatran (150mg): $82 719; Apixaban $85 326 Warfarin $77 813;	Annual warfarin monitoring costs, : INR testing $1005.60	Literature

[f] This study reported predicted costs rather than absolute numbers

Author/Date	Country	Comparison	Costs Included	Time Horizon	Total Mean Costs over Time Horizon	Annual Monitoring Costs	Source of Monitoring Costs
Single Comparisons: NOAC vs. Warfarin							
Janzic 2014	Slovenia	Apixaban (5mg BID); Edoxaban (60mg); Dabigatran (150mg); Rivaroxaban (20mg). All vs. Warfarin	Monitoring costs, event costs (inc. GI bleeds), drug costs, total costs	Lifetime	Dabigatran: €9 479 Rivaroxaban: €10 115; Apixaban €9 600; Edoxaban €9 732 Warfarin (SD): €5 922 Warfarin (GD): €5 938	Monitoring costs, (€): Warfarin, first 3 months (standard dosing) €85.00; Warfarin, first 3 months (genotype-guided dosing) €63.75; Warfarin maintenance phase €147.99; NOAC first year €25.50; NOAC: following years €8.50; pharmacogenetic testing €50	National medical care fee schedule
Kansal(a) 2012	Canada	Dabigatran (150/110mg BID sequential) Rivaroxaban (20mg) All vs. Warfarin	Total costs, management costs (of acute events, bleeds), follow-up costs, drug costs	5 or 10 years	Dabigatran: $59 613. Rivaroxaban: $59 766 Warfarin: total costs not reported	Not reported	N/A
Kongnakorn 2014	Belgium	Apixaban (5mg BID); Dabigatran (110m BID); Dabigatran (150/110mg BID sequential); Rivaroxaban (20mg). All vs. Warfarin	Drug cost, NOAC routine care, Warfarin routine care and monitoring, acute and long-term clinical events costs (inc. GI bleeds), total costs	Lifetime	Dabigatran (150/110mg) : €13 495 Rivaroxaban: €13 625 Dabigatran (110mg): €13 658 Apixaban: €13 992 Warfarin: €12 600	Annual cost: NOAC routine care €91, Warfarin routine care and monitoring €611	Belgian KCE report
Krejczy 2014[g]	Germany	Apixaban (5mg BID); Dabigatran (110mg); Dabigatran	Daily drug costs, monitoring costs, acute event costs (inc. GI bleeds),	20 years	Apixaban: €19 885. Dabigatran (110mg): €20 048; Dabigatran (150mg): €19 537	Annual cost for warfarin therapy: €153	Assumption

g The total costs included in this study were taken from trials: costs for apixaban (ARISTOTLE); dabigatran (RE-LY); rivaroxaban (ROCKET-AF); edoxaban (ENGAGE-AF); costs for warfarin were calculated as an average of the four trials

Author/Date	Country	Comparison	Costs Included	Time Horizon	Total Mean Costs over Time Horizon	Annual Monitoring Costs	Source of Monitoring Costs
Single Comparisons: NOAC vs. Warfarin							
		(150mg); Rivaroxaban (20mg). All vs. Warfarin	rehabilitation costs, costs in case of death, total costs		Rivaroxaban: €19 874 Edoxaban (30mg): €21 052 Edoxaban (60mg): €20 157 Warfarin: €8 838.25		
Lanitis 2014a	France	Apixaban (5mg BID); Dabigatran (110mg); Dabigatran (150mg); Dabigatran (150/110mg sequential); Rivaroxaban (20mg). All vs. Warfarin	Drug costs, acute event costs (inc. GI bleeds), long-term maintenance costs and monitoring costs, total costs	Lifetime	Apixaban: €20 281 Dabigatran (110mg): €20 648 Dabigatran (150mg): €20,281 Dabigatran (150/110mg): €20 290 Rivaroxaban: €20 473 Warfarin: €17 966	Annual cost: NOAC routine care €202, Warfarin routine care and monitoring: €336	Literature, publicly available tariffs
Ravasio 2014	Italy	Warfarin, Apixaban (5mg BID); Rivaroxaban (20mg); All vs. Dabigatran (150/110mg sequential)	Only direct costs included. Drug costs, event costs (inc. GI bleeds), monitoring costs, total costs	Lifetime	Dabigatran: €16 861 Rivaroxaban: €17 275; Apixaban: €16 479 Warfarin: €14 279	Annual mean cost per patient for monitoring: NOACs, €0; Warfarin €318,41	Local administrative database
Rognoni2014 (a)[h]	Italy	Apixaban (5mg BID); Dabigatran (150mg); Rivaroxaban (20mg). All vs. Warfarin	Direct costs only: testing and monitoring costs, costs of acute events (inc. GI bleeds)	Lifetime	Apixaban: €19 539 Dabigatran: €20 000 Rivaroxaban: €20 017 Warfarin: €13 685	Annual mean monitoring cost VKA (Based on 13.9 visits Anti-coagulation clinics): €348.89 NOAC (Based on one ECG & one cardiologic visit per year): €29.50	National medical care fee schedule

[h] The total costs included in this study were stratified by $CHADS_2$ subgroups, therefore the costs presented in this review are an average of the costs across all the strata

Author/Date	Country	Comparison	Costs Included	Time Horizon	Total Mean Costs over Time Horizon	Annual Monitoring Costs	Source of Monitoring Costs
Single Comparisons: NOAC vs. Warfarin							
Verhoef 2014	UK and Netherlands	Apixaban; Dabigatran; Rivaroxaban vs. Coumarin derivatives (Acenocoumarol/Phenprocoumon in Netherlands. All vs Warfarin in the UK)	Monthly drug costs, monitoring costs, event costs (inc. GI bleeds)	Lifetime	The Netherlands: Coumarin derivative €8 829; Rivaroxaban €14 510; Apixaban €13 583; Dabigatran €14 294. The UK: Coumarin derivative €7 775; Rivaroxaban €12 893; Apixaban €12 992; Dabigatran €12 927	Annual VKA monitoring costs: Netherlands - €222.13 (based on 21.4 INR measurement visits). UK - £304 (based on 10 INR measurement visits)	Dutch publicly available tariffs, UK NICE report
Wisløff 2014	Norway	Apixaban (5mg BID); Dabigatran (150/110mg sequential); Rivaroxaban (20mg). All vs. Warfarin	Drug costs, monitoring costs, lifetime costs, incremental costs, event costs (inc GI bleeds), total costs	Lifetime	Apixaban: €50 402; Dabigatran (110mg): €54 104; Rivaroxaban: €50 611; Warfarin: €47 498; Dabigatran (150/110mg): €49 821	Annual mean warfarin monitoring costs: €640	Assumption
NOAC vs. other VKA							
Barón 2015	Spain	Apixaban (5mg BID) vs. Acenocoumarol (5mg/day)	Monitoring costs (including costs of renal monitoring), management costs, drug costs (including for dyspepsia), indirect health costs, event costs (inc GI bleeds), total costs	Not reported	Apixaban: €18 029 Acenocoumarol: €15 541	Annual INR monitoring: estimated €320 per annum. All patients annual renal monitoring: €14.76	Literature, assumptions
Kourlaba 2014	Greece	Rivaroxaban (20mg) vs. Acenocoumarol (up to 2.5mg/day)	Drug costs, monitoring costs, event costs (inc bleeds), patient reimbursed transportation costs, total costs	Lifetime	Rivaroxaban: €7 868. VKA (Acenocoumarol): €8 107.	Annual monitoring costs (€): Rivaroxaban €52; Acenocoumarol (VKA) €3 981	Expert opinion
Pletscher 2013	Switzerland	Dabigatran (150/110mg BID sequential) vs. Phenprocoumon	Drug costs and monitoring, event costs (inc. GI bleeds), follow-up costs, total costs	Lifetime	Total costs not reported	Annual mean costs Swiss Francs (CHF) 511.	Literature

Author/Date	Country	Comparison	Costs Included	Time Horizon	Total Mean Costs over Time Horizon	Annual Monitoring Costs	Source of Monitoring Costs
Single Comparisons: NOAC vs. Warfarin							
Wouters 2013	Belgium	Dabigatran (150/110mg BID sequential) vs. Phenprocoumon/Acenocoumarol mix	Drug costs, INR costs of monitoring for Warfarin, acute event costs (inc, GI bleeds), discontinuation costs, total costs	Lifetime	Dabigatran: €13 333 Warfarin: €12 454	Annual cost of monitoring: €722.88 INR Monitoring: (€) GP visit - €29.52; INR test - €17.20	Publicly available tariffs, assumptions
NOAC vs. Warfarin and other VKA							
Andrikopoulos	Greece	Dabigatran (150mg BID or 110mg BID) vs. Acenocoumarol (5mg/day) and Warfarin	Drug costs, event costs (inc. bleeds), follow-up costs, monitoring costs, total costs	Lifetime	Dabigatran (150mg): €35 614. Dabigatran (110mg): €35 614; Acenocoumarol: €30 683; Warfarin: €30 683	Annual cost of Warfarin monitoring: outside range €397; within range €301	MoH and National School of Public Health database
NOAC vs. NOAC							
Athanasakis 2015	Greece	Dabigatran (150mg BID); Dabigatran (110mg BID); Rivaroxaban (20mg); All vs. Apixaban (5mg)	Direct medical costs only. Drug costs; Clinical event costs (acute, inc. bleeds); Maintenance costs per month, monitoring costs, total costs	Lifetime	Apixaban: €9601.11. Dabigatran (110mg): €8618.48; Dabigatran (150mg): €8746.65. Rivaroxaban: €9336.48	Discounted monitoring costs per treatment (lifetime horizon). Apixaban = €25.12; Dabigatran 110 = €30.81; Dabigatran 150 = €31.60; Rivaroxaban = €28.28	Unclear
Canal Fontcuberta 2015	Spain	Apixaban (5mg BID) vs. Rivaroxaban (20mg)	Only direct costs included. For the Spanish NHS perspective: acute event costs (inc. GI bleeds), drug costs, follow-up costs, costs of monitoring, total costs	Lifetime	Apixaban: €18 029; Rivaroxaban:€17 914	Annual NOAC monitoring costs: €1 476	Literature, publicly available tariffs
Costa 2015	Portugal	Dabigatran (150/110mg sequential); Rivaroxaban (15-20mg);	Direct costs only. Pharmaceutical costs, monitoring costs, clinical event costs (inc. GI bleeds), total costs	Lifetime	Dabigatran: €9 571 Rivaroxaban: €10 129 Apixaban: €9 998	Annual monitoring costs: Dabigatran: €1311 Rivaroxaban: €1 278	National registries, expert opinion

Author/Date	Country	Comparison	Costs Included	Time Horizon	Total Mean Costs over Time Horizon	Annual Monitoring Costs	Source of Monitoring Costs
Single Comparisons: NOAC vs. Warfarin							
		All vs. Apixaban (2.5-5mg BID)				Apixaban: €1 255	
Lip 2014	UK	Dabigatran (150/110mg BID); Rivaroxaban (20mg) All vs. Apixaban (5mg BID)	Drug cost, monitoring costs, maintenance costs, acute cost per episode (inc. GI bleeds)	Lifetime	Total costs not reported (just daily costs)	Annual monitoring costs £248.28; dyspepsia £83.19 per year; Annual renal monitoring test £3.00	Lip 2014
Lip 2015	UK	Apixaban (5mg BID) vs. Edoxaban (60mg & 30mg)	Direct medical costs: daily drug cost, acute care cost (inc. GI bleeds), long-term maintenance cost per month, monitoring costs	Lifetime	Apixaban: €10 879; Edoxaban (30mg): €10 927 Edoxaban (60mg): €10 631	Annual monitoring costs: Apixaban: €109; Edoxaban (30mg): €109 Edoxaban (60mg): €116	Literature, expert opinion
Zheng 2014	UK	Apixaban (5mg BID); Rivaroxaban (20mg) All vs. Dabigatran (150/110mg sequential)	Drug costs per day; Monitoring cost per year (Warfarin); event costs per episode (inc. GI bleeds); follow-up costs; one-time discontinuation costs; total costs	Lifetime	Dabigatran: £23 342. Rivaroxaban: £25 220; Apixaban: £24 014. Warfarin: £24 680.	Annual mean INR Monitoring for warfarin: £455.22 (as part of indirect meta-analysis between NOACs)	UK NICE report

8.3.9.4 Outcomes

Table 19 shows the outcomes reported, including both total and incremental outcomes. Twenty four studies considered both LYs gained as well as QALYs in their evaluation. Three studies exclusively reported incremental outcomes.[53, 125, 148]

8.3.9.5 NOACs versus VKAs

All studies reported improved outcomes when comparing NOACs with VKAs. The incremental LYs gained reported ranged between a minimum of +0.02[135] to a maximum of +0.56[128]. Incremental QALYs ranged from a minimum of +0.02[135] to a maximum of +0.68[137].

- Out of the 14 studies which evaluated the effectiveness of apixaban to VKAs, the mean incremental LYs gained was +0.33 and mean incremental QALYs were +0.27
- Out of the 24 studies which evaluated the effectiveness of dabigatran to VKAs, the mean incremental LYs gained was +0.68 and mean incremental QALYs were +0.41
- Out of the 13 studies which evaluated the effectiveness of rivaroxaban to VKAs, the mean incremental LYs gained was +0.14 and mean incremental QALYs were +0.19
- Out of the 3 studies which evaluated the effectiveness of edoxaban to VKAs, the mean incremental LYs gained was +0.74 and mean incremental QALYs were +0.32

8.3.9.6 NOACs versus NOACs

Six studies compared NOACs versus NOACs. Five out of the six studies reported apixaban as producing the most improved outcomes. [53, 150-153] The remaining study showed dabigatran to dominate in terms of outcomes.[154]

Table 19 – Incremental and total outcomes

Author/Date	Country	Comparison	Outcomes Measured	Total Life-Years	Incremental LYs	Total QALYs	Incremental QALYs
Single Comparisons: NOAC vs. Warfarin							
Chevalier 2014	France	Dabigatran (150/110mg BID sequential) vs. Warfarin (Fluindione)	QALYs	N/A	N/A	Dabigatran 150/110mg: 7.94; Warfarin (Fluindione): 7.70	+0.24
Davidson 2013	Sweden	Dabigatran (150/110mg BID sequential) vs. Warfarin	LYs, QALYs	Dabigatran 150/110mg: 12.11; Warfarin: 11.83	+0.28	Dabigatran 150/110mg: 8.60; Warfarin: 8.31	+0.29
Dorian 2014	UK	Apixaban (5mg BID) vs. Warfarin	LYs, QALYs	Apixaban: 11.14; Warfarin: 10.88	+0.56	Apixaban: 6.26; Warfarin: 6.08	+0.18
Freeman 2011	USA	Dabigatran (150mg BID or 110mg BID) vs. Warfarin	QALYs	N/A	N/A	Dabigatran 110mg: 10.70; Dabigatran 150mg: 10.84; Warfarin: 10.28	Dabigatran 150mg: +0.56 Dabigatran 110mg: +0.42
González-Juanatey 2012	Spain	Dabigatran (150/110mg BID sequential) vs. Warfarin	LYs, QALYs	Dabigatran 150/110mg: 11.39; Warfarin: 11.13	+0.26	Dabigatran 150/110mg: 8.73; Warfarin: 8.45	+0.28
Kamel 2012	USA	Apixaban (5mg BID) vs. Warfarin	QALYs	N/A	N/A	Apixaban: 4.19; Warfarin: 3.91	+0.28
Kansal(b) 2012	UK	Dabigatran (150/110mg BID sequential) vs. Warfarin	QALYs	N/A	N/A	Dabigatran 150/110mg: 8.06; Warfarin: 7.82	+0.24
Kleintjens 2013	Belgium	Rivaroxaban (20mg or 15mg daily) vs. Warfarin	LYs, QALYs	Rivaroxaban: 10.62; Warfarin: 10.51	+0.11	Rivaroxaban: 8.21; Warfarin: 8.12	+0.09

Author/Date	Country	Comparison	Outcomes Measured	Total Life-Years	Incremental LYs	Total QALYs	Incremental QALYs
Krejczy 2015	Germany	Edoxaban (60mg BID or 30mg BID) vs. Warfarin	QALYs	N/A	N/A	Edoxaban 30mg: 7.65; Edoxaban 60mg: 7.69; Warfarin: 7.48	Edoxaban 30mg: +0.17 Edoxaban 60mg: +0.21
Langkilde 2012	Denmark	Dabigatran (150/110mg BID sequential) vs. Warfarin	QALYs	N/A	N/A	Dabigatran 150/110mg: 8.59; Warfarin: 8.32	+0.27
Lanitis 2014b	Sweden	Apixaban (5mg BID) vs. Warfarin	LYs, QALYs	Apixaban: 11.37; Warfarin: 11.11	+0.26	Apixaban: 6.71; Warfarin: 6.51	+0.20
Mensch 2015	Germany	Rivaroxaban (20mg) vs. Warfarin	QALYs	N/A	N/A	Rivaroxaban: 11.06; Warfarin: 10.35	+0.71
Morais 2014	Portugal	Rivaroxaban (20mg or 15mg daily) vs. Warfarin	LYs, QALYs	Rivaroxaban: 5.00; Warfarin: 4.98	+0.02	Rivaroxaban: 3.83; Warfarin: 3.81	+0.02
Nshimyumukiza 2013	Canada	Dabigatran (150mg BID) vs. Warfarin (standard dosing) Dabigatran (150mg BID) vs. Warfarin (genetic guided dosing)	QALYs	N/A	N/A	Dabigatran 150mg: 0.24; Warfarin: 0.01	+0.24
Pink 2011	UK	Dabigatran (150/110mg BID sequential or 150mg BID or 110mg BID) vs. Warfarin	LYs, QALYs	Dabigatran 150/110mg: 11.04; Dabigatran 110mg: 10.94; Dabigatran 150mg: 11.05; Warfarin: 10.85	Dabigatran 150mg: +0.20 Dabigatran 150/110mg: +0.19 Dabigatran 110mg: +0.09	Dabigatran 150/110mg: 6.53; Dabigatran 110mg: 6.48; Dabigatran 150mg: 6.54; Warfarin: 6.39	Dabigatran 150/110mg: +0.14 Dabigatran 110mg: +0.09 Dabigatran 150mg: +0.15
Rognoni 2014(b)	Italy	Edoxaban (60mg BID) vs. Warfarin	LYs, QALYs	Edoxaban: 13.036; Warfarin: 12.295	+0.74	Edoxaban: 9.722; Warfarin: 9.047	+0.68

Author/Date	Country	Comparison	Outcomes Measured	Total Life-Years	Incremental LYs	Total QALYs	Incremental QALYs
Shah 2011	USA	Dabigatran (150mg BID or 110mg BID) vs. Warfarin	QALYs	N/A	N/A	Dabigatran 150mg: 8.65; Dabigatran 110mg: 8.54; Warfarin: 8.40	Dabigatran 110mg: +0.25 Dabigatran 150mg: +0.14
Sorensen 2011	Canada	Dabigatran (150/110mg BID sequential or 150mg BID or 110mg BID) vs. Warfarin	LYs, QALYs	Exact value not reported	N/A	Dabigatran 150/110mg: 7.07; Warfarin: 6.86	+0.21
Stevanović 2014	Netherlands	Apixaban (5mg BID) vs. Warfarin	LYs, QALYs	Apixaban: 10.44; Warfarin: 10.26	+0.18	Apixaban: 7.18; Warfarin: 7.00	+0.18
Multiple comparisons: NOACs vs. Warfarin							
Coyle 2013	Canada	Dabigatran (150mg or 110mg BID); Apixaban (5mg BID); Rivaroxaban (20mg) All vs. Warfarin	QALYs	N/A	N/A	Dabigatran 150mg: 6.62; Dabigatran 110mg: 6.54; Apixaban: 6.62; Rivaroxaban: 6.54; Warfarin: 6.48	Dabigatran 150mg: +0.14 Dabigatran 110mg: +0.06 Apixaban: +0.14 Rivaroxaban: +0.06
Harrington 2013	USA	Apixaban (5mg BID); Dabigatran (150mg BID); Rivaroxaban (20mg). All vs. Warfarin	QALYs	N/A	N/A	Dabigatran 150mg: 8.41; Apixaban: 8.47; Rivaroxaban: 8.26; Warfarin: 7.97	Dabigatran 150mg: +0.44 Apixaban: +0.50 Rivaroxaban: +0.29
Janzic 2014	Slovenia	Apixaban (5mg BID); Edoxaban (60mg); Dabigatran (150mg); Rivaroxaban (20mg). All vs. Warfarin	QALYs	N/A	N/A	Dabigatran 150mg: 7.43; Apixaban: 7.45; Rivaroxaban: 7.28; Edoxaban: 7.42; Warfarin: 7.22;	Dabigatran 150mg: +0.21 Apixaban: +0.23 Rivaroxaban: +0.06 Edoxaban: +0.20
Kansal(a) 2012	Canada	Rivaroxaban (20mg); Dabigatran (150/110mg BID sequential) All vs. Warfarin	LYs, QALYs	Exact value not reported	Rivaroxaban: +0.07 Dabigatran: +0.23	Exact value not reported	+0.08Rivaroxaban: +0.08 Dabigatran: +0.23

Author/Date	Country	Comparison	Outcomes Measured	Total Life-Years	Incremental LYs	Total QALYs	Incremental QALYs
Kongnakorn 2014	Belgium	Apixaban (5mg BID); Dabigatran (110m BID); Dabigatran (150/110mg BID sequential); Rivaroxaban (20mg). All vs. Warfarin	LYs, QALYs	Dabigatran 150/110mg: 9.70; Dabigatran 110mg: 9.66; Apixaban: 9.80; Rivaroxaban: 9.72; Warfarin: 9.60	Dabigatran 150/110mg: +0.10 Dabigatran 110mg: +0.06 Apixaban: +0.20 Rivaroxaban: +0.22	Dabigatran 150/110mg: 6.88; Dabigatran 110mg: 6.84; Apixaban: 6.96; Rivaroxaban: 6.90; Warfarin: 6.76	Dabigatran 150/110mg: +0.12 Dabigatran 110mg: +0.08 Apixaban: +0.20 Rivaroxaban: +0.14
Krejczy 2014	Germany	Apixaban (5mg BID); Dabigatran (110mg); Dabigatran (150mg); Rivaroxaban (20mg). All vs. Warfarin	QALYs	N/A	N/A	Dabigatran 110mg: 7.68; Dabigatran 150mg: 7.71; Apixaban: 7.75; Rivaroxaban: 7.67; Warfarin: 7.64	Dabigatran 110mg: +0.04 Dabigatran 150mg: +0.07 Apixaban: +0.11 Rivaroxaban: +0.03
Lanitis 2014a	France	Apixaban (5mg BID); Dabigatran (110mg); Dabigatran (150mg); Dabigatran (150/110mg sequential); Rivaroxaban (20mg). All vs. Warfarin	LYs, QALYs	Dabigatran 150/110mg: 8.76; Dabigatran 110mg: 8.72; Dabigatran 150mg: 8.76; Apixaban: 8.84; Rivaroxaban: 8.78; Warfarin: 8.57	Dabigatran 150/110mg: +0.19 Dabigatran 110mg: +0.15 Dabigatran 150mg: +0.19 Apixaban: +0.27 Rivaroxaban: +0.21	Dabigatran 150/110mg: 6.22; Dabigatran 110mg: 6.19; Dabigatran 150mg: 6.22; Apixaban: 6.29; Rivaroxaban: 6.24; Warfarin: 6.10	Dabigatran 150/110mg: +0.12 Dabigatran 110mg: +0.09 Dabigatran 150mg: +0.12 Apixaban: +0.19 Rivaroxaban: +0.14
Ravasio 2014	Italy	Warfarin; Apixaban (5mg BID); Rivaroxaban (20mg); All vs. Dabigatran (combined 150mg or 110mg BID)	LYs, QALYs	Dabigatran 150/110mg: 11.21; Apixaban: 11.13; Rivaroxaban: 10.96 Warfarin: 10.84	Apixaban: +0.29 Rivaroxaban: +0.12 Warfarin: +0.37	Dabigatran 150/110mg: 8.56; Apixaban: 8.49; Rivaroxaban: 8.30 Warfarin 8.18	Dabigatran vs. Apixaban: +0.31 Dabigatran vs. Rivaroxaban: +0.12 Dabigatran vs. Warfarin: +0.38

Author/Date	Country	Comparison	Outcomes Measured	Total Life-Years	Incremental LYs	Total QALYs	Incremental QALYs
Rognoni 2014(a)[i]	Italy	Apixaban (5mg BID); Dabigatran (150mg); Rivaroxaban (20mg). All vs. Warfarin	LYs, QALYs	Dabigatran (150mg): 12.58; Apixaban: 12.44; Rivaroxaban: 12.09; Warfarin: 11.76	Dabigatran 150mg: +0.82 Apixaban: +0.68 Rivaroxaban: +0.33	Dabigatran (150mg): 9.59; Apixaban: 9.40; Rivaroxaban: 9.12; Warfarin: 8.76	Dabigatran 150mg: +0.83 Apixaban: +0.64 Rivaroxaban: +0.36
Verhoef 2014	UK and Netherlands	Apixaban; Dabigatran; Rivaroxaban vs. Coumarin derivative (Acenocoumarol/Phenprocoumon in Netherlands All vs. Warfarin in the UK)	QALYs	N/A	N/A	The Netherlands – Dabigatran: 9.99; Apixaban: 9.99; Rivaroxaban: 9.79; Coumarin Derivative (Acenocoumarol/Phenprocoumon): 9.63; The UK – Dabigatran: 8.43; Apixaban: 8.42; Rivaroxaban: 8.27; Coumarin Derivative (Warfarin): 7.97	The Netherlands - Dabigatran: +0.36 Apixaban: +0.36 Rivaroxaban: +0.16 The UK – Dabigatran: +0.46 Apixaban: +0.45 Rivaroxaban: +0.30
Wisløff 2014	Norway	Apixaban (5mg BID); Dabigatran (150/110mg sequential); Rivaroxaban (20mg). All vs. Warfarin	QALYs	N/A	N/A	Dabigatran 150/110mg: 5.85; Dabigatran 110mg: 5.81; Apixaban: 5.86; Rivaroxaban: 5.81; Warfarin: 5.71	Dabigatran 150/110mg: +0.14 Dabigatran 110mg: +0.10 Apixaban: +0.15 Rivaroxaban: +0.10
NOAC vs. other VKA							
Barón 2015	Spain	Apixaban (5mg BID) vs. Acenocoumarol (5mg/day)	LYs, QALYs	Apixaban: 9.04; Acenocoumarol: 8.85	+0.19	Apixaban: 6.42; Acenocoumarol: 6.23	+0.19

[i] The outcomes included in this study were stratified by $CHADS_2$ subgroups, therefore the outcomes presented in this review are representative of patients with a $CHADS_2$ score of 2

Author/Date	Country	Comparison	Outcomes Measured	Total Life-Years	Incremental LYs	Total QALYs	Incremental QALYs
Kourlaba 2014	Greece	Rivaroxaban (20mg) vs. Acenocoumarol (up to 2.5mg/day)	LYs, QALYs	Rivaroxaban: 8.55; Acenocoumarol: 8.48	+0.07	Rivaroxaban: 6.50; Acenocoumarol: 6.28	+0.22
Pletscher 2013	Switzerland	Dabigatran (150/110mg BID sequential) vs. Phenprocoumon	LYG, QALYs	Total LYs not reported	Dabigatran 110mg: 1.95; Dabigatran 150mg: 2.33; Dabigatran 150/110mg: 2.77	Total QALYs not reported	Dabigatran 110mg: 1.85; Dabigatran 150mg: 2.43; Dabigatran 150/110mg: 2.85
Wouters 2013	Belgium	Dabigatran (150/110mg BID sequential) vs. Phenprocoumon/Acenocoumarol mix	QALYs	N/A	N/A	Dabigatran 150/110mg: 9.51; Warfarin: 9.19	+0.32
NOAC vs. Warfarin and other VKA							
Andrikopoulos 2013	Greece	Dabigatran (150mg BID or 110mg BID) vs. Acenocoumarol (5mg/day) and Warfarin	QALYs	N/A	N/A	Dabigatran 150mg: 10.01; Dabigatran 110mg: 9.94; Acenocoumarol: 9.64 Warfarin: 9.64	Dabigatran 150mg vs Acenocoumarol: +0.37 Dabigatran 110mg vs Acenocoumarol: +0.30 Dabigatran 150mg vs Warfarin: +0.37 Dabigatran 110mg vs Warfarin: +0.30
NOAC vs. NOAC							
Athanasakis 2015	Greece	Dabigatran (150mg BID); Dabigatran (110mg BID); Rivaroxaban (20mg); All vs. Apixaban (5mg)	LYs, QALYs	Dabigatran 150mg: 8.996; Dabigatran 110mg: 8.953	Dabigatran 150mg: +0.07 Dabigatran 110mg: +0.11	Dabigatran 150mg: 6.39; Dabigatran 110mg: 6.35;	Apixaban vs. Dabigatran 150mg: +0.06

Author/Date	Country	Comparison	Outcomes Measured	Total Life-Years	Incremental LYs	Total QALYs	Incremental QALYs
				Rivaroxaban: 9.021 Apixaban: 9.069	Rivaroxaban: +0.05	Rivaroxaban: 6.41 Apixaban: 6.45;	Apixaban vs. Dabigatran 110mg: +0.10 Apixaban vs. Rivaroxaban: +0.04
Canal Fontcuberta 2015	Spain	Apixaban (5mg BID) vs. Rivaroxaban (20mg)	LYs, QALYs	Apixaban: 9.04; Rivaroxaban: 8.98	+0.06	Apixaban: 6.43; Rivaroxaban: 6.32	Apixaban vs. Rivaroxaban: +0.11
Costa 2015	Portugal	Dabigatran (150/110mg sequential); Rivaroxaban (15-20mg); All vs. Apixaban (2.5-5mg BID)	LYs, QALYs	Total LYs not reported	Dabigatran 150/110mg: 0.05; Rivaroxaban: 0.04;	Total QALYs not reported	Apixaban vs. Dabigatran 150/110mg: 0.05; Apixaban vs. Rivaroxaban: 0.03;
Lip 2014	UK	Dabigatran (110mg BID); Rivaroxaban (20mg) All vs. Apixaban (5mg BID)	LYs, QALYs	Apixaban: 11.14; Dabigatran 150mg: 11.02; Dabigatran 110mg: 10.96; Rivaroxaban: 11.06	Dabigatran 150mg: +0.12 Dabigatran 110mg: +0.18 Rivaroxaban: +0.08	Apixaban: 6.26; Dabigatran 150mg: 6.19; Dabigatran 110mg: 6.16; Rivaroxaban: 6.21	Apixaban vs. Dabigatran 150mg: +0.07 Apixaban vs. Dabigatran 110mg: +0.10 Apixaban vs. Rivaroxaban: +0.05
Lip 2015	UK	Apixaban (5mg BID) vs. Edoxaban (60mg & 30mg)	LYs, QALYs	Apixaban: 8.81; Edoxaban 30mg: 8.73; Edoxaban 60mg: 8.76	Apixaban vs Edoxaban (30mg): +0.08 Apixaban vs Edoxaban (60mg): +0.05	Apixaban: 6.26; Edoxaban 30mg: 6.19; Edoxaban 60mg: 6.22	Apixaban vs Edoxaban (30mg): +0.07 Apixaban vs Edoxaban (60mg): +0.04
Zheng 2014	UK	Apixaban (5mg BID); Rivaroxaban (20mg) All vs. Dabigatran (150/110mg sequential)	LYs, QALYs	Dabigatran 150/110mg: 10.04; Apixaban: 9.97; Rivaroxaban: 9.83	Apixaban: +0.07 Rivaroxaban: +0.21	Dabigatran 150/110mg: 7.68; Apixaban: 7.63; Rivaroxaban: 7.47	Dabigatran vs. Apixaban: +0.27 Dabigatran vs. Rivaroxaban: +0.11

8.3.10 Incremental Cost-effectiveness Ratios (ICERs)

Table 20 shows the ICERs reported in the studies included in this review.

8.3.10.1 NOACs versus VKAs

All but one study found that NOACs were cost-effective at relevant country specific thresholds (in some case assumed or "rule-of-thumb thresholds) compared to VKAs. The most commonly compared VKA was warfarin.

The one study that did not show NOACs to be cost effective was from Germany.[140] The authors concluded that current market costs for NOACs were high in relation to the quality of life gained, exceeding a hypothetical German willingness to pay threshold of €50,000. It should be noted that lifetime costs for all NOACs in this study were over double the lifetime costs for Warfarin; a proportionally greater increase than found in most other studies, where differences in lifetime costs tended to be small. The authors also made some changes to utility values for myocardial infarction and major and minor bleeding, as their experience difference from the published data. These changes may have contributed to the high ICERs.

A study in the USA found that while Dabigatran 150mg was cost-effective in AF populations at high risk of haemorrhage or stroke (unless INR control with warfarin was excellent), warfarin was cost-effective in moderate-risk populations (unless INR control was poor).

There was a large range in the ICERs reported for studies comparing NOACs to warfarin. The lowest ICER was €2807 per QALY[117] and the highest €294,349 per QALY –though this highest ICER was an outlier and found in the German study that did not show NOACs to be cost-effective.[140] Both the highest and lowest ICERs were from studies comparing dabigatran to warfarin.

8.3.10.2 NOACs versus NOACs

Six studies compared NOACs vs NOACs; five out of the six found apixaban to be the most cost-effective out of all the NOACs.[53, 150-153] The remaining study found dabigatran to be the most cost-effective drug.[154] This latter study compared dabigatran (sequential dosing 150/110mg) against apixaban and rivaroxaban; the study did not report an exact number for the ICER, but reported dabigatran to dominate over the other two NOACs.[154]

The lowest ICER reported out of the six NOAC vs NOAC studies was €2347/QALY, for apixaban against rivaroxaban.[151] The highest ICER was reported in a study by Athanasakis – €13,727/QALY for apixaban when compared to dabigatran (150mg).[150]

Table 20 – Incremental Cost-Effectiveness Ratios (ICERs)

Author/Date	Country	Comparison	Currency	Base-case ICER/ICUR	Most cost-effective drug at country specific thresholds
Single Comparisons: NOAC vs. Warfarin					
Chevalier 2014	France	Dabigatran (150/110mg BID sequential) vs. Warfarin (Fluindione)	2011 EUR (€)	Dabigatran vs. Warfarin (Fluindione): €15,838/QALY	NOAC
Davidson 2013	Sweden	Dabigatran (150/110mg BID sequential) vs. Warfarin	2010. Calculated in SEK[j]	Dabigatran vs. Warfarin €7,742/QALY	NOAC
Dorian 2014	UK	Apixaban (5mg BID) vs. Warfarin	2011 GBP (£)	Apixaban vs. Warfarin: £11,909/QALY	NOAC
Freeman 2011	USA	Dabigatran (150mg BID or 110mg BID) vs. Warfarin	2011 CAD ($)	Dabigatran 150mg vs. Warfarin: $45,372/QALY	NOAC
González-Juanatey 2012	Spain	Dabigatran (150/110mg BID sequential) vs. Warfarin	2010 EUR (€)	Dabigatran vs. Warfarin: €17 581/QALY	NOAC
Kamel 2012	USA	Apixaban (5mg BID) vs. Warfarin	Year not specified. USD ($)	Apixaban vs. Warfarin: $11,400/QALY	NOAC
Kansal(b) 2012	UK	Dabigatran (150/110mg BID sequential) vs. Warfarin	2010 GBP (£)	Dabigatran vs. Warfarin: £7090/QALY	NOAC
Kleintjens 2013	Belgium	Rivaroxaban (20mg or 15mg daily) vs. Warfarin	2010 EUR (€)	Rivaroxaban vs. Warfarin €8,809/QALY	NOAC
Krejczy 2015	Germany	Edoxaban (60mg BID or 30mg BID) vs. Warfarin	2012 EUR (€)	Edoxaban 30mg vs. Warfarin: €68,275/QALY Edoxaban 60mg vs. Warfarin: €50,411/QALY	NOAC
Langkilde 2012	Denmark	Dabigatran (150/110mg BID sequential) vs. Warfarin	2011 EUR (€)	Dabigatran vs. Warfarin: €6,950/QALY	NOAC

[j] Currency presented in EUR (€) where €1=SEK 9.

Lanitis 2014b	Sweden	Apixaban (5mg BID) vs. Warfarin	2011 Swedish Krona (SEK)	Apixaban vs. Warfarin: SEK 33,458/QALY	NOAC
Mensch 2015	Germany	Rivaroxaban (20mg) vs. Warfarin	2014 EUR (€)	Rivaroxaban vs. Warfarin €15,207/QALY	NOAC
Morais 2014	Portugal	Rivaroxaban (20mg or 15mg daily) vs. Warfarin	2011 EUR (€)	Rivaroxaban vs. Warfarin: €3895/QALY	NOAC
Nshimyumukiza 2013	Canada	Dabigatran (150mg BID) vs. Warfarin (standard dosing) or Warfarin (genetic guided dosing)	2010 CAD ($)	Dabigatran 150mg vs. Standard dosing Warfarin: $4,765/QALY	NOAC
Pink 2011	UK	Dabigatran (150/110mg BID sequential or 150mg BID or 110mg BID) vs. Warfarin	2009 GBP (£)	Dabigatran 150mg vs. Warfarin: £23,082/QALY	NOAC
Rognoni 2014(b)	Italy	Edoxaban (60mg BID) vs. Warfarin	2014 EUR (€)	Edoxaban 60mg vs. Warfarin: €7,713/QALY	NOAC
Shah 2011	USA	Dabigatran (150mg BID or 110mg BID) vs. Warfarin	2010 USD ($)	Dabigatran 150mg vs. Warfarin: $86,000/QALY	NOAC/Warfarin
Sorensen 2011	Canada	Dabigatran (150/110mg BID sequential or 150mg BID or 110mg BID) vs. Warfarin	2010 CAD ($)	Dabigatran 150mg vs. Warfarin: $9,041/QALY	NOAC
Stevanović 2014	Netherlands	Apixaban (5mg BID) vs. Warfarin	2013 EUR (€)	Apixaban vs. VKA (Warfarin): €10,576/QALY	NOAC
Multiple comparisons: NOACs vs. Warfarin					
Coyle 2013	Canada	Dabigatran (150mg or 110mg BID); Apixaban (5mg BID); Rivaroxaban (20mg) All vs. Warfarin	2011 CAD ($)	Dabigatran 150mg vs. Warfarin $20,797/QALY. Dabigatran 150mg dominated Dabigatran 110mg, Apixaban and Rivaroxaban.	NOAC
Harrington 2013	USA	Apixaban (5mg BID); Dabigatran (150mg BID); Rivaroxaban (20mg). All vs. Warfarin	2012 USD ($)	Apixaban vs Warfarin: $15 026/QALY	NOAC
Janzic 2014	Slovenia	Apixaban (5mg BID); Edoxaban (60mg); Dabigatran (150mg); Rivaroxaban (20mg). All vs. Warfarin	2014 EUR (€)	Apixaban vs. Warfarin: €15,679/QALY, Dabigatran vs. Warfarin: €16,959/QALY, Edoxaban vs. Warfarin: €18,994/QALY, Rivaroxaban vs. Warfarin: €66,328/QALY.	NOAC

Kansal(a) 2012	Canada	Dabigatran (150/110mg BID sequential); Rivaroxaban (20mg) vs. Warfarin	Year not specified. Canadian Dollars (CAD)	Dabigatran vs. Warfarin: $6,889/QALY Rivaroxaban vs. Warfarin: $22,475/QALY	NOAC
Kongnakorn 2014	Belgium	Apixaban (5mg BID); Dabigatran (110m BID); Dabigatran (150/110mg BID sequential); Rivaroxaban (20mg). All vs. Warfarin	2013 EUR (€)	ICERs vs. Warfarin: Apixaban €7,212/QALY; Dabigatran (150/110mg), €7,585/QALY; Rivaroxaban, €7,765/QALY Dabigatran (110mg) €13,564/QALY	NOAC
Krejczy 2014	Germany	Apixaban (5mg BID); Dabigatran (110mg); Dabigatran (150mg); Rivaroxaban (20mg). All vs. Warfarin	2012 EUR (€)	Apixaban vs. Warfarin: €57,245/QALY, Rivaroxaban vs. Warfarin: €133,926/QALY, Dabigatran 150mg vs. Warfarin: €163,184/QALY, Dabigatran 110mg vs. Warfarin: €294,349/QALY.	Warfarin
Lanitis 2014a	France	Apixaban (5mg BID); Dabigatran (110mg); Dabigatran (150mg); Dabigatran (150/110mg sequential); Rivaroxaban (20mg). All vs. Warfarin	2012 EUR (€)	Apixaban vs. Warfarin: €12,227/QALY. Others not reported as they did not meet the efficiency frontier.	NOAC
Ravasio 2014	Italy	Warfarin; Apixaban (5mg BID); Rivaroxaban (20mg); All vs. Dabigatran (combined 150mg or 110mg BID)	2014 EUR (€)	Dabigatran (150/110mg) vs. Rivaroxaban: Dabigatran dominates Dabigatran vs. Apixaban: €5787/QALY Dabigatran versus Warfarin: €6800/QALY	Dabigatran
Rognoni 2014(a)	Italy	Apixaban (5mg BID); Dabigatran (150mg); Rivaroxaban (20mg). All vs. Warfarin	2014 EUR (€)	Edoxaban vs. Warfarin: €7,713/QALY	NOAC
Verhoef 2014	UK and Netherlands	Apixaban; Dabigatran; Rivaroxaban vs. Coumarin derivatives (Acenocoumarol/Phenprocoumon in Netherlands All vs. Warfarin in the UK)	2012 EUR (€)	**UK: vs Coumarin derivative** Apixaban vs. Warfarin €13,024/QALY Dabigatran vs. Warfarin €14,626/QALY Rivaroxaban vs. Warfarin €34,248/QALY **Netherlands: vs Coumarin derivative.**	NOAC

				Dabigatran vs. Acenocoumarol/Phenprocoumon €11,171/QALY Apixaban vs. Acenocoumarol/Phenprocoumon €11,470/QALY Rivaroxaban vs. Acenocoumarol/Phenprocoumon€16, 949/QALY	
Wisløff 2014[k]	Norway	Apixaban (5mg BID); Dabigatran (150/110mg sequential); Rivaroxaban (20mg). All vs. Warfarin	2012 EUR (€)[l]	Dabigatran (150/110mg): €15,920/QALY, Apixaban vs. Warfarin: €18,955/QALY, Rivaroxaban vs. Warfarin: €29,990/QALY, Dabigatran (110mg) vs. Warfarin: €66,121/QALY	NOAC
NOAC vs. other VKA					
Barón 2015	Spain	Apixaban (5mg BID) vs. Acenocoumarol (5mg/day)	2012 EUR (€)	Apixaban vs. Acenocoumarol: Spanish NHS €12,825/QALY & Society €9412/QALY	NOAC
Kourlaba 2014	Greece	Rivaroxaban (20mg) vs. Acenocoumarol (up to 2.5mg/day)	2013 EUR (€)	Rivaroxaban dominates VKA	NOAC
Pletscher 2013	Switzerland	Dabigatran (150/110mg BID sequential) vs. Phenprocoumon	2008 Swiss Francs (CHF)	Dabigatran (150/110mg) vs. Phenprocoumon: CHF 25,108/QALY	NOAC
Wouters 2013	Belgium	Dabigatran (150/110mg BID sequential) vs. Phenprocoumon/Acenocoumarol mix	2012 EUR (€)	Dabigatran (150/110mg) vs. Warfarin: €2807/QALY;	NOAC
NOAC vs. Warfarin and other VKA					
Andrikopoulos 2013	Greece	Dabigatran (150mg BID or 110mg BID) vs. Acenocoumarol (5mg/day) and Warfarin	2012 EUR (€)	Dabigatran 150mg vs. Warfarin: €11,400 per QALY. Dabigatran 110mg vs. Warfarin: €16,653 per QALY.	NOAC

[k] The base-case ICERs for this study have been presented for medium risk NVAF patients

[l] Currency presented with conversion rate of €1 = 7.47 Norwegian Kroner (NOK).

				Dabigatran 150mg vs. Acenocoumarol: €11,224/QALY. Dabigatran 110mg vs. Acenocoumarol: €16,437/QALY	
NOAC vs. NOAC					
Athanasakis 2015	Greece	Dabigatran (150mg BID); Dabigatran (110mg BID); Rivaroxaban (20mg); All vs. Apixaban (5mg)	2013 EUR (€)	Apixaban vs. Rivaroxaban: €6936 per QALY; Apixaban vs. Dabigatran (110mg): €9907 per QALY; Apixaban vs. Dabigatran (150mg): €13,727 per QALY	Apixaban
Canal Fontcuberta 2015	Spain	Apixaban (5mg BID) vs. Rivaroxaban (20mg)	2012 EUR (€)	Apixaban vs. Rivaroxaban: From a Spanish NHS perspective €2347/QALY; from a Societal perspective: Apixaban dominates Rivaroxaban	Apixaban
Costa 2015	Portugal	Dabigatran (150/110mg sequential); Rivaroxaban (15-20mg); All vs. Apixaban (2.5-5mg BID)	Year not specified. EUR (€)	Apixaban vs. Dabigatran (150/110mg): €9163/QALY; Apixaban vs. Rivaroxaban: 'dominant'	Apixaban
Lip 2014	UK	Dabigatran (110mg BID); Rivaroxaban (20mg) All vs. Apixaban (5mg BID)	2011 GBP (£)	Apixaban vs Dabigatran (110mg) £4,497/QALY, Apixaban vs. Rivaroxaban £5,305/QALY, Apixaban vs. Dabigatran (150 mg) £9,611/QALY.	Apixaban
Lip 2015	UK	Apixaban (5mg BID) vs. Edoxaban (60mg & 30mg)	2012 GBP (£)	Apixaban vs. Edoxaban: £6,703/QALY	Apixaban
Zheng 2014	UK	Apixaban (5mg BID); Rivaroxaban (20mg) All vs. Dabigatran (150/110mg sequential)	2013 GBP (£)	Dabigatran dominates all	Dabigatran

8.3.11 Sensitivity Analyses

Sensitivity analyses allow the impact of changes within certain parameters to be assessed, revealing the main drivers behind a model's results. All of the included studies performed some kind of sensitivity analysis. Twenty-nine performed univariate/one-way sensitivity analyses; 29 performed probabilistic sensitivity analysis; three performed two-way analyses; one a multiple-way analysis. Seven studies performed deterministic analyses without specifying whether it was univariate or not.

Most studies simply listed which parameters most influenced model outcomes. Overall results were robust for the majority of analyses, although ICERs for NOACs increased when time in therapeutic range was increased (see also section on Subgroup Analysis) and when the cost of monitoring INR was decreased. One study found that when time in therapeutic range exceeded 66.1%, warfarin dominated rivaroxaban.[139]

Other parameters that the results were sensitive to, in some of the studies, included: relative risk for ischemic stroke (15 studies); drug costs (12 studies); utility values for NOACs and VKAs (11 studies); time horizon (8 studies); and monitoring costs (7 studies).

8.3.12 Subgroup Analyses

Eleven studies performed additional subgroup analyses. These analyses most commonly involved stratifying the data by time in therapeutic range (TTR) and risk scores ($CHADS_2$).

There were six studies that used subgroup analyses to look at the most cost-effective drugs according to TTR.[123, 127, 128, 136, 137, 146]. The results were:

- Barón[146]: Apixiban ICER vs acenocoumarol was €7,054 per QALY for the worst controlled patients (under 52.38 TTR) and €12,404 per QALY in best controlled patients (above TTR 76.51%).
- Coyle[123]: For TTR up to 66% dabigatran 150mg was optimal; for TTR above 66% apixaban was superior.
- Davidson[127]: For well controlled warfarin with a TTR of over 72.6% sequential dabigatran had an ICER of €12,449 per QALY. Sequential dabigatran dominated poorly controlled warfarin.
- Dorian[128]: Apixaban remained cost-effective across all TRR levels, including "good clotting control", defined as TTR above 76.5%.
- Pink[136]: Dabigatran 150 mg vs warfarin was within the £30 000 per QALY threshold for all patients other than those with a TTR of 65.5% and above.
- Rogoni (2014b)[137]: Edoxaban delivered an ICER vs warfarin of €10,040 per QALY for patients with a median TTR of 66.4% and above, and €6,479per QALY for those below 66.4%.

There were nine studies that used subgroup analyses to look at response according to $CHADS_2$ score.[120, 121, 123, 127, 128, 137, 143, 145, 149]. The results were as follows:

- Andrikopoulos[149]: For patients with the lowest stroke rate ($CHADS_2$ stroke score of 0), only aspirin was cost-effective. For patients with a moderate stroke rate ($CHADS_2$ score of 1 or 2), warfarin was cost-effective unless the risk of haemorrhage was high or the quality of INR control was poor. For patients with a high stroke risk ($CHADS_2$ score of 3), dabigatran 150mg was cost-effective unless INR control was excellent.
- Coyle[123]: Results were sensitive to $CHADS_2$ score. At a $50,000 per QALY WTP threshold, dabigatran 150mg was optimal for patients with a $CHADS_2$ score of less than 2. At a score of 2 and above dabigatran 150mg remained optimal for patients who had experienced a previous minor stroke, while apixaban was optimal for those without a previous stroke.
- Davidson[127]: Sequential dabigatran became progressively more cost-effective the higher the stroke risk: ICER vs warfarin for patients with a $CHADS_2$ score of 0 to 1 was €20,929, for patients with a score of 2 was €8,216, and a score of 3 to 6 €2,652.
- Dorian[128]: Apixaban compared with warfarin was most favourable in high-risk patients ($CHADS_2$ score of 3 and above) with an ICER of £9,769 per QALY. At $CHADS_2$ score of up to 1 it was £13,152 per QALY, and £13,262 per QALY at a $CHADS_2$ score of 2.
- Freeman[121]: For patients at low risk for stroke ($CHADS_2$ score of 1), low-dose dabigatran was more cost-effective than high-dose dabigatran and cost $40,355 per QALY compared with warfarin. For patients at high

risk for stroke ($CHADS_2$ score of 4), high-dose dabigatran was more cost-effective and cost $39,680 per QALY compared with warfarin.

- Rognoni (2014a)[143]: The NOACs delivered the following ICERs vs warfarin. For patients with a $CHADS_2$ score of 1 or less: dabigatran €7,320 per QALY; apixaban €9,631. For patients with a $CHADS_2$ score of 2: dabigatran €7,609 per QALY; apixaban €9,660; rivaroxaban €20,089. For patients with a $CHADS_2$ score of 3 or above: apixaban €4,723 per QALY; dabigatran €12,029; rivaroxaban €13,063. Apixaban therefore became more cost-effective than dabigatran for patients at higher risk of stroke.
- Rognoni (2014b)[137]: Edoxaban delivered an ICER vs warfarin of €5,363 per QALY for patients with a $CHADS_2$ score of 3 and above, and €9,438 for those with a score below 3.
- Shah[120]: For patients with a $CHADS_2$ score of 0 aspirin was cost-effective. For patients with a $CHADS_2$ score of 1 or 2, warfarin was cost-effective. Dabigatran 150 mg was cost-effective for patients with a $CHADS_2$ of 2 if the risk of haemorrhage was 6% per year, while at a $CHADS_2$ of 3 or above dabigatran 150 mg was always cost-effective.
- Wisløff[145]: Sequential dabigatran 150 was the most cost-effective option for high-risk patients. For medium-risk patients, apixaban was more effective than dabigatran, but dabigatran remained marginally the most cost-effective alternative. Dabigatran 110 mg and warfarin was never cost-effective in either risk group.

While it is important to be cautious in interpreting these results, given the uncertainties around many of the inputs and assumptions used in the economic evaluations described, a pattern does emerge. At low risk, for patients with a $CHADS_2$ score of 0 to 1, warfarin (or even aspirin) seems to be the most cost-effective treatment option. For those at moderate risk, with a score of 2, dabigatran 150mg is often the cost-effective alternative, while for high risk patients ($CHADS_2$ score of 3 and above) apixaban may be optimal.

8.3.13 Studies in Belgium

Three studies of direct relevance to Belgium were identified.[115-117] They are presented in Table 21.

8.3.13.1 Costs

Costs of monitoring and treating patients were based on a combination of Belgian databases, KCE reports, cohort studies and assumptions.

Monitoring costs were included for patients both on NOACs and warfarin. For warfarin monitoring costs, Kongnakorn[115] used data from the Belgian IMA-AIM (Common Sickness Funds Agency) database to estimate for patients on warfarin a median of 15 INR laboratory tests per year and 18 GP consultations. In the model by Kleintjens[116], and using data from the same source, it was assumed that warfarin patients have 15 GP visits and INR laboratory tests per year. For aspirin and rivaroxaban, the model assumed that patients would visit their GP two times per year (range 0–8 GP visits) as no monitoring is required. Finally, Wouters[117] also assumed that warfarin patients would be tested 18 times a year (the authors in this model assumed that patients receiving dabigatran would receive four GP visits a year, therefore 14 incremental GP visits were included in the cost calculation for INR monitoring).

8.3.13.2 Outcomes

Outcomes are mostly taken from the original ARISTOTLE, RE-LY, and ROCKET-AF trials. Network meta-analyses were used when comparing NOACs to one another.

- Kongnakorn used apixaban and warfarin outcomes from ARISTOTLE trial.[60] Outcomes for other NOACs were taken from a network meta-analysis.[155]
- The stroke rate per 100 patient years for patients on apixaban was 0.981, while HRs were as follows: warfarin 1.04 (0.82 to 1.3), dabigatran 110mg 1.17 (0.85 to 1.62), dabigatran 150mg 0.79 (0.55 to 1.1), and rivaroxaban 1.02 (0.76 to 1.37).
- The intracranial haemorrhage rate per 100 patient years for patients on apixaban was 0.33, while HRs were as follows: warfarin 2.43 (1.77 to

3.41), dabigatran 110mg 0.73 (0.42 to 1.24), dabigatran 150mg 1.02 (0.61 to 1.68), and rivaroxaban 1.73 (1.08 to 2.79).

- The systemic embolism rate per 100 patient years for patients on apixaban was 0.09, while HRs were as follows: warfarin 1.12 (0.55 to 2.26), dabigatran 110mg 0.79 (0.29 to 2.07), dabigatran 150mg 0.72 (0.26 to 1.95), and rivaroxaban 0.84 (0.34 to 2.07).
- The CRNM bleed rate per 100 patient years for patients on apixaban was 2.083, while HRs were as follows: warfarin 1.47 (1.26 to 1.71), dabigatran 110mg 1.155 (0.986 to 1.354), dabigatran 150mg 1.303 (1.113 to 1.526), and rivaroxaban 1.52 (1.28 to 1.8).

Kleintjens used ROCKET AF trial.[19] The baseline risk at three months for ischemic stroke was 0.36% (0.27% to 0.45%), and their RR if taking rivaroxaban was 0.94 (0.75 to 1.17). Intracranial bleed three month risk with warfarin was 0.19% (0.03% to 1.04 %), and RR with rivaroxaban of 0.67 (0.47 to 0.93). Risk of systemic embolism on warfarin was 0.05% (0.00 to 0.76 %), with an RR on rivaroxaban of 0.23 (0.09 to 0.61). Risk of extracranial CRNM bleed on warfarin was 2.97% (1.79% to 5.04%), and an RR with rivaroxaban of 1.04% (0.96% to 1.13%)

Wouters used RE-LY trial.[54] Outcomes for other NOACs taken from a network meta-analysis.[156] The model focussed on sequential dabigatran. Patients under 80 years of age would take dabigatran 150mg, while those over 80 years of age take dabigatran 110mg.

- For a patient up to 80 years of age and a CHADS2 score of 2, the annual risk of ischaemic stroke while taken Warfarin was 0.88%, and their RR if taking dabigatran 150mg was 0.77 (0.58 to 1.03). Haemorrhagic stroke annual risk with Warfarin 0.33%, while their RR with dabigatran 150mg was 0.21 (0.09 to 0.47). Systemic embolism risk for Warfarin was 0.15% while RR with dabigatran 150mg was 0.66 (0.3 to 1.47). Annual risk for minor bleeds with Warfarin was 16.06%, while RR with dabigatran 150mg was 0.86 (0.8 to 0.93).
- For a patient of over 80 years of age and a CHADS2 score of 2, the annual risk of ischaemic stroke while taken Warfarin was 1.54%%, and their RR if taking dabigatran 110mg was 0.82 (0.51 to 1.33). Haemorrhagic stroke annual risk with Warfarin 0.63%, while their RR with dabigatran 110mg was 0.26 (0.07 to 0.91). Systemic embolism risk for Warfarin was 0.31% while RR with dabigatran 110mg was 0.51 (0.13 to 2.06). Finally, annual risk for minor bleeds with Warfarin was 17.98%, while RR with dabigatran 110mg was 0.91 (0.78 to 1.07).

8.3.13.3 Base-case results

All three studies found NOACs to be more cost-effective than warfarin.

Kongnakorn[115] compared apixaban, dabigatran (110mg), sequential dabigatran, rivaroxaban and warfarin. They found that all the NOACs were cost-effective compared to warfarin. Amongst the NOACs apixaban was the most cost-effective (at €7,212 per QALY gained), although differences were small (for example dabigatran 150mg was effective at €7,585 per QALY gained and rivaroxaban at €7,765 per QALY gained).

Kleintjens[116] compared rivaroxaban vs warfarin and found the NOAC to be cost-effective (at €8,809 per QALY or €7,493 per life-year gained).

Wouters[117] compared dabigatran vs warfarin and found the NOAC to be cost-effective (at €2,807 per QALY gained).

8.3.13.4 Sensitivity Analyses

Kongnakorn[115] performed univariate sensitivity analyses for discount rates, assumptions around treatment discontinuation, individual utility estimates, individual cost estimates, relative efficacy estimates and stroke risk ($CHADS_2$ score). In addition to this they used probabilistic sensitivity analyses where input parameters were varied over 2000 iterations. They found that their results were mostly robust in sensitivity analyses – dabigatran 110mg being dominated by dabigatran 150mg and rivaroxaban, both of which were extendedly dominated by apixiban. The apixaban vs. warfarin ICER varied from €5,971 to €24,233/QALY and was most sensitive to varying the stroke hazard ratios. Apixaban remained the most cost-effective NOAC during sensitivity analyses. Rivaroxaban and dabigatran 150mg changed places during analyses, due to changes to myocardial infarction and intracranial haemorrhage rates and treatment discontinuation. At WTP thresholds above €10,000 apixaban had the highest probability of being the optimal choice. At a WTP threshold of €30,000, warfarin, dabigatran 110mg, dabigatran 150mg, rivaroxaban and apixaban had a probability of being optimal treatment choice of 0, 1, 8, 9 and 82% respectively.

Kleintjens[116] used one-way sensitivity analyses. They found that the main cost-effectiveness drivers were the number of GP/monitoring visits, baseline intracranial bleed rate, and the treatment discontinuation rates. For example, the ICER was estimated at €5,193 per QALY gained should a patient on rivaroxaban no longer need to visit a physician, but if eight GP visits were required annual it would jump to €19,659 per QALY. A probabilistic sensitivity analyses over 2000 iterations suggest that rivaroxaban is cost-effective compared with warfarin therapy in 66, 79, and 87 % of cases if a willingness-to-pay threshold of €10,000, €20,000 or €35,000 per additional QALY were to be considered, respectively.

Wouters[117] used one-way sensitivity analyses. Three model parameters had a significant impact on the ICER of dabigatran: cost of INR monitoring, the time horizon and the TTR for warfarin patients. They report that their results were robust however, with the ICERs for dabigatran remaining well under the WTP threshold – the ICER never exceeded €11,000 per QALY. The analysis showed that dabigatran remains cost-effective even when TTR reaches a hypothetical value of 80%. They reported that a TTR of 98-99% would be required for warfarin to become more cost-effective than dabigatran. At a WTP of €20,000 per QALY, dabigatran had a 99.85% probability of being cost-effective.

8.3.13.5 Subgroup Analyses

No subgroup analyses were conducted.

However, Wouters[117] performed two scenario analyses in order to better replicate Belgian “real-world” treatment. In their first scenario they assumed “real-world” INR control, as opposed to “trial-like” INR control. The TTR of the trial-like control was taken from the warfarin arm of the RE-LY trial and was 64%. Real-world INR control was estimated to be 53%, based on a cross-sectional study of Belgian clinical practice published in 2006.[157] This scenario led to a decreased ICER for dabigatran of €970 per QALY. The second scenario compared dabigatran to a treatment mix of warfarin (47%), aspirin (35%) or no treatment (18%), which was calculated from a 2010 poster abstract of the Belgica-Stroke study.[158] In this second scenario the ICER for dabigatran increased to €5296 per QALY. This increase was due to the higher incremental cost per patient on dabigatran compared to patients on low-cost aspirin or not being treated at all.

Table 21 – Overview of Belgian studies

Author/Date	Type of Economic Evaluation	Perspective	Time Horizon	Model Design	Discount rate (with justification)
Kongnakorn 2014	CUA	Healthcare payer	Lifetime	Adapted Markov model based on Dorian 2014 and Lip 2014. 6-week cycles.	3% costs, 1.5% outcomes based on Belgian KCE guidelines
Kleintjens 2013	CEA/CUA	Healthcare payer	Lifetime	Original Markov model. 3-month cycles.	3% costs, 1.5% outcomes based on Belgian KCE guidelines
Wouters 2013	CEA/CUA	Healthcare payer	Lifetime	Adapted Markov model – based on Sorensen 2011. 3 month cycles	3% costs, 1.5% outcomes based on Belgian KCE guidelines

Table 22 – Total and monitoring costs: Belgian studies

Author/Date	Intervention vs. Comparator	Cost items included	Monitoring Costs	Costs Sources	Incremental Costs over Time Horizon
Kongnakorn 2014	a) Dabigatran 110mg twice daily b) Sequential dabigatran (150mg/110mg twice daily, switch age 80) Rivaroxaban 20mg once daily c) Apixaban 5mg twice daily vs. Warfarin and, each NOAC vs. NOAC	Drug cost, NOAC routine care, warfarin routine care and monitoring, renal monitoring (applied to 19.6% of dabigatran patients), acute and long-term clinical events	Annual cost: NOAC routine care €91 (68-164), warfarin routine care inc. monitoring €611 (352-721.6)	Official national pricing and reimbursement tariffs (RIZIV/INAMI). Monitoring costs also based on a Belgian KCE report.[159, 160]	vs. Warfarin: Dabigatran (110mg): €1058; Dabigatran (110mg/150mg): €895; Rivaroxaban: €1025; Apixaban: €1,392
Kleintjens 2013	Rivaroxaban 15–20mg once daily vs. Dose-adjusted Warfarin (target INR 2.5)	Drug costs, consultation and INR monitoring costs, IS/HS (Minor, Major), SE, CRNM extracranial bleed, Major extracranial bleed, Intracranial bleed, MI	Annual monitoring costs for NOACs: €58 (inc. two GP visits); Annual warfarin monitoring costs: €672 (based on 15 GP visits and 15 INR tests)	Official national pricing and reimbursement tariffs (RIZIV/INAMI). Monitoring costs from Belgian KCE report. [159, 160]	Rivaroxaban vs. Warfarin: €828

Wouters 2013	Dabigatran (150mg twice daily) until the age of 80 then changed to 110mg twice daily vs. VKA mix of acenocoumarol and phenprocoumon	Drug costs (average cost for VKAs), INR costs of monitoring for warfarin, acute event costs, discontinuation costs.	Annual cost of monitoring: €722.88. INR Monitoring: GP visit - €29.52; INR test - €17.20; Patients tested 18 times a year	Official national pricing and reimbursement tariffs (RIZIV/INAMI). Monitoring costs also based on a Belgian KCE report. [159, 160]	Dabigatran vs VKA mix: €879

Table 23 – Incremental outcomes: Belgian studies

Author/Date	Patient Population	Intervention vs. Comparator	Outcomes sources	Incremental LYs per patient	Incremental QALYs per patient
Kongnakorn 2014	NVAF suitable for VKA treatment	a) Dabigatran 110mg twice daily b) Sequential dabigatran (150mg/110mg twice daily switch age 80) Rivaroxaban 20mg once daily c) Apixaban 5mg twice daily vs. Warfarin and, each NOAC vs. NOAC	Apixaban and warfarin outcomes from ARISTOTLE trial.[46] Outcomes for other NOACs taken from a network meta-analysis.[155]	vs Warfarin: Dabigatran (110mg): +0.06 Dabigatran (150/110mg): +0.10 Rivaroxaban: +0.22 Apixaban: +0.20	vs Warfarin: Dabigatran (110mg): +0.08 Dabigatran (150/110mg): +0.12 Rivaroxaban: +0.14 Apixaban: +0.20
Kleintjens 2013	Base case: NVAF patients with a mean age of 73 years at moderate (CHADS2 score = 2) to high risk of stroke (CHADS2 score = 3 or higher)	Rivaroxaban 15–20mg once daily vs. Dose-adjusted warfarin (target INR 2.5)	ROCKET AF trial.[19]	Rivaroxaban vs. Warfarin: +0.11	Rivaroxaban vs. Warfarin: +0.09
Wouters 2013	Cohort of 10,000 AF patients matching characteristics from RE-LY trial. Mean age of 69	Dabigatran (150mg twice daily) until the age of 80, then changed to 110mg twice daily vs. VKA mix of acenocoumarol and phenprocoumon	RE-LY trial.[54] Outcomes for other VKAs taken from a network meta-analysis.[156]	N/A	Dabigatran vs VKA mix:+0.32

Table 24 – Incremental Cost-effectiveness Ratios (ICERs): Belgian studies

Author/Date	Patient Population	Intervention vs. Comparator	Base case ICER/ICUR	Probability for NOAC to be cost-effective
Kongnakorn 2014	NVAF suitable for VKA treatment	a) Dabigatran 110mg twice daily b) Sequential dabigatran (150mg/110mg twice daily switch age 80) Rivaroxaban 20mg once daily c) Apixaban 5mg twice daily vs. Warfarin and, each NOAC vs. NOAC	Apixaban dominates Dabigatran 110mg, sequential Dabigatran (150/110mg) and Rivaroxaban by extension. ICERs vs. Warfarin: Dabigatran (110mg): €13,564/QALY; Dabigatran (150/110mg): €7,585/QALY; Rivaroxaban €7,765/QALY; Apixaban: €7,212/QALY;	82% at WTP €30,000
Kleintjens 2013	Base case: NVAF patients with a mean age of 73 years at moderate (CHADS2 score = 2) to high risk of stroke (CHADS2 score = 3 or higher)	Rivaroxaban 15–20mg once daily vs. Dose-adjusted warfarin (target INR 2.5)	Rivaroxaban vs. Warfarin €8,809/QALY or €7,493/LY	66%, 79% and 87% at WTP €10,000, €20,000 or €35,000 respectively
Wouters 2013	Cohort of 10,000 AF patients matching characteristics from RE-LY trial. Mean age of 69	Dabigatran (150mg twice daily) until the age of 80, then changed to 110mg twice daily vs. VKA mix of acenocoumarol and phenprocoumon	Dabigatran vs. Warfarin: €2807/QALY;	99.85% at WTP €20,000

8.3.14 NICE Health Technology Assessments

Full analysis of the economic models used for the NICE Single Technology Assessments for rivaroxaban, apixaban, dabigatran and edoxaban was not possible because certain information had been redacted on the grounds of commercial sensitivity. The main conclusions and ICERs are described here:

Rivaroxaban[161]: The manufacturers presented an analysis concluding an ICER of rivaroxaban versus warfarin of £2870 per QALY gained, while the Evidence Review Group working on behalf of NICE presented an ICER of £29,500 per QALY gained. The latter estimate excluded disutility associated with warfarin, and used a lower annual warfarin monitoring cost of £242 per person. The Committee concluded that the cost would lie somewhere between £2870 and £29,500 per QALY gained. The probabilistic sensitivity analysis showed that Rivaroxaban had a 75% probability of being cost-effective at a willingness to pay threshold of £20,000/QALY gained and an 88% probability at a threshold of £30,000/QALY. The Committee therefore concluded that the most plausible ICER for the whole population eligible for rivaroxaban was within the range that could be considered a cost-effective use of NHS resources. NICE typically use a threshold for recommending treatments of between £20,000 and £30,000 per QALY, although guideline committees never use QALYs as the sole determinant in their decisions.

Apixaban[113]: The Evidence Review Group for the NICE guidance found a base case ICER of £12,800 per QALY gained compared to warfarin. The Committee concluded that apixaban had been shown to be cost-effective compared with warfarin, the most plausible ICER being less than £20,000 per QALY gained.

Dabigatran[112]: The Evidence Review Group for the NICE guidance found a base case ICER of £18,900 per QALY gained for the sequential regimen in people starting treatment younger than 80 years, compared with warfarin. The Committee concluded that the most plausible ICERs for the whole population eligible for dabigatran were within the range normally considered cost-effective in the UK context, (i.e. less than £20,000/QALY).

Edoxaban[114]: The Review Group found that edoxaban, dabigatran 110 mg, apixaban and rivaroxaban were strictly dominated by dabigatran 150 mg, which had an ICER of £7645 per additional QALY gained compared to warfarin. However, there were very small differences in QALYs and costs between the newer oral anticoagulants. The Committee concluded that there was insufficient evidence to distinguish between the clinical and cost-effectiveness of edoxaban and the novel oral anticoagulants recommended in previous appraisals (apixaban, dabigatran and rivaroxaban).

8.4 Discussion and conclusions

The economic evaluation literature of NOACs has grown vastly over the last few years, and analyses have been performed across a number of countries worldwide. This review focussed on countries relevant to the Belgian healthcare system. As well as comparing one or more NOACs to warfarin or other VKAs, a number of studies used network analysis to compare NOACs to each other. Most of the studies were sponsored by pharmaceutical companies and many used adaptations of previous models. This section offers a discussion on the key themes that emerged from the research.

8.4.1 Use of adapted models

Many of the evaluations included were adapted from previous models; three of the models were utilised a number of times – Sorensen 2011, Dorian and Lip 2014. It is noted that the overall results for the adapted models were often the same as the outcome of the original model. For example, Sorensen 2011 concluded that dabigatran 150mg was a cost-effective alternative to warfarin, and all ten articles adapted from Sorensen similarly found dabigatran to be the most cost-effective drug.[117, 125, 126, 129, 130, 132, 142, 148, 149, 154] When 110mg and 150mg dabigatran were compared, 150mg always emerged more cost-effective. The single model adapted from Sorensen that compared dabigatran with apixaban and rivaroxaban found dabigatran to be the most cost-effective option.[142] Dorian and all the models adapted from it on the other hand favoured apixaban.[133, 138, 141, 146, 153] Lip 2014 and all but one of the models based on it similarly favoured apixaban[53, 138, 141, 153]; the exception being Athanasakis which did not include apixaban.[150]

8.4.2 Assumptions and sources of data

Lone randomised trials were used to provide data for the NOACs vs warfarin. The ARISTOTLE, RE-LY, ENGAGE AF-TIMI 48, and ROCKET-AF trials were used in all models to inform outcomes and event rates. There were variations between the trials in aspects such as patient population, length of follow up and TTR in the warfarin group, meaning that using the data for indirect comparisons may compromise the results. Also, the RE-LY trial (dabigatran vs warfarin) was not blinded, whereas ROCKET-AF and ARISTOTLE trials were. Un-blinded trials may result in an exaggerated intervention effect, which would in turn impact on cost-effectiveness estimates. Also, these trials often reported outcomes only in the relatively short term – up to two years – whereas the economic models necessarily had to extrapolate outcomes to lifetime horizons.

A number of economic evaluations had to make assumptions on the TTR of patients on warfarin and the costs of INR monitoring. These assumptions and their justifications were often poorly reported. Sensitivity and subgroup analyses suggest that outcomes are very sensitive to such assumptions, and therefore the assumptions used are likely to have a significant impact on the outcomes of the economic model. Some assumptions were based on estimates of real-world practice in the relevant country, which necessarily reduces applicability to countries with different approaches to INR monitoring.

8.4.3 Conflict of interests

Most of the studies were funded by grants from the pharmaceutical industry, mainly from Pfizer, Bristol-Myers Squibb (BMS), Bayer and Boehringer Ingelheim – manufacturers of the NOACs. Although the methodological quality of these studies is likely to be similar to that of non-industry sponsored studies, studies that are sponsored by pharmaceutical companies are considered to be more likely to introduce some bias in reporting.[162, 163] The ARISTOTLE, RE-LY, ENGAGE AF-TIMI 48, and ROCKET-AF trials were also sponsored by the pharmaceutical industry. Eight studies were funded by grants from non-industry institutions. All eight found the NOAC drug(s) to be cost-effective vs VKAs. Of the three non-industry funded studies that included multiple comparisons, one found dabigatran the most cost-effective[123], one favoured apixaban[139], and one found dabigatran and apixaban to be equally effective.

8.4.4 Relevance to Belgian healthcare system

As noted, most of the models described are relevant to specific healthcare systems and as such their applicability to the Belgian healthcare system is limited. An example of how different healthcare systems can influence results is provided in the study by Verhoef who compared the cost-effectiveness of NOACs in the Netherlands and the UK.[144] The two systems primarily differ in that the Netherlands offer specialised anticoagulation clinics while the UK does not. The study authors concluded that the quality of care, reflected in TTR, had an important influence on the ICERs between the countries. In the Netherlands, where patients spend more time in therapeutic range, only apixaban and dabigatran could be considered cost-effective – with apixaban coming out on top. In the UK however, all of apixaban, rivaroxaban, and dabigatran were cost-effective, with dabigatran being the most cost-effective option.

The three studies based in Belgium found that NOACs were cost-effective compared to warfarin. In the one multi-comparison study in Belgium apixaban was found to be the most cost-effective, compared to dabigatran and rivaroxaban. However, the differences between the three were very small.

8.4.5 Conclusions

The Belgian economic evaluations, similar to the literature found for other countries, concluded that despite their greater expense, NOACs are cost-effective against warfarin (assuming typical Belgian WTP thresholds). NOACs reduce the number of strokes and systemic embolisms, and dabigatran and apixaban also reduce the number of major bleed effects.

Identifying the most cost-effective NOAC is challenging. All the models included in this analysis relied on single, industry sponsored, short follow-up trials to estimate the impact of treatment. On top of this weakness, many further assumptions also had to be made about drug costs, monitoring costs and clinical practice (such as INR practice and TTR). Some of the assumptions captured in this regard were compared with the limited administrative Belgian data currently available to help us draw our final conclusions (see section 11 - final conclusion).

Because there have been no head-to-head trials of different NOACs, any assessment of comparative effectiveness had to rely on indirect comparisons.

Keeping these limitations in mind, it is worth reporting that most studies concluded that dabigatran 150mg (or sequential dabigatran, which is 150mg until 80 years old, followed by 110mg thereafter) and apixaban were the most cost-effective NOACs. Also, that low dose dabigatran (110mg) is consistently dominated by high dose dabigatran (150mg) and therefore unlikely to be cost-effective, unless part of a sequential dabigatran strategy. That dabigatran 110mg is generally not cost-effective is not surprising given that it offers results similar to warfarin but is much more expensive. However, longer follow-up trials and head-to-head comparisons of NOACs are needed in order to improve our confidence in these results.

Finally, it is worth noting that there are other differences between the NOACs. For example, as previously discussed, dabigatran, rivaroxaban and edoxaban are associated with more gastrointestinal bleeding than warfarin, while apixaban is not. Rivaroxaban and edoxaban may be more convenient for some due to its single daily dose (compared to twice daily for apixaban and dabigatran), which may result in better compliance. Apixaban reduces the risk of haemorrhage, while dabigatran has been shown to reduce the risk of ischaemic stroke. The choice of NOAC may therefore at least partly be driven by patient choice and need, rather than a strict cost-effectiveness comparison.

Key points

- **41 primary studies from 17 different countries were included in this analysis. A further four NICE Health Technology Assessments from the UK were described. Three Belgian evaluations, performed from a payer perspective, were identified and analysed in more detail.**
- **The economic evaluations suggest that despite their greater expense, NOACs are cost-effective against warfarin. Reduced dose dabigatran (110mg) is consistently dominated by standard dose dabigatran (150mg).**
- **Identifying which is the most cost-effective NOAC is challenging because all models relied on single, industry sponsored, short follow-up trials to estimate the impact of treatment. Many assumptions were made about costs (including monitoring costs). Assessment of comparative effectiveness also relied on indirect comparisons. Despite these limitations, most studies concluded that dabigatran (150mg or sequential dabigatran – i.e. 150mg until 80 years old, followed by 110mg thereafter) and apixaban were the most cost-effective NOACs.**

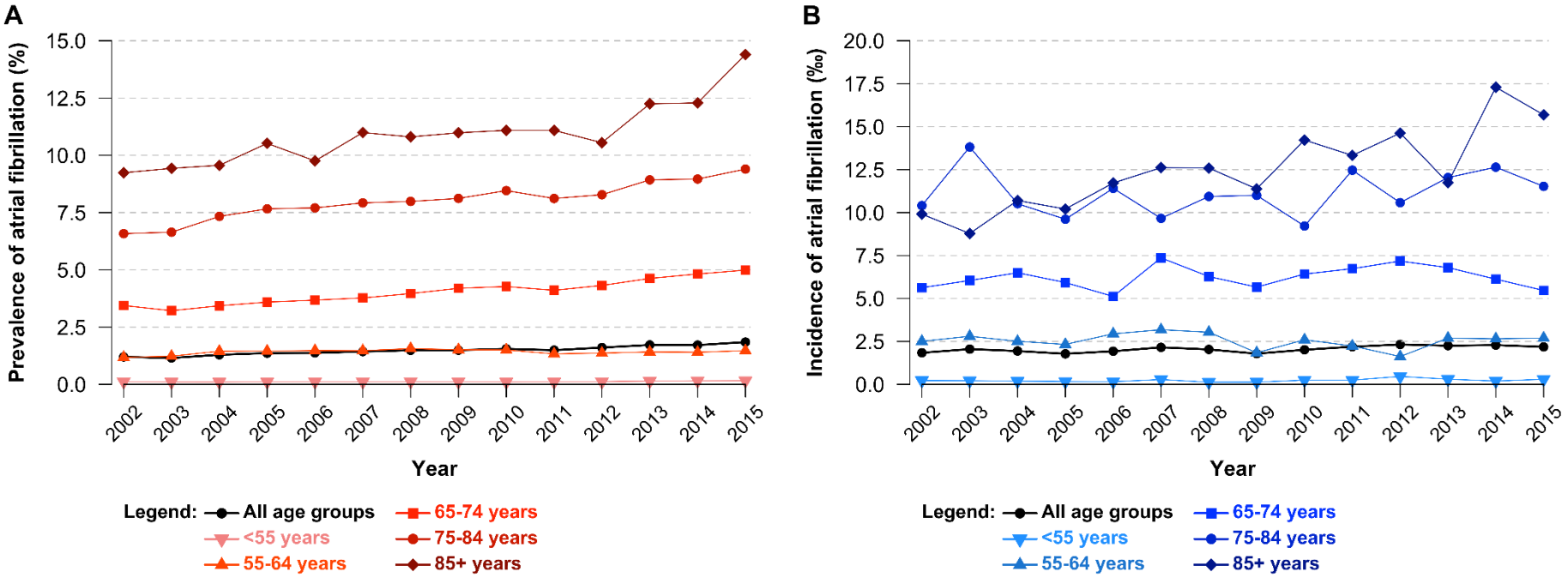
9 FLEMISH GENERAL PRACTITIONERS' DATA

9.1 Introduction

The prevalence of AF in the general population in Flanders (Intego database) increased in the past years, ranging from 1.20% in 2002 to 1.85% in 2015, and also increases with age (Figure 9). Among people aged ≥65 years, the prevalence of AF increased from 5.26% in 2002 to 8.17% in 2015; among people aged ≥75 years, it increased from 7.26% in 2002 to 11.07% in 2015; and among people aged ≥85 years, it increased from 9.24% in 2002 to 14.40% in 2015.

The incidence of AF in the general population also slightly increased in the past years, ranging from 1.8‰ in 2002 to 2.2‰ in 2015, and especially in older age groups (Figure 9B). Among people aged ≥65 years, the incidence of AF increased from 7.4‰ in 2002 to 8.5‰ in 2015; among people aged ≥75 years, it increased from 9.5‰ in 2002 to 11.4‰ in 2015; and among people aged ≥85 years, it increased from 9.0‰ in 2002 to 13.4‰ in 2015.

Figure 9 – Prevalence (A) and incidence (B) of atrial fibrillation in Flanders (Intego) between 2002 and 2015



9.2 Methodology

9.2.1 Description of the Intego database

Intego is a general practice database with information from a total of 79 GP practices across Flanders, and currently covering 440 thousand individual patients[22]. All information is routinely collected and derived from the patient electronic health record during daily practice. The network was founded in 1994 and data is sent to a central database at regular intervals. Its initial aim was to collect incidence rates of diagnoses presented to the GP. Almost half of the Belgian GPs work in solo-practices, without additional staff and rather demand driven. The patient population of Intego is representative of the Flemish population on age, gender and average income. The number of patients included in Intego in 2015 represented 1.92% of the total Flemish population, and 1.10% of the total Belgian population.

At the start of the Intego-project it was decided to use the medical electronic health record (Medidoc®) which was one of the few existing packages in Belgium allowing routine input of coded diagnoses and other coded data. All data are recorded by the GP using keywords in a predetermined field in the electronic health record. Each of the 67 500 keywords is associated with a unique program-specific internal code and can be linked to classifications as ICPC-2 (International Classification of Primary Care, 2nd edition). Drugs are classified according to the WHO's Anatomical Therapeutic Chemical (ATC) classification system. It has to be stated that there might be an underestimation of prescriptions in the Intego database as almost only electronic prescriptions are recorded in the database. Therefore, prescriptions made by hand, at home visit, or in nursing homes are not included if they are not added by the GP in the electronic medical file of the patient. In addition, only prescriptions made by GPs are recorded in the database, and not prescriptions made by specialists.

9.2.2 Clinical research questions

One of the aims of the present KCE report was to describe anticoagulation practice in Belgium. In Belgium all reimbursed medicines are registered in the Pharmanet database[20]. This database can be used for scientific research, e.g. for the identification of patients treated with anticoagulants. However, these databases are not linked to medical diagnoses. As a consequence, neither the clinical indication for an anticoagulant, nor the stroke risk profile of the patients involved, is known. Therefore, before analysing Belgian anticoagulation practice (Chapter 10), we used the Flemish Intego database for a description of AF patients. The first part of this chapter was intended to validate a proxy for the $CHADS_2$ and CHA_2DS_2-VASc scores that we used in the analysis of the Belgian Pharmanet data. In the second part of the study we provide data on anticoagulation practice in people with AF, and particularly the change in the anticoagulant prescription practice in people with AF since the introduction of NOACs on the Belgian market.

9.2.3 Patient selection

For the first part of the study, all patients who were in the yearly contact group of the years 2009 to 2015 were selected (N=292 563) (Figure 10). The yearly contact group comprises patients who had at least one contact with their GP in a specific year. Among these patients, patients with no prescription of an oral anticoagulant (OAC) were excluded, as well as patients in whom the first OAC was prescribed before 2009.

In total, 1 590 patients with a new chronic prescription of an OAC between 2009 and 2015 were included in the analysis. A prescription was considered chronic if a patient had ≥1 prescription of OAC in the first 6 months of a year and ≥1 prescription of OAC in the last 6 months of a year. $T0_{OAC}$ was defined as the first day of a chronic prescription of an OAC.

Separate analyses were also performed in the 1 312 patients who had ≥1 year of follow-up (FUP) before $T0_{OAC}$ and ≥6 months of FUP after $T0_{OAC}$ in the Intego database (n=1 312/1 590, 82.5%). This minimum FUP period was chosen as the time period for medications included in the proxies was the year before $T0_{OAC}$, and we allowed a period of 6 months after $T0_{OAC}$ for the registration of comorbidities by the GP in the Intego database. A description of the 2 168 patients with a first prescription of OAC between 2009 and 2015 but without any chronic prescription in these years is provided in the Appendix to this report.

For the second part of the study, all people who had at least one contact with their GP between 2002 and 2015 were first selected (Figure 11). Among these 382 628 people, those who had a new diagnosis of AF recorded between 2002 and 2015 (incident cases of AF) were selected. Among the 3 705 incident cases of AF, 3 201 people had a follow-up of ≥1 year after the diagnosis of AF ($T0_{AF}$) and were included in the subsequent analyses to allow a minimum period of time to start oral anticoagulation.

Figure 10 – Flowchart describing patient selection (first part of the study)

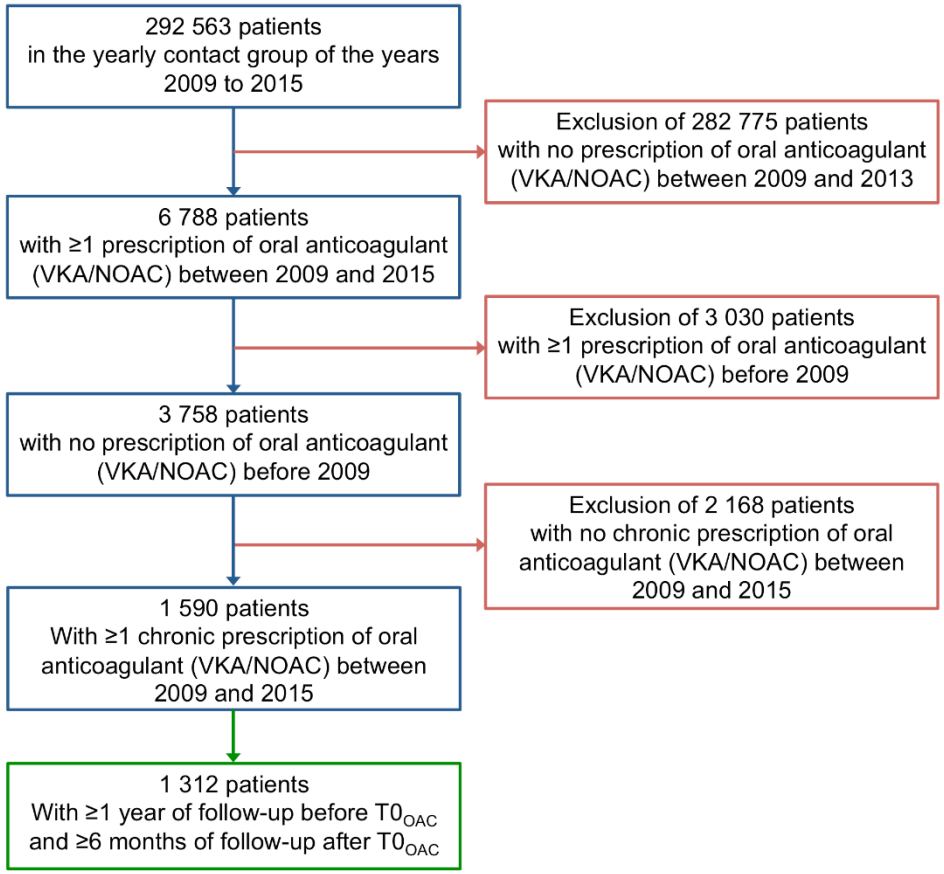
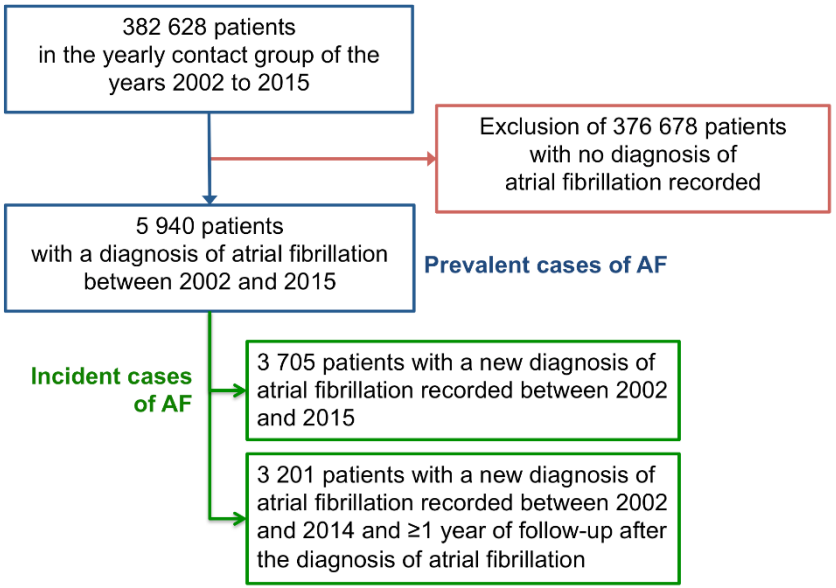


Figure 11 – Flowchart describing patient selection (second part of the study)



9.2.4 Definition of clinical variables and medications

9.2.4.1 Definition of oral anticoagulants (OACs) and other medications

In the present study, VKAs and NOACs were included as OACs (Table 25). Only chronic prescriptions of OACs were considered, i.e. if a patient had ≥1 prescription of OAC in the first 6 months of a year and ≥1 prescription of OAC in the last 6 months of year. If a VKA and a NOAC were prescribed in a given year, the last OAC prescribed in that year was considered, unless elsewhere specified.

Table 25 – Definition of oral anticoagulants, based on the ATC code

Type of OAC	Name of the OAC	ATC code
VKA	Warfarin	B01AA03
	Phenprocoumon	B01AA04
	Acenocoumarol	B01AA07
NOAC	Dabigatran etexilate	B01AE07
	Rivaroxaban	B01AF01
	Apixaban	B01AF02

Several other medications were also recorded in all patients. These medications included antiplatelet agents, medications of the cardiovascular system (amiodarone, diuretics, beta-blockers, calcium antagonists, ACE inhibitors, AT II antagonists) and anti-diabetic drugs. A prescription of one of these drugs was considered if ≥2 prescriptions were recorded in a specific year.

Table 26 – Definition of medications recorded (≥2 prescriptions in a year)

Medicine	ATC code
Antiplatelet agent	B01AC
Amiodarone	C01DB01
Diuretics	C03
Beta-blockers	C07AA and C07AB
Dihydropyridine	C08CA
Verapamil	C08DA01
Diltiazem	C08DB01
ACE inhibitors	C09A and C09B
AT II antagonists	C09C, C09D and C09X
Anti-diabetic drugs	A10

9.2.4.2 *Definition of CHA2DS2-VASc and CHADS2 scores*

CHA2DS2-VASc and CHADS2 scores were calculated based on ICPC-2 codes (Table 27). In the first part of the study, these scores were computed at T0OAC, whereas in the second part, they were computed at T0AF.

Table 27 – Definition of variables used in CHA_2DS_2-Vasc and $CHADS_2$ scores

CHA_2DS_2-VASc	$CHADS_2$	Items	ICPC-2 code	Number of points in the CHA_2DS_2-VASc score	Number of points in the $CHADS_2$ score
C	C	Presence of congestive heart failure/left ventricular dysfunction	K77	1	1
H	H	History of hypertension	K86, K87	1	1
A_2	A	Age ≥75 years	/	2	1
D	D	Presence of diabetes	T89, T90	1	1
S_2	S_2	History of thromboembolic event (transient ischemic attack, stroke)	K89, K90	2	2
V		History of vascular disease (acute myocardial infarction, peripheral arterial disease)	K75, K92	1	/
A		Age ≥65 years and <75 years	/	1	/
Sc		Gender: female	/	1	/
		Maximum score		*9*	*6*

9.2.4.3 *Definition of clinical indications for a prescription of oral anticoagulants*

In the first part of this study, diagnoses considered as potential clinical indications for the prescription of an OAC were the presence of atrial fibrillation (AF), a deep vein thrombosis, a lung embolism or a valve disease, as defined by their ICPC-2 codes (Table 28). The actual date of the first chronic prescription of an OAC was defined as T0OAC. As a delay is possible between the registration of a disease in the Intego database and the day of diagnosis, a patient with a diagnosis registered up to 6 months after T0OAC was also considered as having the diagnosis at our study's T0OAC.

Table 28 – Definition of clinical indications for OACs in the first part of the study

Clinical indication for prescriptions of OACs	ICPC-2 code	Time period for registration in the Intego database at $T0_{OAC}$
Atrial fibrillation	K78	Recorded ever before $T0_{OAC}$+6 months
Deep vein thrombosis	K94	Recorded between $T0_{OAC}$-6 months and $T0_{OAC}$+6 months
Lung embolism	K93	Recorded between $T0_{OAC}$-6 months and $T0_{OAC}$+6 months
Valve disease	K83	Recorded ever before $T0_{OAC}$+6 months

"Valve disease" as such is no indication for anticoagulation.

9.2.4.4 *Definition of proxies for CHA2DS2-VASc and CHADS2 scores*

In the first part of this study, a proxy for the CHA2DS2-VASc score and the CHADS2 score was built based on age, gender and medications prescribed. In these proxies, the number of points for age and gender were the same as those used in the real scores (see Table 27). In addition, medications that could be prescribed to treat comorbidities used in the real scores were registered (Table 29). These medications were: diuretics, ACE inhibitors, AT II antagonists, calcium antagonists (dihydropyridine, verapamil, diltiazem), beta-blockers, and anti-diabetic drugs. A proxy for the CHA2DS2-Vasc score and the CHADS2 score was then built, as defined in Table 30.

Table 29 – Definition of medications used in the proxies for CHA_2DS_2-VASc and $CHADS_2$ scores

Medicine	ATC code	Reason for inclusion based on diagnoses included in the CHA_2DS_2-Vasc and $CHADS_2$ scores
Diuretics	C03	Used in the treatment of heart failure and hypertension
ACE inhibitors	C09A and C09B	Used in the treatment of heart failure, hypertension and myocardial infarction
AT II antagonists	C09C, C09D and C09X	Used in the treatment of heart failure, hypertension and myocardial infarction
Dihydropyridine	C08CA	Used in the treatment of hypertension
Verapamil	C08DA01	Used in the treatment of arrhythmias, hypertension and AF rate control
Diltiazem	C08DB01	Used in the treatment of hypertension and AF rate control
Beta-blockers	C07AA and C07AB	Used in the treatment of hypertension, arrhythmias and myocardial infarction (secondary prevention) and AF rate control
Anti-diabetic drugs	A10	Used in the treatment of diabetes

Table 30 – Definition of variables used in the proxies* for CHA_2DS_2-VASc and $CHADS_2$ scores

Variable included in the proxy	Number of points in the proxy for the CHA_2DS_2-VASc score	Number of points in the proxy for the $CHADS_2$ score
Gender: Female	1	/
Age ≥65 years and <75 years	1	/
Age ≥75 years	2	1
At least 2 prescriptions of a dihydropyridine in the year before $T0_{OAC}$	1	1
At least 2 prescriptions of verapamil/diltiazem in the year before $T0_{OAC}$	1	1
At least 2 prescriptions of ACE inhibitors in the year before $T0_{OAC}$	2	2
At least 2 prescriptions of ATII antagonists in the year before $T0_{OAC}$	2	2
At least 2 prescriptions of diuretics in the year before $T0_{OAC}$	2	2
At least 2 prescriptions of beta blockers in the year before $T0_{OAC}$	1	1
At least 2 prescriptions of anti-diabetic drugs in the year before $T0_{OAC}$	1	1

**Drugs included in the proxy are defined in Table 29*

9.2.5 Statistical analysis

Continuous variables were summarized using medians [P_{25}; P_{75}] and were compared between two groups using the Mann-Whitney U test. Categorical variables were summarized using proportions and were compared between two groups using Pearson's chi-squared test, Pearson's chi-squared test with Yates continuity correction, Fisher's exact test or Fisher-Freeman-Halton's exact test, depending on the condition of validity of each test.

The accuracy of the proxies for CHA_2DS_2-VASc and $CHADS_2$ scores compared to the real scores in Intego was evaluated by calculating their sensitivity, specificity, positive predictive value, negative predictive value, as well as the Cohen's kappa coefficient and the 95% confidence interval. The Cohen's kappa coefficient measured the agreement between the proxy and the real score. The higher the coefficient, the higher the agreement. Cohen's kappa (κ) coefficient <0.20 indicated a very weak agreement, between 0.21 and 0.40 indicates a weak agreement, between 0.41 and 0.60 and moderate agreement, between 0.61 and 0.80 a good agreement, and between 0.81 and 1.00 a very good agreement.

In the second part of the study, the time to the first chronic prescription was also analysed with a survival analysis. A log-rank test was used to compare the survival distributions between categories of years of diagnosis of AF (2002-2006, 2007-2009, 2010-2012, and 2013-2014) at 6 months, 1 year, 2 years, 3 years after $T0_{AF}$, and for the whole FUP period.

All analyses were performed using R software version 3.2.3 (Free Software Foundation, Inc., Boston, MA, USA). All p-values <0.05 were considered statistically significant.

9.3 Results

9.3.1 Prescription of oral anticoagulants in general practice in the general population and validation of proxies for the CHA_2DS_2-VASc and $CHADS_2$ scores (part 1)

9.3.1.1 Description of OAC prescriptions in general practice between 2009 and 2015

Among the 292 563 patients recorded in the Intego database between 2009 and 2015, 6 788 patients received at least one prescription of an OAC (2.3%) (Figure 10).

Among these patients, 44.6% received at least one prescription of an OAC before 2009, and 55.4% received the first prescription of OAC for the first time between 2009 and 2015. Among the latter group, 1 590 patients received a chronic prescription of OAC between 2009 and 2015. These 1 590 patients were included in the following analyses and belong to the group named “all patients”. Among these patients, separate analyses were performed in the 1 312 patients (82.5%) who had ≥1 year of FUP before T0OAC and ≥6 months of FUP after T0OAC. In this group, only a part of patients with their first chronic prescription of OAC in 2015 were included because of the minimum FUP period required. In this group of patients, the median number of OAC prescriptions in the first year after T0OAC was 7 (Table 31). The median number of OAC prescriptions during the whole follow-up period after T0OAC in that group was 12, with a median follow-up time of 2.8 years.

Table 31 – Description of the pattern of OAC prescriptions and of patient FUP

Variable	All patients (N=1 590) Median [P_{25}; P_{75}] (Min-Max) or n (%)	Patients with a FUP period ≥1 year before $T0_{OAC}$ and ≥6 months after $T0_{OAC}$ (N=1 312) Median [P_{25}; P_{75}] (Min-Max) or n (%)	Patients with a FUP period <1 year before $T0_{OAC}$ or <6 months after $T0_{OAC}$ (N=278) Median [P_{25}; P_{75}] (Min-Max) or n (%)
Number of OAC prescriptions per patient in the first year ≥ $T0_{OAC}$	7 [5; 9] (2-30)	7 [5; 9] (2-30)	7 [5; 9] (2-19)
Number of OAC prescriptions per patient ≥ $T0_{OAC}$ until the end of follow-up	12 [8; 23] (3-77)	12 [8; 22] (3-77)	13 [8; 24.8] (3-61)
Duration of the follow-up ≥ $T0_{OAC}$, in years	2.8 [1.8; 4.2] (0.0-7.0)	2.8 [1.8; 4.1] (0.6-7.0)	2.9 [1.7; 4.8] (0-6.8)
Year of the first chronic prescription of OAC			
2009	*186 (11.7)*	*165 (12.6)*	21 (7.6)
2010	*192 (12.1)*	*163 (12.4)*	29 (10.4)
2011	*261 (16.4)*	*174 (13.3)*	87 (31.3)
2012	*239 (15.0)*	*206 (15.7)*	33 (11.9)
2013	*296 (18.6)*	*255 (19.4)*	41 (14.7)
2014	*353 (22.2)*	*295 (22.5)*	*58 (20.9)*
2015	*63 (4.0)*	*54 (4.1)*	*9 (3.2)*

9.3.1.2 Type of OAC prescribed in general practice between 2009 and 2015

Among all patients, 71.8% had a VKA prescribed as the first chronic OAC (Table 32), and one-quarter of them received ≥1 prescription of a NOAC after T0OAC. Among the 28.2% of all patients who received a NOAC as the first chronic OAC prescribed, 5.3% of them received ≥1 prescription of a VKA after T0OAC.

Among patients with ≥1 year of FUP before T0OAC and ≥6 months of FUP after T0OAC, similar percentages were observed (Table 32). In this group of patients, the proportion of VKA as the first chronic OAC prescribed between 2009 and 2011, i.e. before the reimbursement of NOACs in AF patients in Belgium, was 99.8%, versus 50.1% after the reimbursement of NOACs (between 2012 and 2015).

Table 32 – Repartition of patients according to the type of the first chronic OAC (VKA/NOAC) prescribed between 2009 and 2015, and the switch to another category of OAC until the end of follow-up

First chronic OAC prescribed at $T0_{OAC}$	All patients n (%)	Patients with a FUP period ≥1 year before $T0_{OAC}$ and ≥6 months after $T0_{OAC}$ n (%)
VKA	**1 141 (71.8%)**	**904 (68.9%)**
With no prescription of a NOAC after $T0_{OAC}$	*873 (76.5%)*	*694 (76.8%)*
With ≥1 prescription of a NOAC after $T0_{OAC}$	*268 (23.5%)*	*210 (23.2%)*
NOAC	**449 (28.2%)**	**408 (31.1%)**
With no prescription of a VKA after $T0_{OAC}$	*425 (94.7%)*	*386 (94.6%)*
With ≥1 prescription of a VKA after $T0_{OAC}$	*24 (5.3%)*	*22 (5.4%)*
Total	***1 590 (100.0%)***	***1 312 (100.0%)***

9.3.1.3 Characteristics of patients with a chronic OAC prescription in general practice between 2009 and 2015

In the group of patients with ≥1 year of FUP before T0OAC and ≥6 months of FUP after T0OAC, almost half of them were aged ≥75 years (Table 33). Approximately 60% of the patients had a diagnosis of AF recorded in the database at T0OAC, almost 6% a deep vein thrombosis, 5% a lung embolism, 13% a valve problem, and almost 30% had no recorded clinical indication for a chronic prescription of OAC. A statistically significant difference was found between patients who received a VKA or a NOAC as the first chronic OAC for age (41.0% aged ≥75 years in the VKA group versus 56.9% in the NOAC group) and for the proportion of patients with AF (53.2% in the VKA group versus 71.1% in the NOAC group), with a deep vein thrombosis (7.2% in the VKA group versus 2.7% in the NOAC group), and a lung embolism (7.0% in the VKA group versus 1.2% in the NOAC group) (Table 33).

In the group of patients with ≥1 year of FUP before T0OAC and ≥6 months of FUP after T0OAC, 28 patients had a diagnosis of AF recorded after T0OAC, in addition to the 771 patients who had a diagnosis of AF recorded at T0OAC.

Almost 80% of the patients were classified at high risk of stroke at T0OAC by the CHA2DS2-VASc score ≥2 and 45% by the CHADS2 score ≥2 (Table 33). These proportions were significantly different between the VKA group and the NOAC group. Indeed, the proportion of patients classified at high risk of stroke by the CHA2DS2-VASc score was 73.6% in the VKA group and 89.2% in the NOAC group. The proportion of people with a CHADS2 score ≥2 was of 42.0% in the VKA group and 50.0% in the NOAC group.

A complete table containing all variables included in the CHA2DS2-VASc and CHADS2 scores, prescriptions of other medications and proxies for the CHA2DS2-VASc and CHADS2 scores at T0OAC is available in appendices (0).

Table 33 – Comparison of patients' characteristics at T0 according to the first OAC prescribed between 2009 and 2015*

Variables	Total (N=1 312) Median [P_{25}; P_{75}] or n (%)	VKA as first OAC prescribed (N=904) Median [P_{25}; P_{75}] or n (%)	NOAC as first OAC prescribed (N=408) Median [P_{25}; P_{75}] or n (%)	p-value**
Patients' characteristics at $T0_{OAC}$				
Age, years	73 [66; 80]	72 [64; 79]	76 [70; 81]	<0.001
Age group				<0.001[a]
<65 years	287 (21.9)	251 (27.8)	36 (8.8)	
65-74 years	422 (32.2)	282 (31.2)	140 (34.3)	
≥75 years	603 (46.0)	371 (41.0)	232 (56.9)	
Females	559 (42.6)	377 (41.7)	182 (44.6)	0.325[a]
Indication for an OAC prescription at $T0_{OAC}$				
Atrial fibrillation	771 (58.8)	481 (53.2)	290 (71.1)	<0.001[a]
Deep vein thrombosis	76 (5.8)	65 (7.2)	11 (2.7)	<0.001[a]
Lung embolism	68 (5.2)	63 (7.0)	5 (1.2)	<0.001[a]
Valve problems	165 (12.6)	122 (13.5)	43 (10.5)	0.135[a]
No indication recorded	373 (28.4)	270 (29.9)	103 (25.2)	0.306[a]
CHA_2DS_2-VASc and $CHADS_2$ scores at $T0_{OAC}$				
CHA_2DS_2-VASc score	3 [2; 4]	3 [1; 4]	3 [2; 4]	<0.001[a]
0	*88 (6.7)*	*84 (9.3)*	*4 (1.0)*	
1	*195 (14.9)*	*155 (17.1)*	*40 (9.8)*	
≥2	*1 029 (78.4)*	*665 (73.6)*	*364 (89.2)*	
$CHADS_2$ score	1 [1; 2]	1 [0; 2]	1.5 [1; 2]	<0.001[a]
0	*306 (23.3)*	*250 (27.7)*	*56 (13.7)*	
1	*422 (32.2)*	*274 (30.3)*	*148 (36.3)*	
≥2	*584 (44.5)*	*380 (42.0)*	*204 (50.0)*	

** Patients included in this table had a FUP ≥1 year before T0OAC and ≥6 months after T0OAC*

*** Continuous variables were compared between the 2 groups using the Mann-Whitney U test; categorical variables were compared between the 2 groups using Pearson's chi-squared test (a) or Pearson's chi-squared test with Yates continuity correction (b) according to the conditions of validity.*

Because of the low absolute number of patients in certain categories, inferences should be made cautiously.

9.3.1.4 *Comparison of the proxy CHA2DS2-VASc and CHADS2 scores and the real scores in the Intego database*

As shown in Table 34, the concordance between the proxy CHA2DS2-VASc based on demographic pharmaceutical data and the real CHA2DS2-VASc score based on diagnoses (scores categorized in low, intermediate and high risk) at T0OAC was moderate (Cohen's kappa coefficient (95%CI): 0.536 (0.483; 0.588)).

As shown in Table 35, the prevalence of a low-risk CHA2DS2-VASc score (score of 0) was low (6.7%). The probability that patients with a proxy CHA2DS2-VASc of 0 truly have a CHA2DS2-VASc score of 0, as measured by the PPV is good (66.7%). The corresponding NPV, i.e. the probability that patients with a proxy CHA2DS2-VASc ≥1 truly have a CHA2DS2-VASc score ≥1 is very good (97.6%). The accuracy was this proxy was moderate to good (Cohen's kappa coefficient (95%CI): 0.639 (0.553; 0.724)).

As shown in Table 36, the prevalence of a high-risk CHA2DS2-VASc score (score ≥2) was high (78.4%). The probability that patients with a proxy CHA2DS2-VASc of ≤1 truly have a CHA2DS2-VASc score of ≤1 is good (PPV: 71.0%). The corresponding NPV, i.e. the probability that patients with a proxy CHA2DS2-VASc ≥2 truly have a CHA2DS2-VASc score ≥2 is very good (90.4%). The accuracy was this proxy was moderate to good (Cohen's kappa coefficient: 0.589 (0.534; 0.643)).

Finally, the PPV of the proxy for the CHADS2 score (0 versus ≥1) was lower than the accuracy of the proxy CHA2DS2-VASc score, with a lower sensitivity, specificity, PPV, NPV and a moderate Cohen's kappa coefficient (κ=0.582) (Table 37).

In conclusion, the proxy CHA2DS2-VASc score demonstrated a good PPV and a very good NPV when differentiating people at high risk of stroke (≥2) versus people at low or intermediate risk of stroke (≤1). However, it has to be noted that 5.6% of the patients were wrongly classified at low or intermediate risk by the proxy. Nevertheless, this proxy could be used in further analyses when diagnoses are not available. Regarding the proxy CHADS2 score, the accuracy was lower than the proxy CHA2DS2-VASc score. Therefore, the use of this proxy is not recommended when diagnoses are not available.

Table 34 – Comparison of the proxy for CHA_2DS_2-VASc score and the real CHA_2DS_2-VASc score (risk categories) at $T0_{OAC}$

		Real CHA_2DS_2-VASc score at $T0_{OAC}$			
		0	1	≥2	
Proxy CHA_2DS_2-VASc score at $T0_{OAC}$	0	58 (4.4%)	20 (1.5%)	9 (0.7%)	87
	1	14 (1.1%)	89 (6.8%)	65 (5.0%)	168
	≥2	16 (1.2%)	86 (6.6%)	955 (72.8%)	1 029
		88	195	1 029	1 312

Cohen's kappa coefficient (95%CI) = 0.536 (0.483; 0.588)

Patients included in this table had a FUP ≥1 year before $T0_{OAC}$ and ≥6 months after $T0_{OAC}$

Table 35 – Comparison of the proxy for the CHA_2DS_2-VASc score and the real CHA_2DS_2-VASc score (0 *versus* ≥1) at $T0_{OAC}$

		Real CHA_2DS_2-VASc score at $T0_{OAC}$		
		0	≥1	
Proxy CHA_2DS_2-VASc score at $T0_{OAC}$	0	58 (4.4%)	29 (2.2%)	87
	≥1	30 (2.3%)	1 195 (91.1%)	1 225
		88	1 224	1 312

Sensitivity (95%CI) = 0.659 (0.550; 0.757) PPV (95%CI) = 0.667 (0.557; 0.764)
Specificity (95%CI) = 0.976 (0.966; 0.984) NPV (95%CI) = 0.976 (0.965; 0.983)
Cohen's kappa coefficient (95%CI) = 0.639 (0.553; 0.724)

Patients included in this table had a FUP ≥1 year before T0OAC and ≥6 months after T0OAC

Table 36 – Comparison of the proxy for the CHA_2DS_2-VASc score and the real CHA_2DS_2-VASc score (≤1 *versus* ≥2) at $T0_{OAC}$

		Real CHA_2DS_2-VASc score at $T0_{OAC}$		
		≤1	≥2	
Proxy CHA_2DS_2-VASc score at $T0_{OAC}$	≤1	181 (13.8%)	74 (5.6%)	255
	≥2	102 (7.8%)	955 (72.8%)	1 057
		283	1 029	1 312

Sensitivity (95%CI) = 0.640 (0.581; 0.696) PPV (95%CI) = 0.710 (0.650; 0.765)
Specificity (95%CI) = 0.928 (0.911; 0.943) NPV (95%CI) = 0.904 (0.884; 0.921)
Cohen's kappa coefficient (95%CI) = 0.589 (0.534; 0.643)

Patients included in this table had a FUP ≥1 year before T0OAC and ≥6 months after T0OAC

Table 37 – Comparison of the proxy $CHADS_2$ score and the real $CHADS_2$ score (0 *versus* ≥1) at $T0_{OAC}$

		Real $CHADS_2$ score at $T0_{OAC}$		
		0	≥1	
Proxy $CHADS_2$ score at $T0_{OAC}$	0	174 (3.3%)	91 (6.9%)	265
	≥1	132 (10.1%)	915 (69.7%)	1 047
		306	1 006	1 312

Sensitivity (95%CI) = 0.569 (0.511; 0.625) PPV (95%CI) = 0.657 (0.596; 0.714)
Specificity (95%CI) = 0.910 (0.890; 0.927) NPV (95%CI) = 0.874 (0.852; 0.893)
Cohen's kappa coefficient (95%CI) = 0.502 (0.445; 0.558)

Patients included in this table had a FUP ≥1 year before T0OAC and ≥6 months after T0OAC

9.3.2 Trends in prescriptions of OACs in general practice in people with atrial fibrillation (part 2)

9.3.2.1 Characteristics of patients newly diagnosed with AF (incident cases)

Table 38 shows the characteristics of people with AF at the time of diagnosis of AF (T0AF), among people with ≥1 year of FUP after T0AF. Approximately one-fifth to one-quarter of patients were aged less than 65 years at T0AF, and half were aged ≥ 75 years. Somewhat less than half of people were females. At T0AF, 41.0% of patients had a history of hypertension, 17.2% had diabetes, 13.0% a history of a vascular disease (myocardial infarction and/or peripheral arterial disease), 12.9% had a history of a thromboembolic event (TIA and/or stroke), and 8.9% had a heart failure.

The year before T0AF, 5.7% of people had a chronic prescription of OAC. The proportion of people with ≥2 prescriptions of antiplatelet agents was of 16.6% the year before T0AF. The prescription of other medications is found in Table 38.

The proportion of people with ≥2 prescriptions of amiodarone rose to 12.5% the year after T0AF, from 1.1% the year before T0AF. The proportion of people with ≥2 prescriptions of beta-blockers more than doubled, almost doubled for diuretics, and was 1.5 times higher for ACE inhibitors in the year after T0AF compared to the year before T0AF (Table 38).

Regarding the repartition of patients according to their CHA2DS2-VASc score at T0AF, among those with ≥1 year of FUP after T0AF, approximately three-quarter of the new cases with AF had a CHA2DS2-VASc ≥2 at T0AF, approximately 9% had a CHA2DS2-VASc score of 0 and approximately 15% had a CHA2DS2-VASc score of 1 are provided in the Appendix to this report. Among people with a CHA2DS2-VASc score of 1, one-quarter were females (26.6%, n=132/497). The proportion of people with a CHA2DS2-VASc score ≥2 at T0AF varies between 69.7% in 2007 and 81.1% in 2014.

Table 38 – Characteristics of patients* with AF at $T0_{AF}$

Variable	At $T0_{AF}$ (N=3 201) Median [P_{25}; $P7_5$] or n (%)
Patients' characteristics	
Age, in years	74 [65; 81]
Age group	
<65 years	*739 (23.1)*
65-74 years	*896 (28.0)*
≥75 years	*1 566 (48.9)*
Females	1 478 (46.2)
Comorbidities represented in the CHA_2DS_2-VASc and $CHADS_2$ scores	
Heart failure	284 (8.9)
History of hypertension	1 313 (41.0)
Diabetes	551 (17.2)
History of thromboembolic event (stroke and/or TIA)	414 (12.9)
Vascular disease (history of MI and/or PAD)	415 (13.0)
OAC in the past year (chronic prescription)	182 (5.7)
Other medications in the past year (≥2 prescriptions)	
Antiplatelet agents	532 (16.6)
Antiplatelet agents and OACs	
No chronic OAC and no antiplatelet agent	2 534 (79.2)
No chronic OAC and prescription of an antiplatelet agent	485 (15.2)

Chronic prescription of an OAC and no antiplatelet agent	135 (4.2)
Chronic prescription of an OAC and prescription of an antiplatelet agent	47 (1.5)
Diuretics	400 (12.5)
ACE inhibitors	464 (14.5)
ATII antagonists	245 (7.7)
Dihydropyridine	303 (9.5)
Verapamil	17 (0.5)
Diltiazem	54 (1.7)
Anti-diabetics	267 (8.3)
Beta-blockers	599 (18.7)
Amiodarone	36 (1.1)

**Patients included in this table had ≥ 1 year of FUP after T0AF*

TIA: transient ischemic attack; MI: myocardial infarction; PAD: peripheral arterial disease

9.3.2.2 Oral anticoagulation in patients with AF

In patients diagnosed with AF in 2002 and with ≥1 year of FUP, one-third of them had ≥1 prescription of an OAC in the year after $T0_{AF}$ (Figure 12). Among patients, 48.5% of them had a chronic prescription (Figure 13). In patients diagnosed in 2014, the proportion of people with ≥1 prescription of OAC in the year after $T0_{AF}$ was of 72.7%, and 62.4% of them received a chronic prescription.

Figure 13 shows the proportion of patients with a chronic prescription of an OAC started in the year after $T0_{AF}$ and the evolution over the following years, among those with ≥1 year of FUP after $T0_{AF}$. This proportion doubled between patients diagnosed in 2002 (16.0%) and those diagnosed in 2011 (32.0%), almost tripled between 2002 and 2014 (45.4%), and reached the maximal value in 2014. Analysing the whole FUP period, the proportion of people with AF who received a chronic prescription of OACs ever after $T0_{AF}$ increased with years (Table 39). Indeed, it was 36.4% in patients diagnosed with AF between 2002 and 2006, and 46.8% in patients diagnosed with AF diagnosed between 2013 and 2014. In addition, the proportion of patients who received the first OAC prescription in the year after $T0_{AF}$ also increased with years, being 45.2% for patients diagnosed in the years 2013-2014, from 21.8% for patients diagnosed in 2002-2006 (Table 39). Finally, the proportion of patients receiving a chronic OAC the year after $T0_{AF}$ compared to ever after $T0_{AF}$ represented 60.0% of the patients diagnosed in 2002-2006, compared to 96.4% in the years 2013-2014.

The proportion of people with a VKA prescribed was 16.0% in patients diagnosed in 2002, reached the maximum value before the marketing of NOACs, in 2010, with 30.3%, and dropped to 11.1% in those diagnosed in 2014. On the contrary, the proportion of people with a NOAC prescribed was 0.4% in patients diagnosed with AF in 2010 and reached 34.3% in those diagnosed in 2014.

Among people with a chronic OAC prescribed in the year after $T0_{AF}$, the proportion of NOACs represented 39.6% of the prescriptions in 2012, 57.5% in 2013, and 75.6% in 2014 (Figure 13).

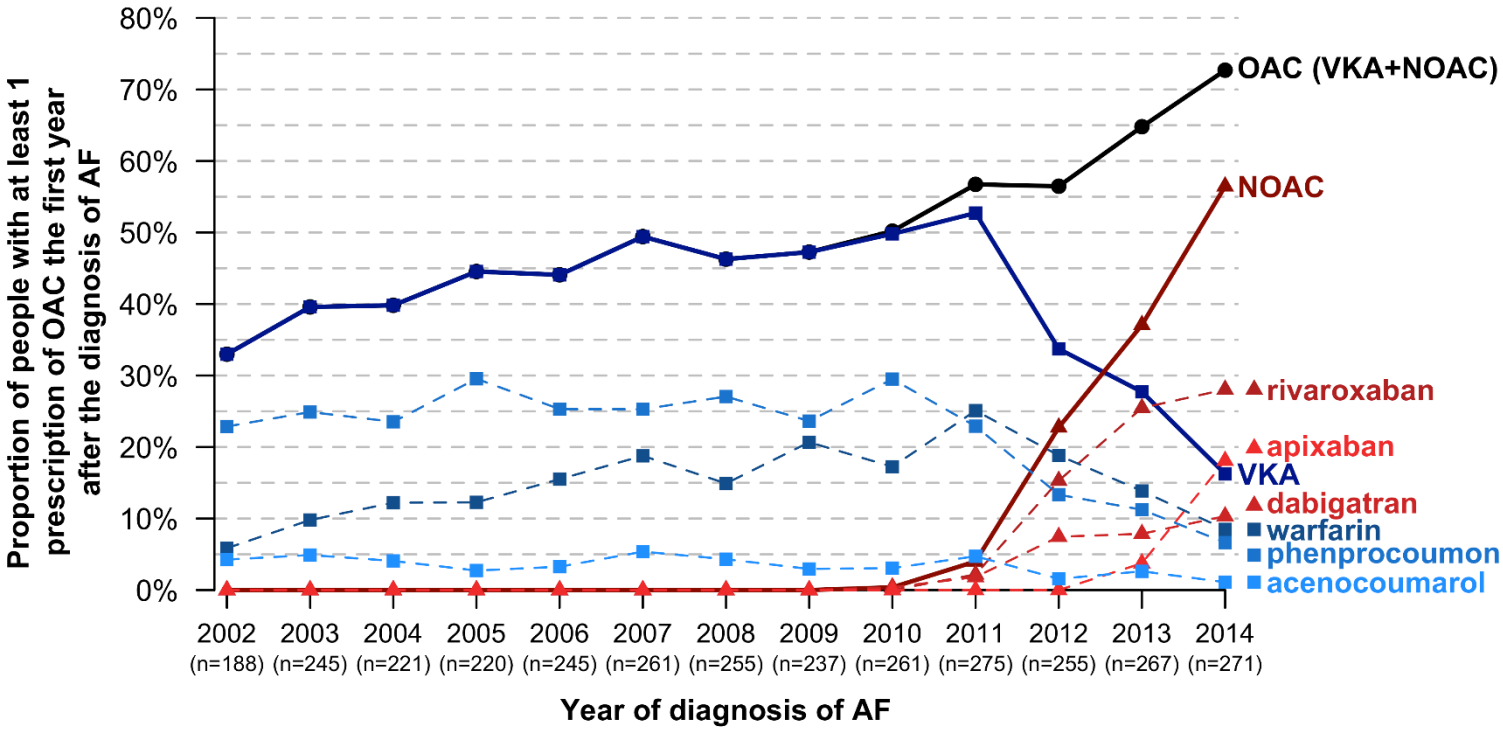
Among patients with a clearly accepted indication for a prescription of an OAC, i.e. those with a CHA_2DS_2-VASc score ≥2 at $T0_{AF}$, 35.4% of patients diagnosed with AF in 2002 received ≥1 prescription of an OAC (Figure 14), and 49.0% of them received a chronic prescription (Figure 15). In patients diagnosed in 2014, the proportion of people with ≥1 prescription of OAC in the year after $T0_{AF}$ was of 75.5%, and 64.5% of them received a chronic prescription. In the same group of patients with a CHA_2DS_2-VASc score ≥2 at $T0_{AF}$, the proportion of people with a chronic prescription of an OAC started in the year after $T0_{AF}$ increased with years, and was 17.4% in patients diagnosed with AF in 2002, 34.3% in patients diagnosed with AF in 2011 and 48.6% in patients diagnosed with AF in 2014 (Figure 15). The proportion of VKAs, compared to NOACs, represented 90.1% of the prescriptions in patients diagnosed in 2011 and dropped to 23.4% in patients diagnosed in 2014.

Finally, Figure 16 and Figure 17 show the evolution of the proportion of people with a chronic prescription of OAC in the first year after $T0_{AF}$ over the years and by CHA_2DS_2-VASc score at $T0_{AF}$. This proportion was similar between the three CHA_2DS_2-VASc score risk categories (0, 1, ≥2) in the years 2002-2006 (Figure 17). For people with a CHA_2DS_2-VASc score of 0 a slight decrease in the years 2010-2014 compared to the previous years is

observed. For people with a CHA_2DS_2-VASc score of 1, the proportion of anticoagulated patients was similar between the years 2002-2006 to 2010-2012 (±22%), and almost doubled in the years 2013-2014 (40.2%). For people with a CHA_2DS_2-VASc score ≥2, the proportion of anticoagulated patients linearly increased between the years 2002-2006 (21.4%) to the years 2013-2014, achieving 49.6% in the years 2013-2014 (Figure 17).

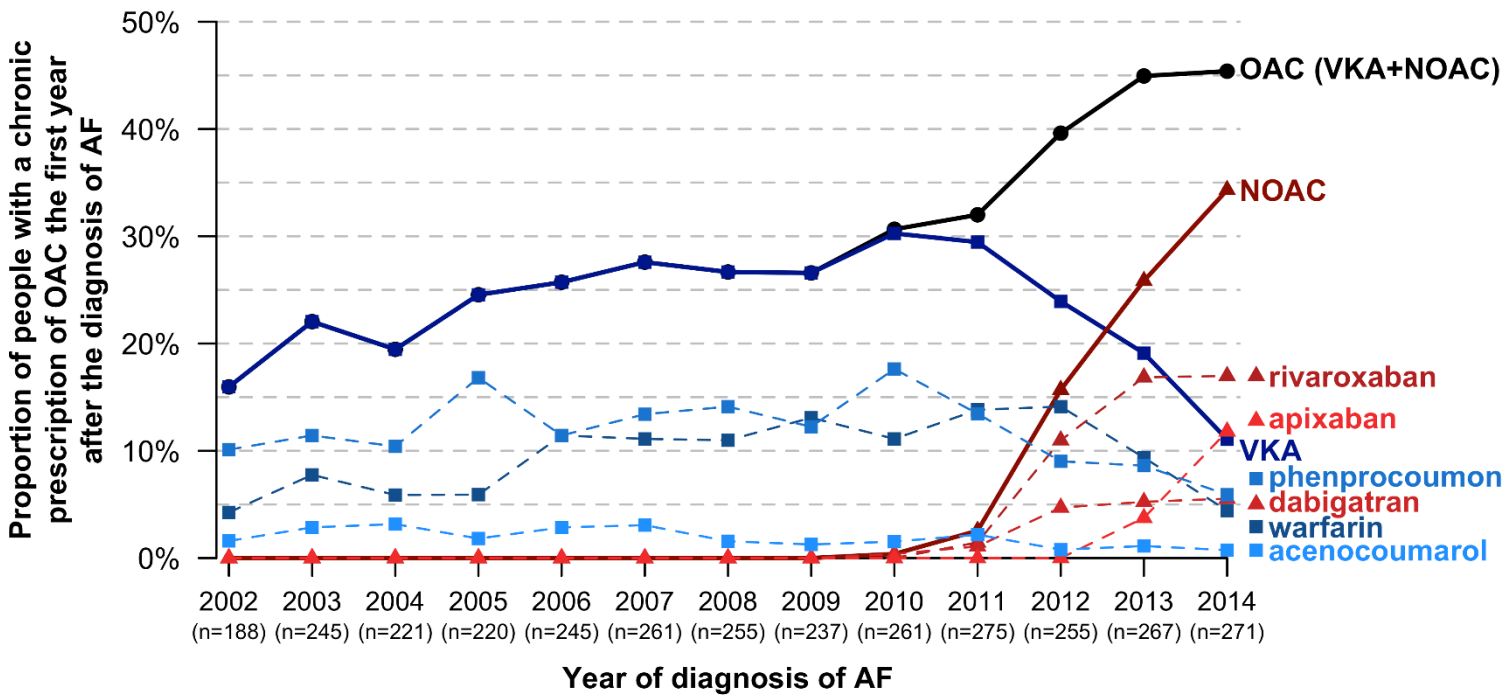
In conclusion, people at high risk of stroke were more and more treated with OACs in the year after the diagnosis of AF between 2002 and 2014, whereas people at low risk of stroke were less and less anticoagulated between 2002 and 2014.

Figure 12 – Evolution of the proportion of people* with AF with ≥1 prescription of OAC in the first year after $T0_{AF}$



** Patients included in this figure had ≥ 1 year of FUP after T0AF*

Figure 13 – Evolution of the proportion of people* with AF with a chronic prescription of OAC started in the first year after $T0_{AF}$



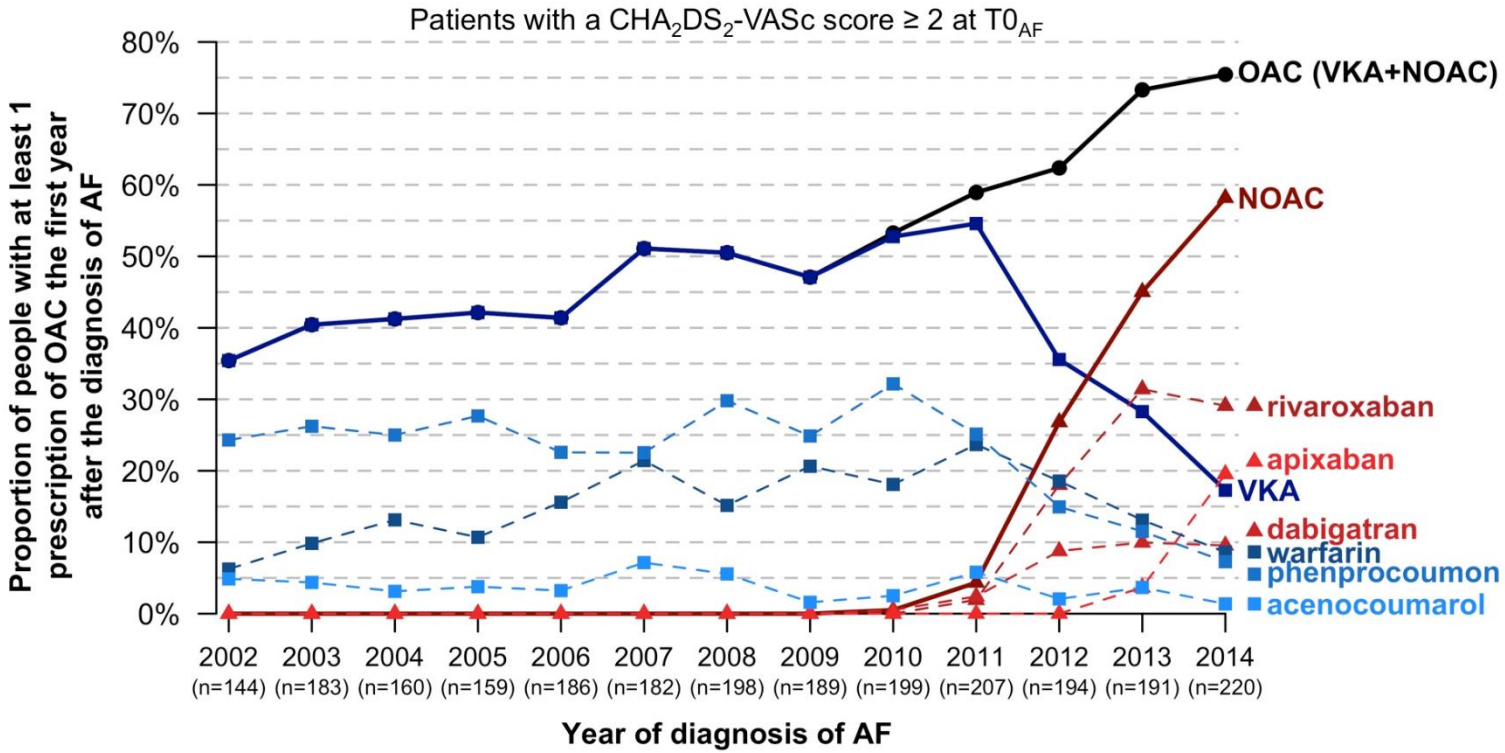
** Patients included in this figure had ≥ 1 year of FUP after T0AF*

Table 39 – Type of OAC prescribed at $T0_{AF}$ in the year after $T0_{AF}$ and the whole follow-up period*

Variable	Total (N=3 201) n (%)	Diagnosis of AF between 2002 and 2006 (N=1 119) n (%)	Diagnosis of AF between 2007 and 2009 (N=753) n (%)	Diagnosis of AF between 2010 and 2012 (N=791) n (%)	Diagnosis of AF between 2013 and 2014 (N=538) n (%)
Chronic OAC started in the year after $T0_{AF}$	959 (30.0)	244 (21.8)	203 (27.0)	269 (34.0)	243 (45.2)
VKA as first OAC, among those with an OAC prescribed	*764 (79.7)*	*244 (100.0)*	*203 (100.0)*	*232 (86.2)*	*85 (35.0)*
NOAC as first OAC, among those with an OAC prescribed	*195 (20.3)*	*0 (0.0)*	*0 (0.0)*	*37 (13.8)*	*158 (65.0)*
Chronic OAC started ever after $T0_{AF}$	1 316 (41.1)	407 (36.4)	305 (40.5)	352 (44.5)	252 (46.8)
VKA as first OAC, among those with an OAC prescribed	*1 026 (78.0)*	*389 (95.6)*	*278 (91.1)*	*270 (76.7)*	*89 (35.3)*
NOAC as first OAC, among those with an OAC prescribed	*290 (22.0)*	*18 (4.4)*	*27 (8.9)*	*82 (23.3)*	*163 (64.7)*
Number of people followed-up until 2012 or after	2 415 (75.4)	599 (53.5)	536 (71.1)	742 (93.8)	538 (100.0)

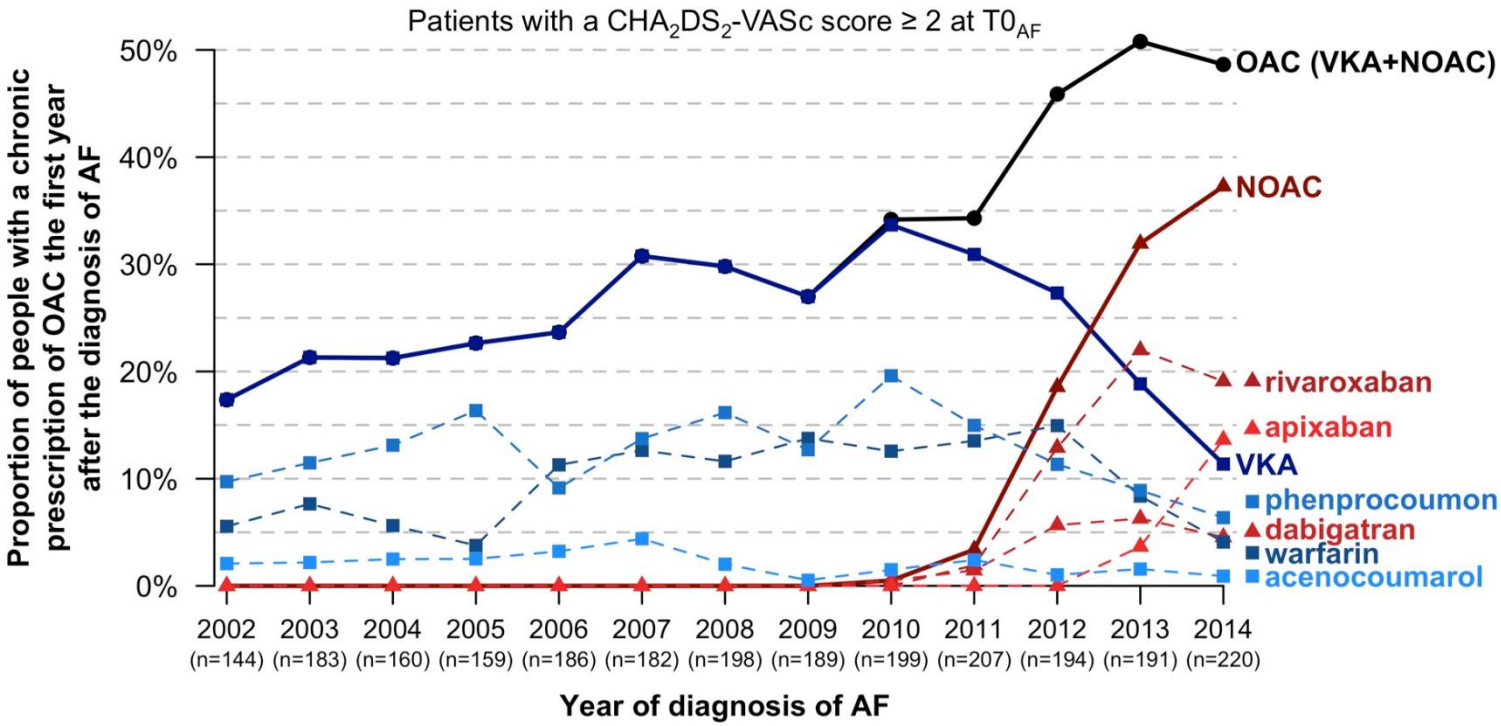
**Patients included in this table had ≥ 1 year of FUP after T0AF*

Figure 14 – Evolution of the proportion of people* with AF with ≥1 prescription of OAC in the first year after $T0_{AF}$, and a CHA_2DS_2-VASc score ≥2 at $T0_{AF}$



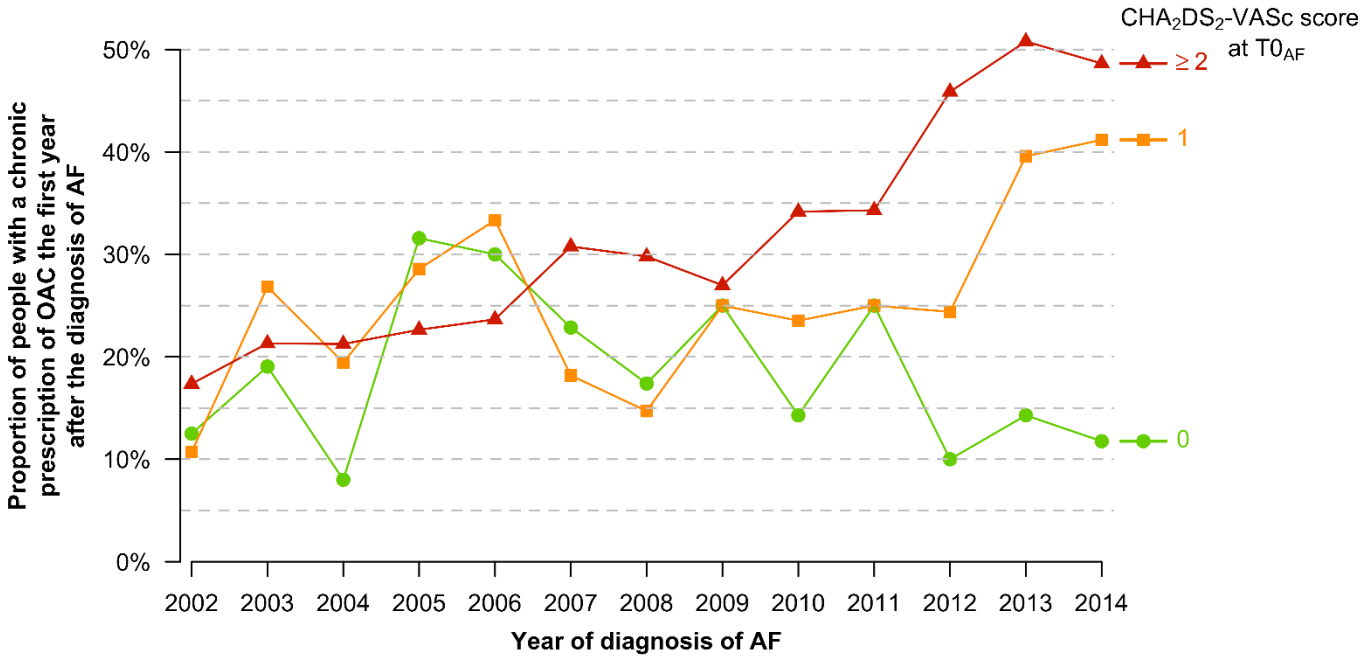
**Patients included in this figure had ≥ 1 year of FUP after T0AF*

Figure 15 – Evolution of the proportion of people* with AF with a chronic prescription of OAC started in the first year after $T0_{AF}$, and a CHA_2DS_2-VASc score ≥2 at $T0_{AF}$



**Patients included in this figure had ≥ 1 year of FUP after T0AF*

Figure 16 – Proportion of people* with a chronic prescription of OAC started in the first year after $T0_{AF}$, per CHA_2DS_2-VASc score risk category at $T0_{AF}$

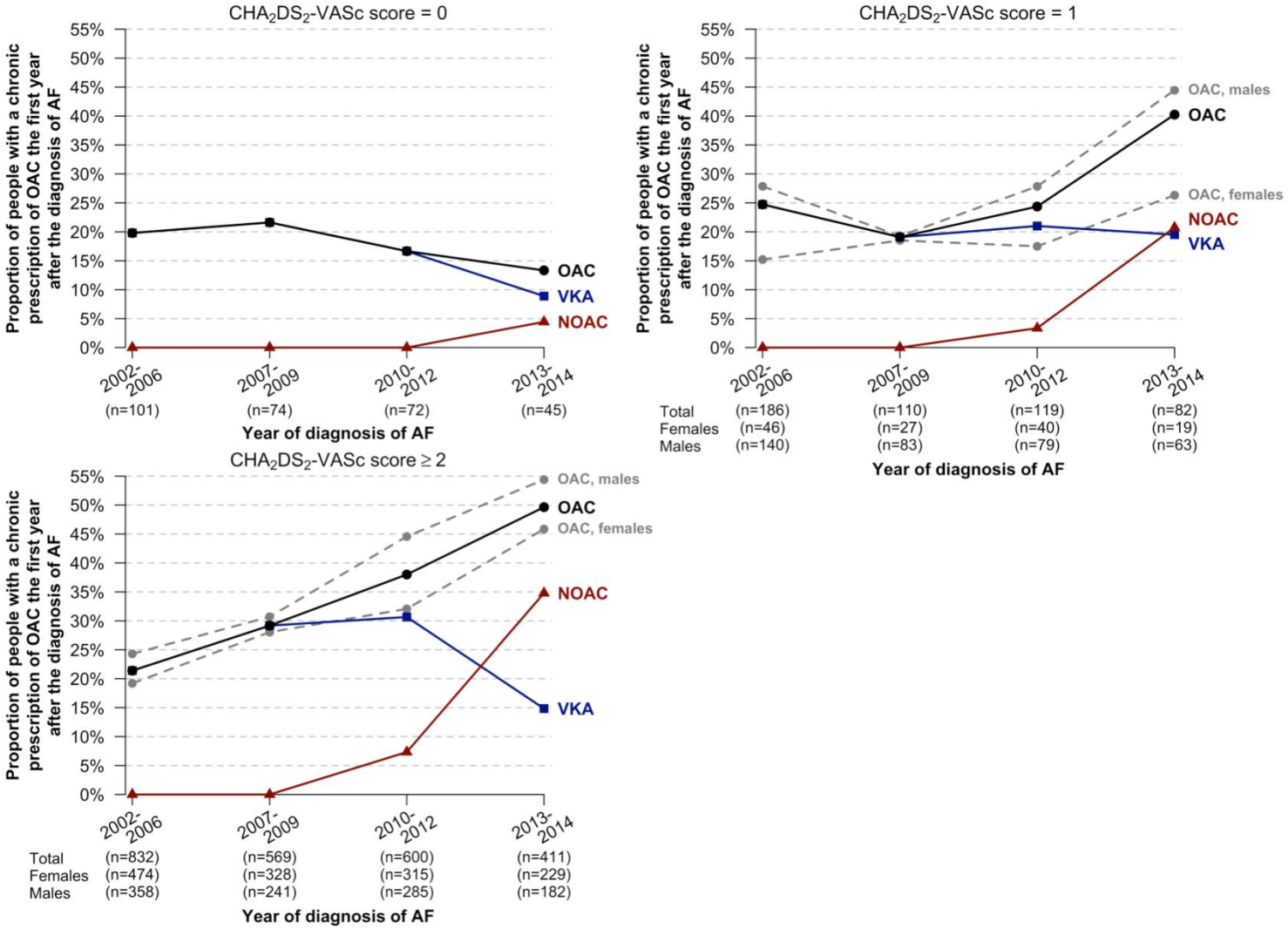


CHA_2DS_2-VASc score	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
=0	n=16	n=21	n=25	n=19	n=20	n=35	n=23	n=16	n=28	n=24	n=20	n=28	n=17
=1	n=28	n=41	n=36	n=42	n=39	n=44	n=34	n=32	n=34	n=44	n=41	n=48	n=34
≥ 2	n=144	n=183	n=160	n=159	n=186	n=182	n=198	n=189	n=199	n=207	n=194	n=191	n=220

**Patients included in this figure had ≥ 1 year of FUP after $T0_{AF}$*

Proportions must be interpreted with caution considering the low number of patients per category per year

Figure 17 – Proportion of people* with an OAC started in the year after $T0_{AF}$ by CHA_2DS_2-VASc score at $T0_{AF}$



**Patients included in this figure had ≥ 1 year of FUP after T0AF. Proportions must be interpreted with caution considering the low number of patients per year for people with a CHA2DS2-VASc score of 0, and in males and females*

9.3.2.3 Analysis of time to the first chronic prescription of OAC

To analyse if the time to the first chronic prescription of OAC was different with years, and particularly since the marketing of NOACs, a survival analysis was performed.

In brief, for people with a CHA_2DS_2-VASc score of 0 at $T0_{AF}$, the proportion of people with a chronic oral anticoagulation started was not different between categories of year of diagnosis of AF at 6 months, 1 year, 2 years or 3 years after $T0_{AF}$ as shown the Appendix to this report. For people with a CHA_2DS_2-VASc score of 1 at $T0_{AF}$, the proportion of people with a chronic oral anticoagulation started was higher at 6 months, 1 year and 2 years after $T0_{AF}$ in patients diagnosed in 2013-2014 than in patients diagnosed before those years as shown the Appendix to this report.

For patients with a CHA_2DS_2-VASc score ≥2 at $T0_{AF}$, the proportion of people with a chronic oral anticoagulation started at 6 months, and 1 to 3 years after $T0_{AF}$ increased significantly with years of diagnosis of AF (Table 40and Figure 18). This proportion was of 50% 1 year after $T0_{AF}$ for people diagnosed with AF between 2013 and 2014, whereas it was less than 50% up to 3 years after $T0_{AF}$ for patients diagnosed in previous years.

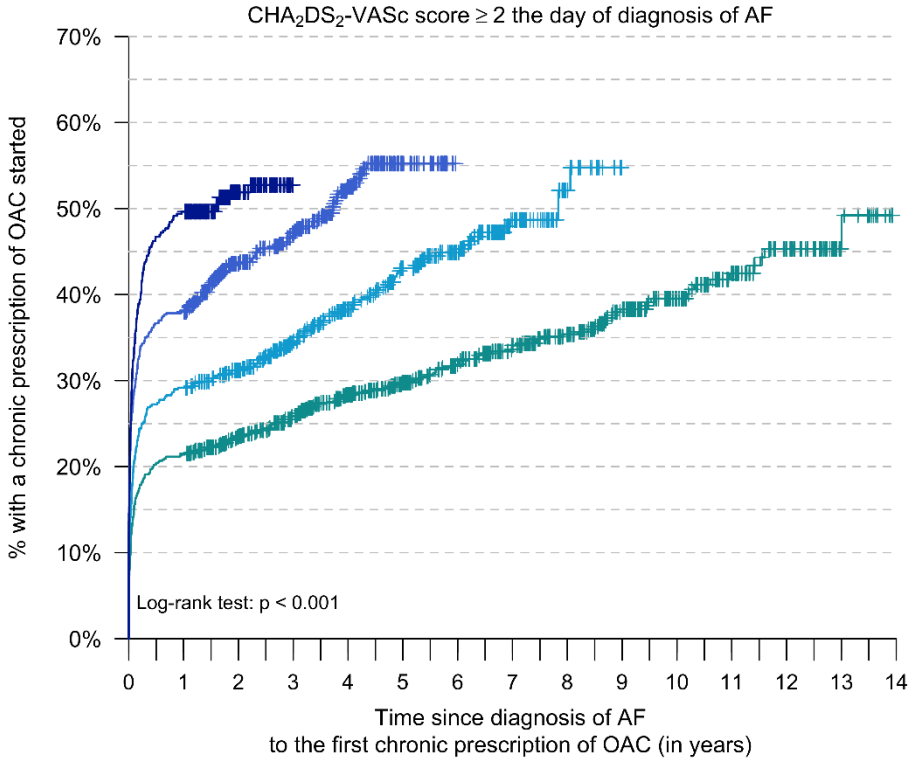
Table 40 – Proportion of OAC prescriptions in AF patients* with a CHA_2DS_2-VASc score ≥2 at $T0_{AF}$, 6 months to 3 years after $T0_{AF}$

Variable	Total	Diagnosis of AF between 2002 and 2006	Diagnosis of AF between 2007 and 2009	Diagnosis of AF between 2010 and 2012	Diagnosis of AF between 2013 and 2014	Log-rank test: p-value
Number of people at $T0_{AF}$	2 412	832	569	600	411	
Oral anticoagulation at 6 months						<0.001
Number of people anticoagulated	737	170	155	220	192	
Proportion of people anticoagulated (95%CI)	0.306 (0.288-0.324)	0.204 (0.178-0.233)	0.272 (0.238-0.311)	0.367 (0.33-0.407)	0.467 (0.42-0.517)	
Oral anticoagulation at 1 year						<0.001
Number of people anticoagulated	776	178	166	228	204	
Proportion of people anticoagulated (95%CI)	0.322 (0.303-0.341)	0.214 (0.188-0.243)	0.292 (0.256-0.331)	0.380 (0.343-0.42)	0.496 (0.449-0.546)	
Oral anticoagulation at 2 years						<0.001
Number of people anticoagulated	838	194	177	258	209	
Proportion of people anticoagulated (95%CI)	0.347 (0.329-0.367)	0.233 (0.206-0.263)	0.311 (0.275-0.351)	0.430 (0.391-0.471)	0.509 (0.461-0.558)	
Oral anticoagulation at 3 years						<0.001
Number of people anticoagulated	888	212	193	273	210	
Proportion of people anticoagulated (95%CI)	0.368 (0.349-0.388)	0.255 (0.227-0.286)	0.339 (0.302-0.38)	0.455 (0.416-0.496)	0.511 (0.464-0.56)	

**Patients included in this table had ≥ 1 year of FUP after T0AF*

95%CI: 95% confidence interval

Figure 18 – Time to the first chronic prescription of OAC in AF patients* with a CHA_2DS_2-VASc score ≥2 at $T0_{AF}$



Year of AF diagnosis	Number of people not anticoagulated at time t														
2002-2006	832	654	580	513	443	381	332	277	227	179	122	80	48	14	/
2007-2009	569	403	354	284	224	171	128	66	19	/	/	/	/	/	/
2010-2012	600	372	264	203	106	32	/	/	/	/	/	/	/	/	/
2013-2014	411	207	66	/	/	/	/	/	/	/	/	/	/	/	/

**Patients included in this figure had ≥ 1 year of FUP after T0AF*

The log-rank test was computed for the whole FUP period

9.3.2.4 *Analysis of OAC prescriptions in a patients with AF and aged ≥75 years*

Patient characteristics at the time of diagnosis of AF ($T0_{AF}$)

Among patients aged ≥75 years at $T0_{AF}$, 28.9% (n=452/1 566) had a chronic prescription of OAC started in the first year after $T0_{AF}$. The median CHA_2DS_2-VASc score was 4, and the median $CHADS_2$ score was 2 (Table 41). Indeed patients aged ≥75 years have 2 points in the CHA_2DS_2-VASc score due to their age.

In comparison to people aged ≥75 years who received an OAC in the first year after $T0_{AF}$, those who didn't were older (difference in the median age of 2 years), diagnosed in the earliest years, females, and with a higher proportion of heart failure. All other comorbidities of the CHA_2DS_2-VASc and $CHADS_2$ scores were not statistically significant. In addition, patients who didn't receive an OAC in the first year after $T0_{AF}$ also received less frequently cardiovascular medications and anti-diabetics than those who received an OAC: more than three times less ATII antagonists; more than two times less ACE inhibitors, dihydropyridine, beta-blockers, and amiodarone; and two times less anti-diabetics, diuretics, and diltiazem.

Table 41 – Characteristics of patients* with AF aged ≥75 years at $T0_{AF}$, and comparisons according to the chronic prescription of an OAC

Variable	People aged ≥75 years Median [P_{25}; $P7_5$] or n (%) (N=1 566)	People aged ≥75 years and with no oral anticoagulation started in the first year after $T0_{AF}$ Median [P_{25}; $P7_5$] or n (%) (N=1 114)	People aged ≥75 years and with an oral anticoagulation started in the first year after $T0_{AF}$ Median [P_{25}; $P7_5$] or n (%) (N=452)	p-value**
Patients' characteristics				
Age, in years	81 [78; 85]	82 [78; 86]	80 [78; 84]	<0.001
Year of diagnosis of AF				<0.001
2002-2006	*537 (34.3)*	*442 (39.7)*	*95 (21.0)*	
2007-2009	*235 (15.0)*	*167 (15.0)*	*68 (15.0)*	
2010-2012	*514 (32.8)*	*348 (31.2)*	*166 (36.7)*	
2013-2014	*280 (17.9)*	*157 (14.1)*	*123 (27.2)*	
Females	877 (56.0)	654 (58.7)	223 (49.3)	<0.001
Comorbidities of the CHA_2DS_2-VASc and $CHADS_2$ scores				
Heart failure	197 (12.6)	155 (13.9)	42 (9.3)	0.012
History of hypertension	735 (46.9)	507 (45.5)	228 (50.4)	0.076
Diabetes	280 (17.9)	194 (17.4)	86 (19.0)	0.451

History of thromboembolic event (stroke and/or TIA)	270 (17.2)	195 (17.5)	75 (16.6)	0.665
Vascular disease (history of MI and/or PAD)	250 (16.0)	190 (17.1)	60 (13.3)	0.064
CHA_2DS_2-VASc score	4 [3; 5]	4 [3; 5]	4 [3; 5]	0.087
$CHADS_2$ score	2 [1; 3]	2 [1; 3]	2 [1; 3]	0.618
OAC started in the past year (chronic prescription)	452 (28.9)	/	/	
Other medications in the past year (≥2 prescriptions)				
Antiplatelet agents	296 (18.9)	221 (19.8)	75 (16.6)	0.137
Diuretics	476 (30.4)	268 (24.1)	208 (46.0)	<0.001
ACE inhibitors	319 (20.4)	159 (14.3)	160 (35.4)	<0.001
ATII antagonists	131 (8.4)	57 (5.1)	74 (16.4)	<0.001
Dihydropyridine	178 (11.4)	91 (8.2)	87 (19.2)	<0.001
Verapamil	10 (0.6)	8 (0.7)	2 (0.4)	0.733
Diltiazem	32 (2.0)	18 (1.6)	14 (3.1)	0.060
Anti-diabetics	150 (9.6)	83 (7.5)	67 (14.8)	<0.001
Beta-blockers	536 (34.2)	278 (25.0)	258 (57.1)	<0.001
Amiodarone	179 (11.4)	95 (8.5)	84 (18.6)	<0.001

** Patients included in this table had ≥ 1 year of FUP after T0AF*

*** Categorical variables were compared between the 2 groups using Pearson's chi-squared test or Fisher's exact test, (for verapamil) and continuous variables were compared between the 2 groups using the Mann-Whitney U test*

TIA: transient ischemic attack; MI: myocardial infarction; PAD: peripheral arterial disease

Prescriptions of OACs in patients aged ≥75 years

All patients with AF aged ≥75 years have a minimal CHA2DS2-VASc score of 2 at T0AF. This is a clear indication that an OAC must be started, unless contraindications.

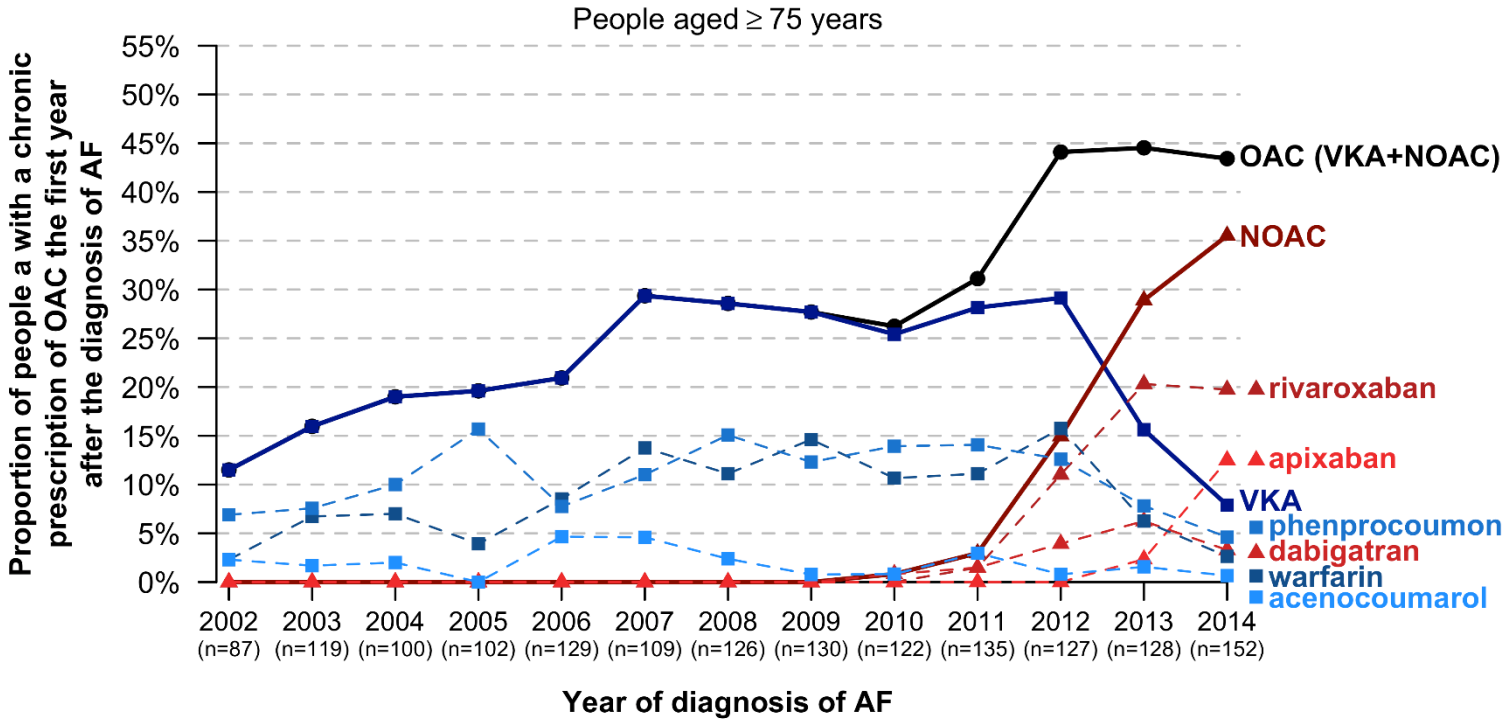
Figure 19 shows the proportion of people aged ≥75 years at T0AF with a chronic prescription of OAC started in the year after T0AF and the evolution over the years. This proportion more than doubled between 2002 (11.5%) and 2010 (26.2%) and reached the maximal value for patients diagnosed with AF in 2013 (44.5%). The proportion of people with a VKA prescribed reached the maximal value in 2007 (29.4%) and 2012 (29.1%), and decreased to 7.9% in 2014. On the contrary, the proportion of people with a NOAC prescribed increased from 2010 to 2014, and was of 35.5% in 2014.

Among people with an OAC prescribed in the year after T0AF, the proportion of VKAs represented 100.0% of the prescriptions until 2009, 96.9% in 2010 and decreased to 18.2% in 2014. In 2014, the proportions of rivaroxaban and apixaban alone outreached the proportion of all VKA prescribed.

Among people with a CHADS2 score of 1 at T0AF, the proportion of patients with an OAC started in the first year after T0AF increased between years 2002-2006 (21.8%) and 2010-2012 (36.2%) and was similar in the years 2013-2014 (35.5%) (Figure 19). These proportions of anticoagulation were similar in males and females in years 2002-2006 to 2010-2012, but a difference between males (51.2%) and females (23.1%) was observed in the years 2013-2014. This result must be interpreted with caution considering the low number of patients in each group.

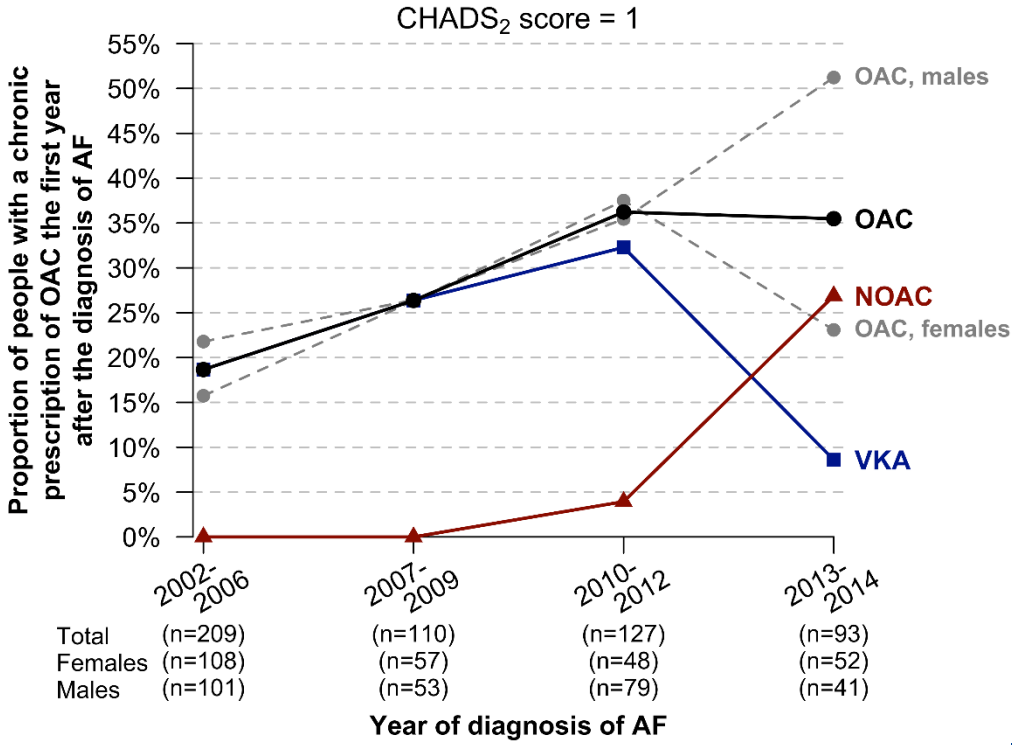
Among people with a CHADS2 score ≥2 at T0AF, the proportion of patients with an OAC started started in the first year after T0AF increased with years (17.1% in 2002-2006 to 48.1% in 2013-2014) (Figure 20). A difference of approximately 8% was observed in all years between males and females, males being more anticoagulated than females.

Figure 19 – Evolution of the proportion of people* aged ≥75 years with AF with a chronic OAC started in the first year after $T0_{AF}$



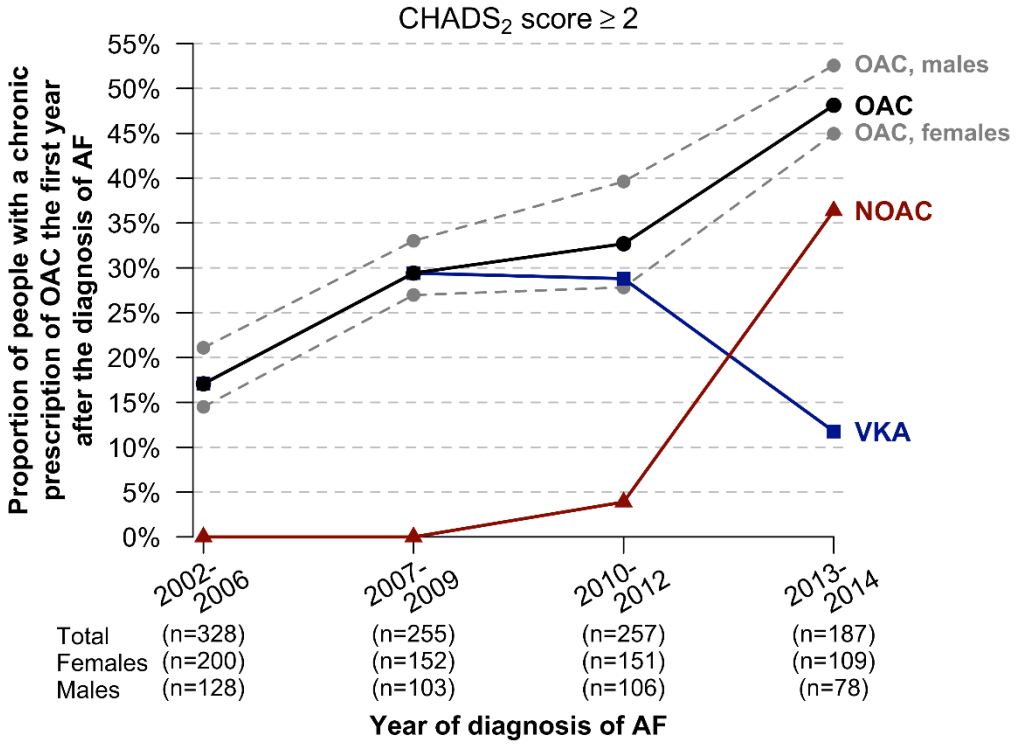
** Patients included in this figure had ≥ 1 year of FUP after $T0_{AF}$*

Figure 20 – Evolution of the proportion of people* with AF aged ≥75 years with a $CHADS_2$ score of 1 at $T0_{AF}$ and a chronic OAC started in the first year after $T0_{AF}$



** Patients included in this figure had ≥ 1 year of FUP after $T0_{AF}$*

Figure 21 – Evolution of the proportion of people* with AF aged ≥75 years with a $CHADS_2$ score ≥2 at $T0_{AF}$ and a chronic OAC started in the first year after $T0_{AF}$



** Patients included in this figure had ≥ 1 year of FUP after $T0_{AF}$*

9.4 Conclusions

9.4.1 *Prescription of oral anticoagulants in general practice in the general population and validation of proxies for the CHA_2DS_2-VASc and $CHADS_2$ scores (part 1)*

In conclusion, the proxy CHA2DS2-VASc score demonstrated a good PPV and a very good NPV when differentiating people at high risk of stroke (≥2) versus people at low or intermediate risk of stroke (≤1). However, it has to be noted that 5.6% of the patients were wrongly classified at low or intermediate risk by the proxy. Nevertheless, this proxy could be used in further analyses when diagnoses are not available. Regarding the proxy CHADS2 score, the accuracy was lower than the accuracy of the proxy CHA2DS2-VASc score. Therefore, we decided not to use it in further analyses.

9.4.2 *Trends in prescriptions of oral anticoagulants in general practice in people with atrial fibrillation (part 2)*

In patients with AF, the proportion of patients who had an oral anticoagulation started in the first year after their diagnosis increased with years, and especially in patients diagnosed after the reimbursement of NOACs (Figure 13). For patients diagnosed with AF in 2014, this proportion reached 45.4%, from 16.0% in 2002. In patients diagnosed with AF in 2013 and 2014, the proportion of patients with a NOAC prescribed outreached the proportion of patients with a VKA prescribed. Nowadays, NOAC seems then to be the first choice OAC.

Another important finding was that the proportion of anticoagulated patients with AF varies with years and according to patient's CHA2DS2-VASc score at T0AF. Indeed, this proportion seems to decrease with years in patients with a CHA2DS2-VASc score of 0 at T0AF, whereas it linearly increased with years in patients with a CHA2DS2-VASc score of ≥2 at T0AF (Figure 17). The same observation applies when analysing the time to the first chronic prescription of OACs, i.e. in patients with a CHA2DS2-VASc score of ≥2 at T0AF, almost half of the patients diagnosed in the years 2013-2014 have an oral anticoagulation started in the year after T0AF compared to one-third of those diagnosed in the years 2002-2006 (Figure 18).

Although clinicians are doing a better job over the past years, half of the patients who need an oral anticoagulation (with a CHA2DS2-VASc score ≥2 at T0AF) are still not anticoagulated. In conclusion, there is still a room for improvement in the field of anticoagulation in patients with AF. However, it has to be stated that there might be an underestimation of OAC prescriptions in the Intego database as almost only electronic prescriptions are recorded in the database. Therefore, prescriptions made by hand, at home visit, or in nursing homes are not included if they are not added by the GP in the electronic medical file of the patient. In addition, only OACs prescribed by GPs are recorded in the database, and not prescriptions made by specialists. Furthermore, it could be that people do not receive an OAC because they have a contraindication for it or because they are at high risk of major bleeding, as measured by the HAS-BLED or the HEMORR2HAGES scores. Unfortunately, these scores could not be calculated based on data included in the Intego database.

It is presently not known to what extent the INTEGO database reflects overall Belgian practice. The Intego patient population is representative for the Flemish population regarding age and gender and represents ±2% of the total Flemish population. As previously studied the prevalence of AF in the INTEGO database is comparable to the prevalence in the Rotterdam study and the incidence in INTEGO was slightly lower than the incidence in the Rotterdam Study.

10 ANALYSIS OF BELGIAN DATA

10.1 Introduction

The purpose of the chapter is to analyse the evolution of the use of anticoagulants over the years in Belgium, to identify the clinical profile of the AF patients treated with an anticoagulant, and to document the changes in anticoagulation practice since the introduction and reimbursement of the NOACs on the Belgian market.

10.2 Methods

10.2.1 General Methodology

Databases

The databases used for this section of the project is the Belgian Inter-Mutualistic Agency (IMA/AIM) database. It contains, for each individual patient, healthcare reimbursed expenditure (both in ambulatory and hospital setting), reimbursed pharmaceuticals data and population characteristics data. The period covered is from 2004 to 2015 for pharmaceuticals data, and from 2004 to 2014 for demographic data. Data of 2015 were not fully complete at the time of analysis but the pharmaceuticals data are used to have at least one year of follow-up in our analyses. Ambulatory pharmaceuticals data anno 2015 can be assumed to be almost complete.

Selection criteria and definitions

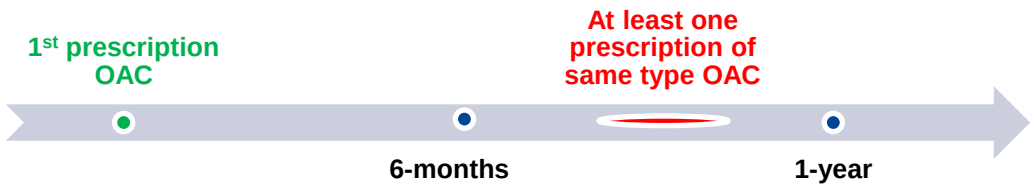
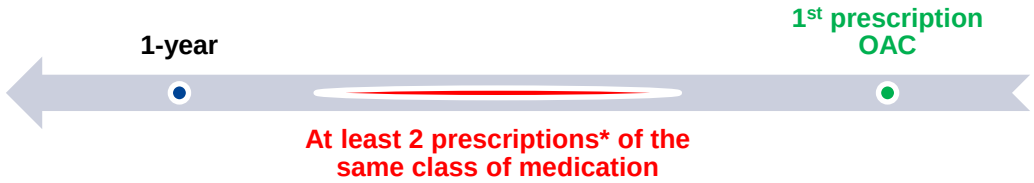
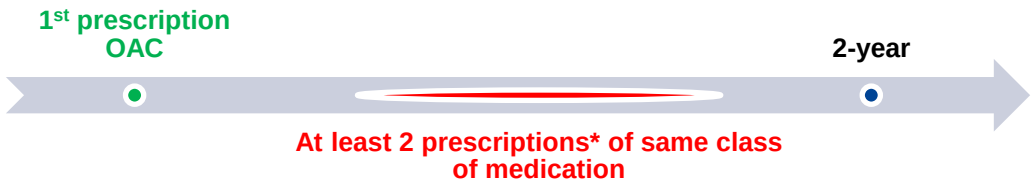
The identification of the patients taking an anticoagulant was made based on the ATC codes linked to the medications (cf. Chapter 9).
In order to identify patients that are being prescribed life-long anticoagulation for the prevention of stroke in AF, and to distinguish them from those that are taking an anticoagulant for other indications, such as venous thromboembolism, we defined the concept of "***chronic AF user***".

In order to assess the risk of stroke of chronic AF users, we use proxies for the CHA_2DS_2-VASc and $CHADS_2$ scores based on pharmaceuticals data from the IMA – AIM database. The definitions of medications used in the proxies and the definitions of the proxies are the same as those described in Chapter 9. T_0 is defined here as the first date of prescription of an anticoagulant included in the database.

Table 42 - Definitions

	Definition
NOAC user	Patients with at least one pack of medication under ATC codes in ambulatory delivery: **B01AF01** (Rivaroxaban), **B01AF02** (Apixaban), **B01AE07** (Dabigatran etexilate)
VKA user	Patients with at least one pack of medication under ATC codes in ambulatory delivery: **B01AA03** (Warfarin), **B01AA04** (Phenprocoumon), **B01AA07** (Acenocoumarol)
VKA/NOAC Chronic AF user	A VKA/NOAC chronic Atrial Fibrillation (AF) user is defined as a patient with at least one other prescription of VKA/NOAC between 6 months and one year after first prescription of VKA/NOAC, respectively. In case there is a delay of more than one year between 2 prescriptions, the first date will not be considered in the definition of chronicity.
Antiplatelets (except aspirin)	ATC codes: B01ACxx with xx different than [06;08;09;11;13;16;17]
Aspirin (acetylsalicylic acid)	ATC code= B01AC06 or N02BA01
Renal function test	Nomenclature codes = 540330 or 540341
INR	Nomenclature codes = 554573 and 554584

Figure 22 − Graphical display of definition

Definition	Figure
VKA/NOAC chronic AF user	
medication taken for chronic care before anticoagulation medication (prior medications)	
medication taken for chronic care after anticoagulation medication (co-medications)	

**except for antiplatelets – at least 1 prescription*

10.3 Data limitations

Working with administrative databases is subjected to some limitations in interpretation of the results. Here are the limitations encountered in this project:

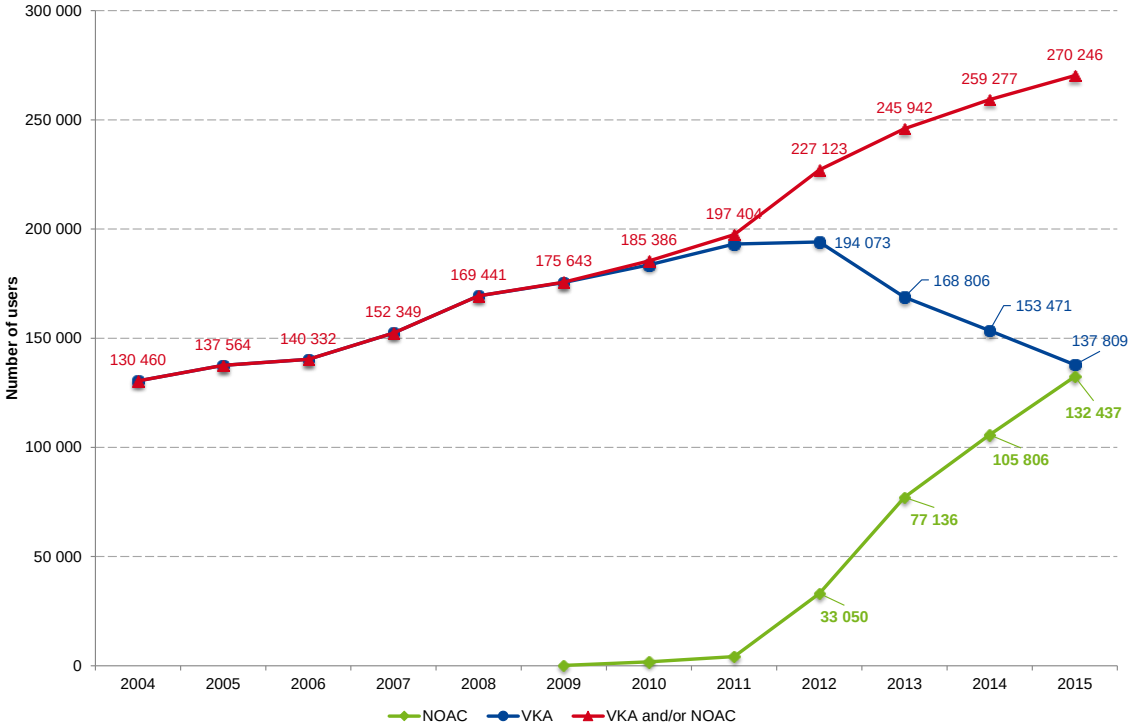
- IMA database contains only the reimbursed data
- The database does not contain diagnoses, therefore patients with AF have to be identified indirectly. We assume that most patients that are taking an anticoagulant for more than 1 year have a diagnosis of AF. We defined those patients as "***chronic AF user***".
- The prescription of certain drugs is used for identifying diseases. For example, a patient taking an antidiabetic is considered a diabetic, a patient taking an ACE inhibitor can be considered having hypertension and/or heart failure ...
- Patient switching from VKA to NOAC but without a new prescription of the NOAC in the 6 to 12-months after first NOAC prescription were not consider into our analyses.

10.4 Results

10.4.1 Evolution over time

The number of patients with at least one prescription of an anticoagulant (VKA and/or NOAC) almost doubled in 10 years (from 130 460 patients in 2004, to 259 277 in 2014 - Figure 23). In 2014, around 2.5% of the population has taken at least one anticoagulant medication. From Figure 24, we can see that the most frequent anticoagulant prescribed was the Acenocoumarol until 2014 (around 66 200 patients). Later on, it was Rivaroxaban (estimation of 72 500 patients in 2015).

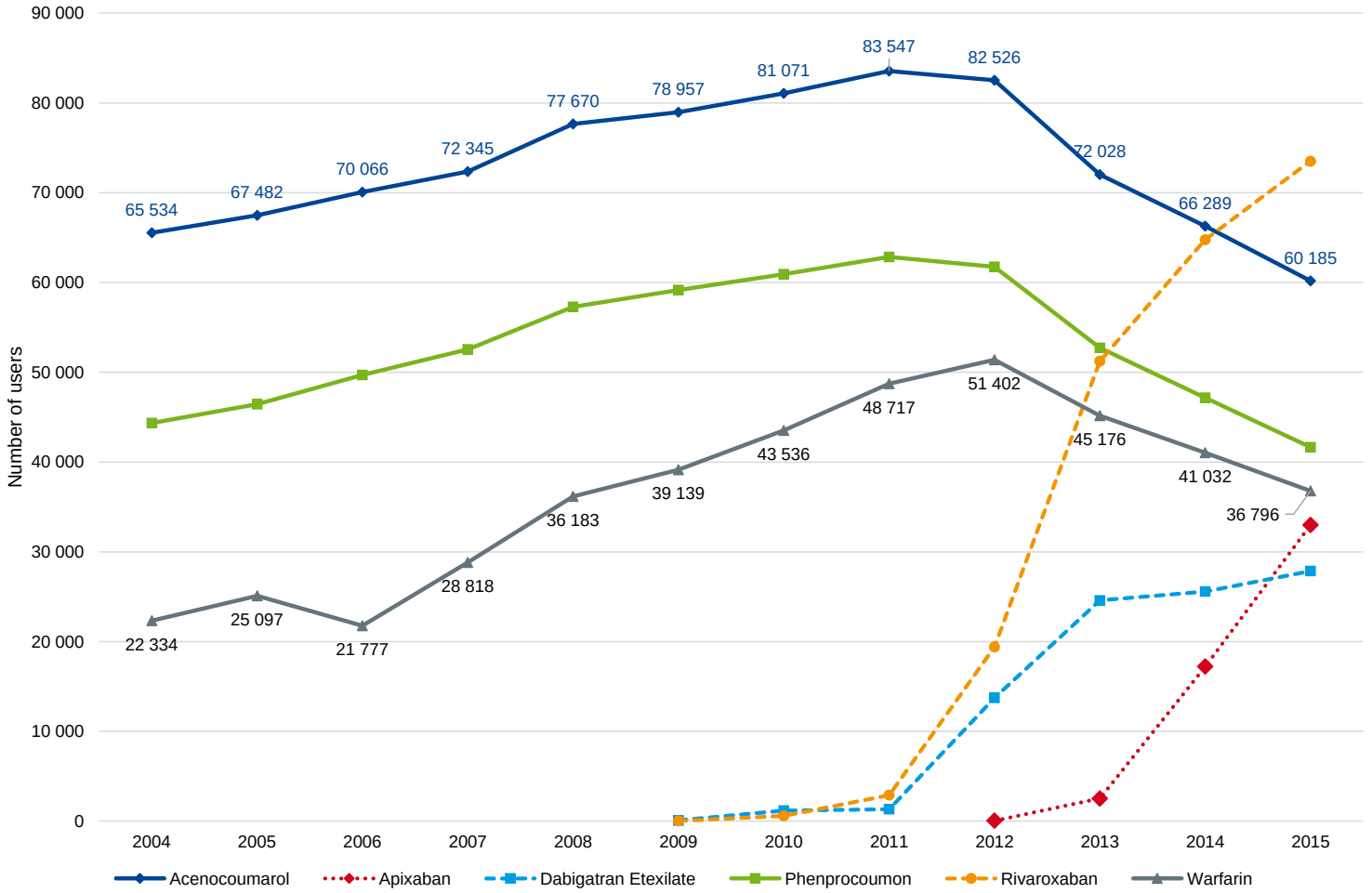
Figure 23 – Number of patients with at least one prescription of an anticoagulant (2004 – 2015)



**The 2015 data can be subject to certain adjustments/rectifications.*

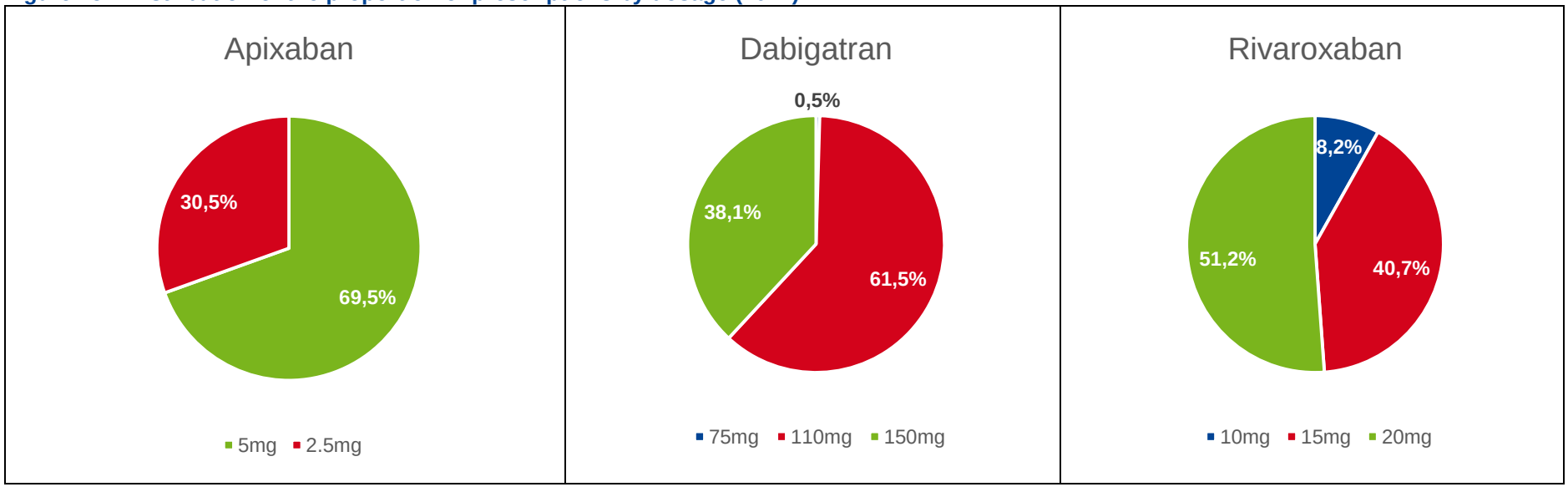
Source: IMA database

Figure 24 – Number of patients with at least one prescription by anticoagulant (2004 – 2015)



**All data on 2015 are not available in the IMA database. Source: IMA database*

Figure 25 – Distribution of the proportion of prescriptions by dosage (2014)



10.4.2 Profile of the anticoagulant users

The following conventions will be taken for the analyses on the profile of the anticoagulant users:

- **Year of first use of anticoagulant**: year of the first prescription of anticoagulant (whether VKA or NOAC);
- **Type of first anticoagulant** = VKA or NOAC depending on the first prescription of anticoagulant registered in the IMA database
- **Evaluable patients**: Patients with first prescription of anticoagulant between 2005 and 2014 and considered as chronic AF user. Patients with prescription of first anticoagulant medication in 2004 were not considered because there is no certainty that the patient was not yet under this medication before 2004. The definition of "chronic AF users" (see Table 42) was built in order to identify patients with atrial fibrillation.

From Table 44, we can see that the majority (60%) of new chronic AF users during the period 2012-2014 were receiving NOAC as first choice of OAC. Moreover, Rivaroxaban was the main OAC prescribed (34%) in newly diagnosed AF chronic users during this period.

Table 43 – Age at first prescription (Chronic AF users)

	VKA	NOAC	All
Period 2005-2011	N=154 016	N=139	N=154 155
Missing	112 (0.1%)	0 (0.01%)	112 (0.1%)
< 65y	37 711 (24.5%)	54 (38.8%)	37 765 (24.5%)
65y to <75y	39 735 (25.8%)	59 (42.4%)	39 794 (25.8%)
75y to <85y	58 562 (38.0%)	25 (18.0%)	58 587 (38.0%)
85y+	17 896 (11.6%)	1 (0.7%)	17 897 (11.6%)
Median (Q1-Q3)	74 (65 – 81)	67 (60-72)	
Period 2012-2014	N=39 424	N=59 095	N=98 519
Missing	14 (0.01%)	15 (0.01%)	29 (0.0%)
< 65y	12 525 (31.8%)	5 816 (9.8%)	18 341 (18.6%)
65y to <75y	8 935 (22.7%)	17 697 (29.9%)	26 632 (27.0%)
75y to <85y	12 301 (31.2%)	25 108 (42.5%)	37 409 (38.0%)
85y+	5 649 (14.3%)	10 459 (17.7%)	16 108 (16.4%)
Median (Q1-Q3)	73 (61-81)	77 (70-83)	

Source: IMA – AIM database

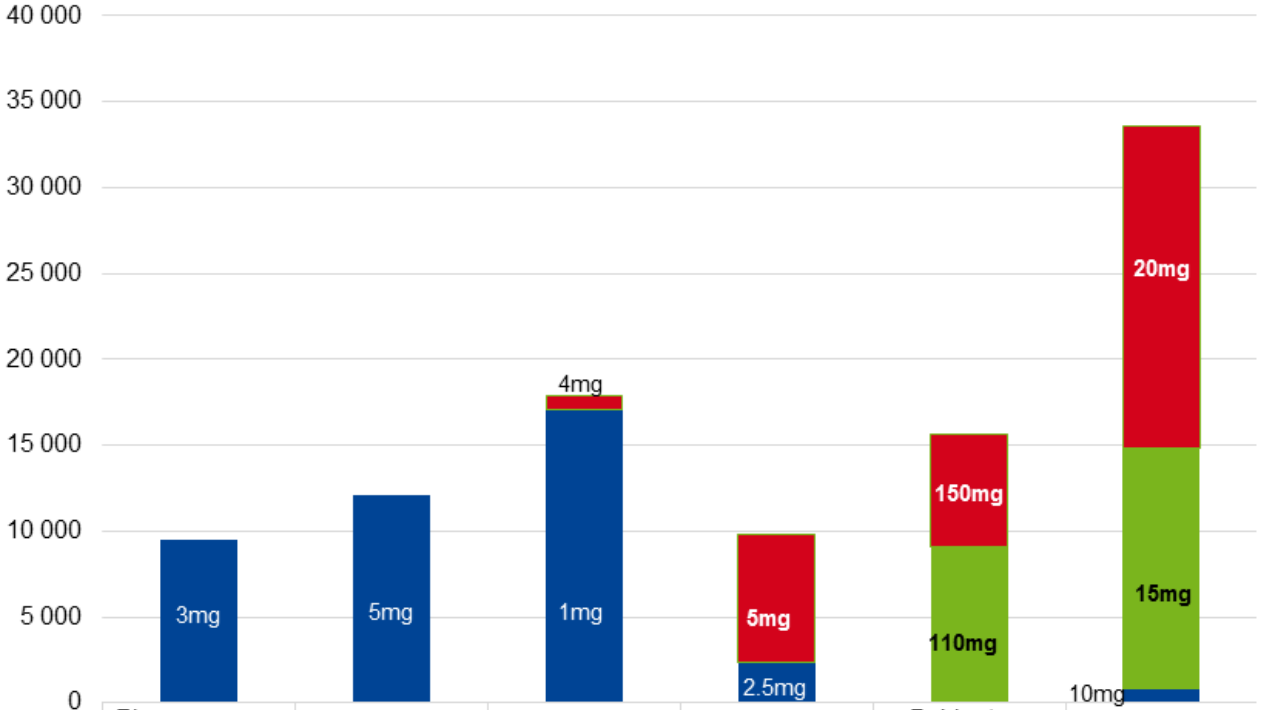
Table 44 – Number of Chronic AF users by period

First OAC prescribed	Period 2005-2011 N=154 155 n(%)	Period 2012-2014 N=98 519 n(%)	Overall N=252 674 n(%)
VKA	**154 016 (99.9%)**	**39 424 (40.0%)**	**193 440 (76.6%)**
Acenocoumarol	68 012 (44.1%)	17 880 (18.1%)	85 892 (34.0%)
Warfarin	37 947 (24.6%)	12 068 (12.2%)	50 015 (19.8%)
Phenprocoumon	48 057 (31.2%)	9 476 (9.6%)	57 533 (22.8%)
NOAC	**139 (0.1%)**	**59 095 (60.0%)**	**59 234 (23.4%)**
Rivaroxaban	89 (0.1%)	33 613 (34.1%)	33 702 (13.3%)
Dabigatran Etexilate	50 (0.0%)	15 668 (15.9%)	15 718 (6.2%)
Apixaban	0 (0.0%)	9 814 (10.0%)	9 814 (3.9%)

Different doses of the oral anticoagulants are available on the market. For VKA, there is only one dose by OAC except for Acenocoumarol which exists in tabs of 1mg and 4mg. From Figure 26, we see that the majority (76%) of patients taking Apixaban (*Eliquis*®) as first OAC were prescribed the dose of 5mg. For patient under Dabigatran Etexilate (*Pradaxa*®), 58% and 48% of the patients were prescribed tabs of 110mg and 150mg respectively. For Rivaroxaban (*Xarelto*®) users, the 20mg was the dose the most prescribed (56%) followed by the 15mg (42%).

Figure 27 shows the dosage of NOAC as first intent according to the age of patients (below 80 years or 80+). We see that, in general, for Dabigatran Etexilate, elder patients are given more frequently low or medium dose formulation (110mg) than highest dose formulation (150mg). This trends is less perceivable for patients taking Rivaroxaban or Apixaban as first intent. Below the age of 80 years, 6.8% of apixaban users take the 2.5 mg dose, 33.1% of the dabigatran users take the 110 mg dose and 25.9% of the rivaroxaban users take the 15 mg dose. For patients of 80+years, those percentages raise to respectively, 49.7% for Apixaban 2.5mg, 96.6% for Dabigatran 110mg and 66.3%for Rivaroxaban 15mg.

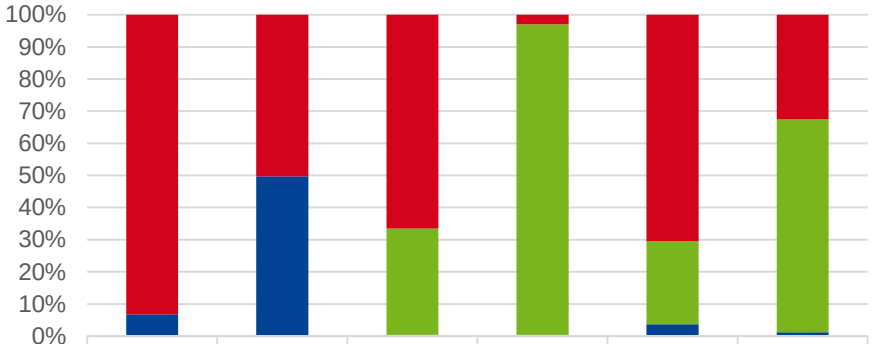
Figure 26 − Number of patients by type and dosage of first prescribed OAC - Chronic AF users 2012-2014



	Phenprocoumon	Warfarin	Acenocoumarol	Apixaban	Dabigatran Etexilate	Rivaroxaban
	VKA				NOAC	
High dosage			802	7 487	6 571	18 793
Medium dosage					9 041	14 001
Low dosage	9 476	12 068	17 078	2 327	56	819

Source: IMA – AIM database

Figure 27 − Distribution of patients by dosage of NOAC and age category (2012-2014)



	< 80y	80y+	< 80y	80y+	< 80y	80y+
	APIXABAN		DABIGATRAN ETEXILATE		RIVAROXABAN	
High	93,2%	50,3%	66,5%	3,0%	70,4%	32,6%
Medium			33,1%	96,6%	25,9%	66,3%
Low	6,8%	49,7%	0,4%	0,4%	3,6%	1,2%

Source: IMA – AIM database

10.4.2.1 Patients characteristics

As described in Table 45, for the period 2012-2014, the proportion of patients of 65y+ is higher in the group of patients with prescribed NOAC (90.2%) than in the group of patients with prescribed VKA (68.2%) as first anticoagulant drug intent. This is probably induced by the Belgian reimbursement conditions, favouring VKAs in younger patients. In Chapter 9, based on INTEGO data, we saw that those proportions of patients aged 65+ were 84.4% and 70.9% respectively for NOAC and VKA users which shows that patients included in the INTEGO database does not completely match the patients included in our analyses at least based on the age. There was around 50% of males and females.

Table 45 – Age at first prescription (Chronic AF users)

	VKA	NOAC	All
Period 2005-2011	N=154 016	N=139	N=154 155
Missing	112 (0.1%)	0 (0%)	112 (0.1%)
< 80y	108 311 (70.3%)	136 (97.8%)	108 447 (70.3%)
80y+	45 592 (29.6%)	3 (2.2%)	45 595 (29.6%)
Median (Q1-Q3)	74 (65 – 81)	67 (60-72)	74 (65 - 81)
Period 2012-2014	N=39 424	N=59 095	N=98 519
Missing	14 (0.01%)	15 (0.01%)	29 (0.0%)
< 80y	27 318 (69.3%)	36 058 (61.0%)	63 376 (64.3%)
80+	12 092 (30.7%)	23 022 (39.0%)	35 114 (35.6%)
Median (Q1-Q3)	73 (61-81)	77 (70-83)	76 (67 - 82)

Source: IMA – AIM database

Table 46 – Age at first prescription of NOAC (Chronic NOAC AF users) – Period 2012-2014

	Apixaban N=9 814	Dabigatran N=15 668	Rivaroxaban N=33 613	All NOAC N=59 095
Period 2012-2014				
Missing	2 (0.0%)	7 (0.0%)	6 (0.0%)	15 (0.0%)
< 80y	5 940 (60.5%)	9 554 (61.0%)	20 564 (61.2%)	36 058 (61.0%)
80+	3 872 (39.5%)	6 107 (39.0%)	13 043 (38.8%)	23 022 (39.0%)
Median (Q1-Q3)	77 (70 - 83)	77 (70. - 82)	77.0 (69 – 83)	77 (70 - 83)

Source: IMA – AIM database

10.4.2.2 Assessment of baseline stroke risk

In order to estimate the prescription of anticoagulants by baseline stroke risk, we estimated CHA2DS2-VASc scores based on age, gender and pharmaceutical data. The possible outcomes in this exercise were CHA2DS2-VASc score=0, score=1 or score>1. If a patient took a drug that could only indicate 1 disease (e.g. antidiabetic indicates diabetes), this particular drug was assigned 1 point. For calcium antagonists, we considered dihidropyridine derivatives indicative for hypertension only (neglecting their potential use for angina pectoris). Diltiazem and verapamil could be used for treating hypertension or for rate control in AF. Although in case of rate control, they would not need 1 point in the CHA2DS2-VASc score, we nevertheless attributed 1 point since it might have been that a patient was taking this drug for hypertension. A patient taking a diuretic, an ACE inhibitor, or an AT-II receptor blocker was classified in the category CHA2DS2-VASc score>1 since any of these drugs might have been indicated for more than 1 cardiovascular disease. In this way, we remain conservative, i.e. we avoid misclassifying patients in the lower risk

(CHA2DS2-VASc 0 or 1) strata. For example, a man, 60 yrs. old, with AF who takes an ACE inhibitor will be attributed a score of >1, although he might be receiving this drug only for hypertension (and hence would have a score=1).

An overestimation of AF patients with a CHA2DS2-VASc=0 score may nevertheless still result from the (inevitable) inclusion of patients with recurrent thromboembolic disease, who have no associated cardiovascular disease (they may even have no AF).

The use of beta-blockers remains problematic in assessing CHA2DS2-VASc score. Many AF patients use beta blockers for rate control and in the absence of other disease we would not give them a CHA2DS2-VASc point. Other AF patients could however use a beta blocker for hypertension, heart failure and/or for secondary prevention after a myocardial infarction. Since we don't know the proportion of patients in each of those two categories (rate control vs. other indications) we calculated two proxy scores: one in which the use of a beta-blocker was given 1 point (i.e. the beta-blocker is considered an indication for an associated cardiovascular disease) and one in which the use of a beta-blocker was given 0 points (i.e. the beta-blocker is considered to be used for rate control only).

These proxy scores for CHA2DS2-VASc score built on the pharmaceutical data was validated (cf. Chapter 9) on a sample of patients from INTEGO database. For the CHADS2, it was not so obvious and therefore we decide not to use this proxy in our analyses. Therefore, we used only the proxy for CHA2DS2-VASc score in following analyses.

The proportion of chronic AF users with a proxy CHA2DS2-VASc score=0 in the most conservative approach (Table 47 and Figure 28) has declined from 6.7% (2005-2011) to 4.1% (2012-2014). A similar trend was observed in patients with a proxy CHA2DS2-VASc=1, showing a respective decline from 11.0 to 7.7%. These trends may indicate a diminishing tendency of overtreatment. Patients starting treatment with a NOAC had a higher proxy CHA2DS2-VASc but that can at least be explained partly by their higher age, induced by reimbursement restrictions for NOACs. 90% of NOAC users are aged above 65 yrs. (and therefore with already 1 point for the score determination) compared to a bit less than 70% for VKA users.

Table 47 – Proxy CHA2DS2-VASc score at the time of first prescription (Chronic AF users) – conservative approach

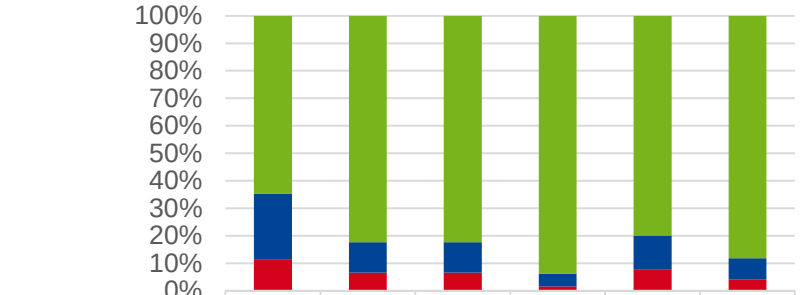
Period	VKA	NOAC	ALL
2005-2011	**N=154 015**	**N=139**	**N=154 154**
Proxy CHA2DS2-VASc Score = 0	10 335 (6.7%)	16 (11.5%)	10 351 (6.7%)
Proxy CHA2DS2-VASc Score = 1	16 848 (10.9%)	33 (23.7%)	16 881 (11.0%)
Proxy CHA2DS2-VASc Score > 1	126 777 (82.3%)	90 (64.7%)	126 867 (82.3%)
Missing	55 (0.01%)	0 (0%)	55 (0.01%)
2012-2014	**N=39 424**	**N=59 095**	**N=98 519**
Proxy CHA2DS2-VASc Score = 0	3 049 (7.7%)	998 (1.7%)	4 047 (4.1%)
Proxy CHA2DS2-VASc Score = 1	4 888 (12.4%)	2 744 (4.6%)	7 632 (7.7%)
Proxy CHA2DS2-VASc Score > 1	31 477 (79.8%)	55 348 (93.7%)	86 825 (88.1%)
Missing	10 (0.01%)	5 (0.01%)	15 (0.01%)

Source: IMA – AIM database

From a more liberal approach (all beta blockers used for rate control), we see that the percentage of patients with proxy CHA2DS2-VASc = 1 is much higher but the percentage of patients with CHA2DS2-VASc = 0 does not increase much (Figure 28).

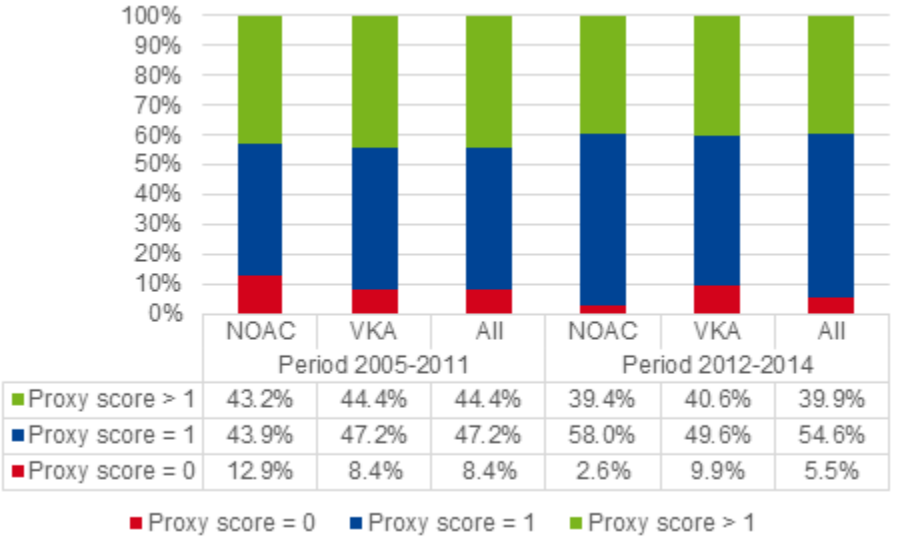
Figure 28 − Proxy CHA2DS2-VASc scores according to conservative and liberal approach

Beta-blocker indicates associated cardiovascular disease



	2005-2011			2012-2014		
	NOAC	VKA	ALL	NOAC	VKA	ALL
Proxy score > 1	64,7%	82,3%	82,3%	93,7%	79,8%	88,1%
Proxy score = 1	23,7%	10,9%	11,0%	4,6%	12,4%	7,7%
Proxy score = 0	11,5%	6,7%	6,7%	1,7%	7,7%	4,1%

Beta-blocker is used for rate control



	Period 2005-2011			Period 2012-2014		
	NOAC	VKA	All	NOAC	VKA	All
Proxy score > 1	43.2%	44.4%	44.4%	39.4%	40.6%	39.9%
Proxy score = 1	43.9%	47.2%	47.2%	58.0%	49.6%	54.6%
Proxy score = 0	12.9%	8.4%	8.4%	2.6%	9.9%	5.5%

10.4.2.3 Prior and concomitant medications

Table 48 shows that about half of the patients starting anticoagulation medication in the period 2012-2014 took beta-blockers in the year preceding the start of OAC treatment, and about one third was also treated with aspirin or another antiplatelet drug. An increased risk of bleeding induced by the combined use of OAC and antiplatelets has been documented, and guidelines recommend to strictly limit this combination in the context of acute coronary syndromes or stenting.[164] Table 49 shows the number of patients using a prior medication which was considered in the determination of the CHA2DS2-VASc score. For the period 2012-2014, small differences were observed between the VKA and NOAC chronic users.

Table 48 – Prior medication* in the year before first OAC intake (Chronic AF users)

	VKA	NOAC	All
Period 2005-2011	N=154 015	N=139	N=154 154
Beta-blockers	60 975 (39.6%)	32 (23.0%)	61 007 (39.6%)
Verapamil-Diltiazem	6 404 (4.2%)	1 (0.7%)	6 405 (4.2%)
Antiplatelet (excluding aspirin)	14 665 (9.5%)	1 (0.7%)	14 666 (9.5%)
Aspirin	18 613 (12.1%)	23 (16.5%)	18 636 (12.1%)
Aspirin and/or antiplatelet	31 005 (20.1%)	24 (17.3%)	31 029 (20.1%)
Period 2012-2014	N=39 424	N=59 095	N=98 519
Beta-blockers	16 313 (41.4%)	32 569 (55.1%)	48 882 (**49.6%**)
Verapamil-Diltiazem	1 216 (3.1%)	2 389 (4.0%)	3 605 (3.7%)
Antiplatelet (excluding aspirin)	2 943 (7.5%)	4 486 (7.6%)	7 429 (7.5%)
Aspirin	11 296 (28.7%)	20 030 (33.9%)	31 326 (31.8%)
Aspirin and/or antiplatelet	13 138 (33.3%)	22 808 (38.6%)	35 946 (36.5%)

Source: IMA – AIM database

**prior medication = at least 2 prescriptions of the medications except for antiplatelet (at least one prescription) in the year preceding first prescription of OAC.*

Table 49 – Other prior medications* in the year before first OAC intake (Chronic AF users)

	VKA	NOAC	All
Period 2005-2011	N=154 015	N=139	N=154 154
Diabetes	24 226 (15.7%)	4 (2.9%)	24 230 (15.7%)
AT2	24 268 (15.8%)	22 (15.8%)	24 290 (15.8%)
ACE	42 530 (27.6%)	20 (14.4%)	42 550 (27.6%)
Diuretics	46 893 (30.4%)	20 (14.4%)	46 913 (30.4%)
Calcium	27 642 (17.9%)	13 (9.4%)	27 655 (17.9%)
Period 2012-2014	N=39 424	N=59 095	N=98 519
Diabetes	7 188 (18.2%)	10 801 (18.3%)	17 989 (18.3%)
AT2	6 929 (17.6%)	13 230 (22.4%)	20 159 (20.5%)
ACE	10 471 (26.6%)	18 327 (31.0%)	28 798 (29.2%)
Diuretics	11 484 (29.1%)	17 615 (29.8%)	29 099 (29.5%)
Calcium	6 626 (16.8%)	11 399 (19.3%)	18 025 (18.3%)

Source: IMA – AIM database

**prior medication = at least 2 prescriptions of the medications in the year preceding first prescription of OAC.*

As described in Table 50, for first OAC users in the years 2005 to 2011, there were 4% who had at least one prescription of a non-aspirin antiplatelet and 14% who had at least 2 prescriptions of aspirin within the 2 years following the first OAC intake, i.e. concomitantly to the AOC. Those percentages were respectively, 3% and 16% for first OAC users in the years 2012 to 2014. In the last period, the percentage of patients taking aspirin in combination with a VKA (21%) was higher than in those taking a NOAC (13%) as first intent, although this difference may not be relevant given the low absolute numbers in the NOAC population.

Table 50 – Co-medications* (Chronic AF users)

	VKA	NOAC	All
Period 2005-2011	N=154 015	N=139	N=154 154
Antiplatelets (excluding aspirin)	6 327 (4.1%)	2 (1.4%)	6 329 (4.1%)
Aspirin	21 309 (13.8%)	30 (21.6%)	21 339 (13.8%)
Aspirine and/or Antiplatelets	26 056 (16.9%)	32 (23.0%)	26 088 (16.9%)
Aspirin alone	19 729 (12.8%)	30 (21.6%)	19 759 (12.8%)
Period 2012-2014	N=39 424	N=59 095	N=98 519
Antiplatelets (excluding aspirin)	1 456 (3.7%)	1 498 (2.5%)	2 954 (3.0%)
Aspirin	8 341 (21.2%)	7 633 (12.9%)	15 974 (16.2%)
Aspirin and/or Antiplatelets	9 224 (23.4%)	8616 (14.6%)	17 840 (18.1%)
Aspirin alone	7 768 (19.7%)	7118 (12.0%)	14 886 (15.1%)

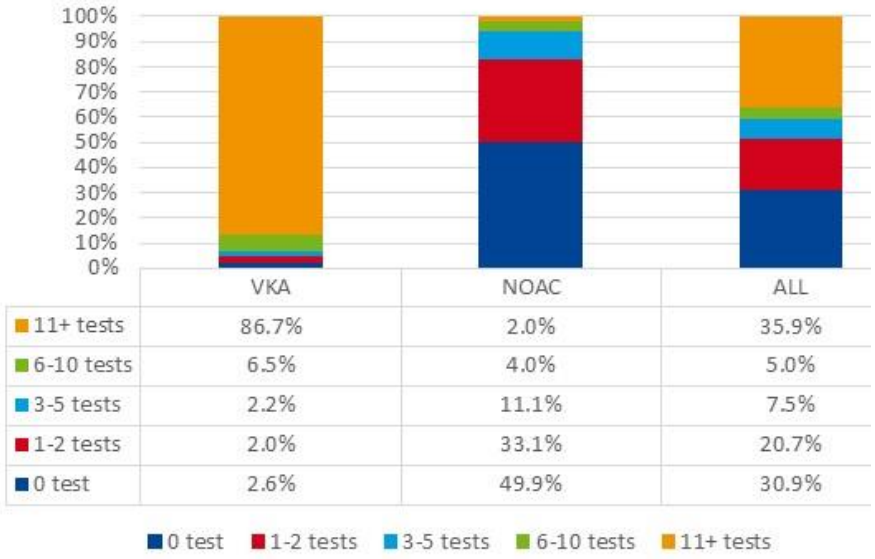
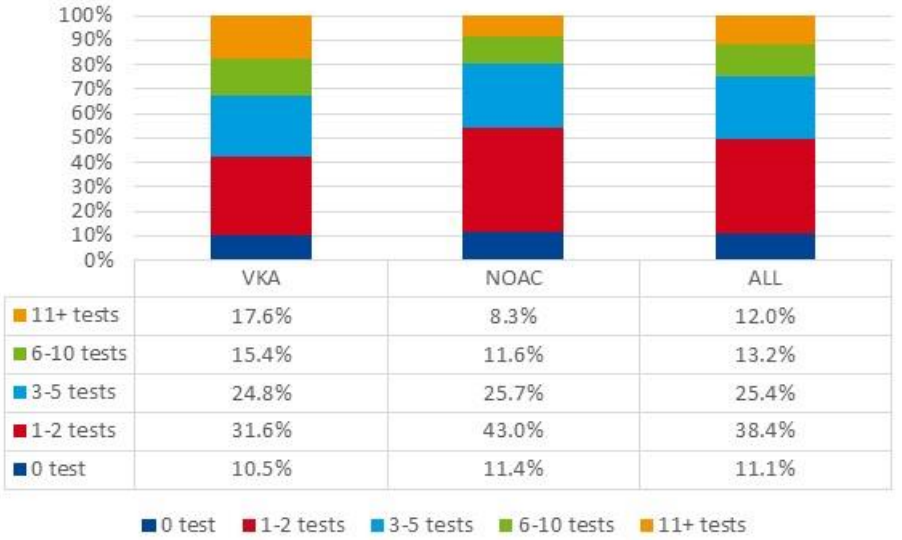
Source: IMA – AIM database

**Co-medication = at least 2 prescriptions of the medications except for antiplatelet (at least one prescription) in the 2 years following first prescription of OAC.*

10.4.2.4 Laboratory Tests

Not unexpectedly, there is a difference in the number of INR tests performed between the VKA chronic AF users and NOAC chronic AF users. The number of INR tests performed might be (slightly) underestimated since non-reimbursed point of care tests could not counted. According to our external experts, this should however only represent a limited number of cases. Figure 29 shows that for period 2012-2014, there were 87% of patients under VKA who had more than 10 test performed in the year following first prescription and 50% of patients under NOAC had no tests performed at all in the year. For renal tests (creatinine), we see from the figure that the patients under VKA have also slightly more renal test performed than patient under NOAC.

Figure 29 − Percentage of patients by number of tests performed in the year following first OAC prescription for chronic use – Chronic AF users (period 2012-2014)

Number of INR tests	Number of renal tests
	
VKA: Median (Q1-Q3) = 19 (14 – 27) NOAC: Median (Q1-Q3) = 1 (0 – 2)	VKA: Median (Q1-Q3) = 3 (1 – 6) NOAC: Median (Q1-Q3) = 2 (2 – 5)

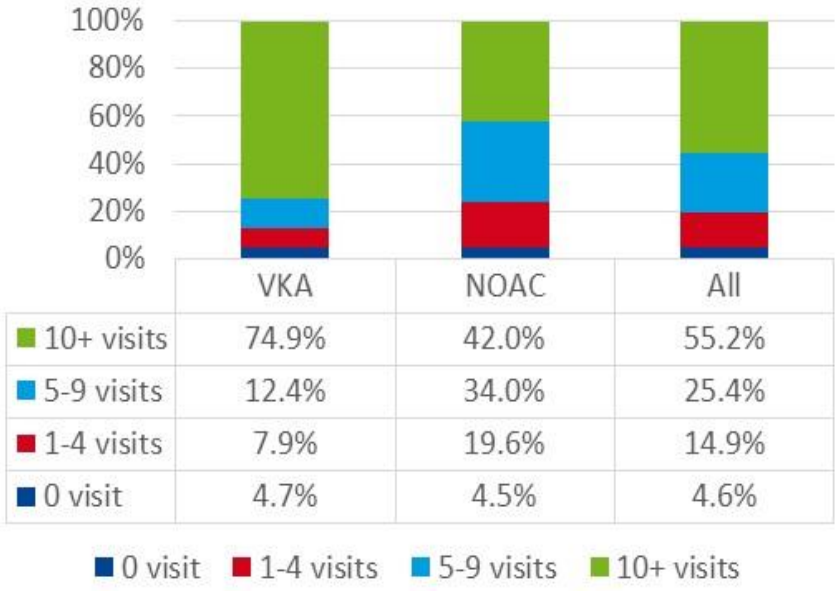
Source: IMA – AIM database. INR test: nomenclature codes 554573 & 554584. Renal test: nomenclature codes: 540330 & 540341.

10.4.2.5 Visits/consultations to Physicians

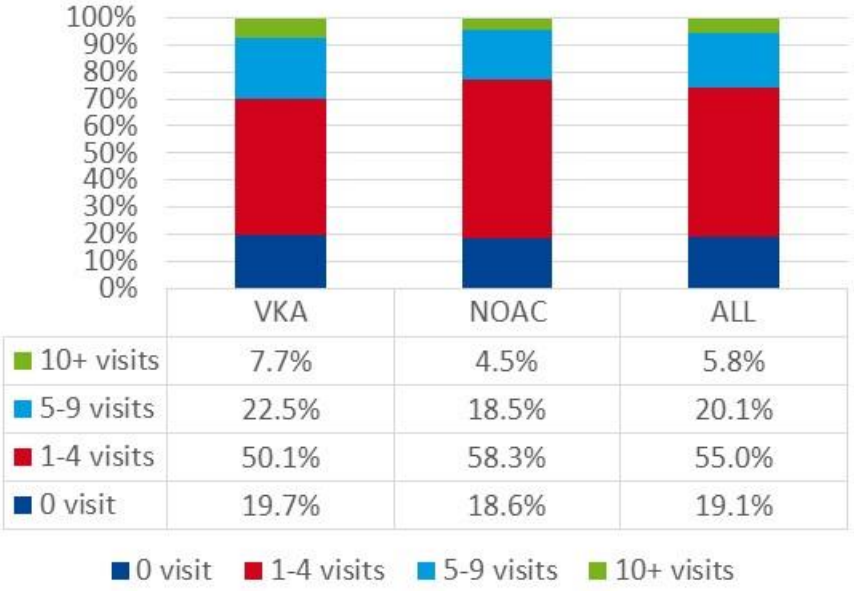
From Figure 30, we see that patients taking VKA had more visits to the GP in the year following first OAC prescriptions than NOAC chronic users. Seventy five percent (75%) of VKA users have at least 10 visits to the GP (median (Q1-Q3): 17 visits (9-24)). They have also more visit to the specialists (in cardiology or not) than NOAC chronic users. However, overall, there is one fifth (20%) of chronic AF users who have no visiting any specialist in the year following first prescription and around one third (33%) no specialist in cardiology.

Figure 30 − Number of visits in the year following first OAC prescription for chronic use– Chronic AF users (period 2012-2014)

Number of visits to the GP in the year following first prescription



Number of visits to a Specialist (in cardiology or not) in the year following first prescription



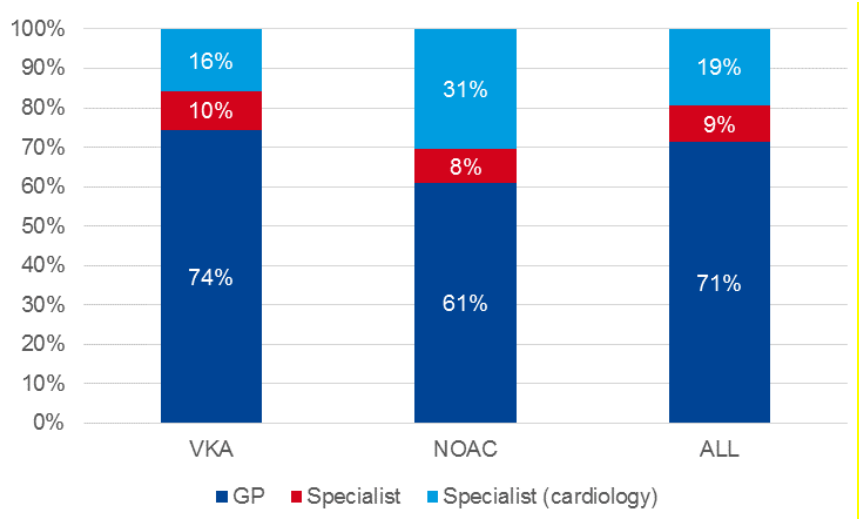
VKA: Median (Q1-Q3) = 17 (9 – 24)	VKA: Median (Q1-Q3) = 3 (1 – 5)
NOAC: Median (Q1-Q3) = 8 (5 -13)	NOAC: Median (Q1-Q3) =2 (1 – 4)

Source: IMA – AIM database

10.4.2.6 First prescriber of OAC

From our data (Figure 31), it appears that the first OAC prescription was performed by a General Practitioner (GP) (61% in NOAC chronic users and 74% VKA chronic users). The specialist in cardiology prescribed the first OAC in 30% of the NOAC chronic users versus in 16% in VKA chronic users. These proportions are somewhat unexpected. It might be that cardiologists propose a GP to start anticoagulation, but that the very act of making the prescription is done by the GP.

Figure 31 − First physician prescribing OAC (Period 2005-2014)



Source: IMA – AIM database

10.4.2.7 Switchers

Overall the VKA chronic AF users who did not die before 2012, there were 14% of them who switch to the use of NOAC in a chronic way (meaning that they had at least one second prescription of NOAC between 6mths and 1 year after the first NOAC prescription). For 4% of chronic VKA users, they have at least one prescription of NOAC but they were not considered as chronic users. For patients prescribed VKA during the period 2012-2014, there were less switchers probably due to the fact that the period of observation is smaller and more of them are prescribed a NOAC from the start.

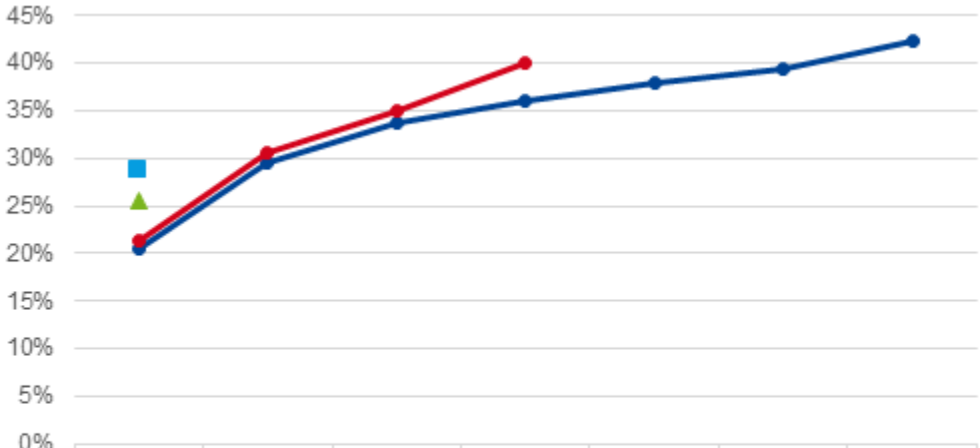
Table 51 − Switchers between VKA and NOAC – VKA Chronic AF users

	Period VKA first prescription		
	2005-2011	2012-2014	Total
	N=123 459	N=37 657	N=161 116
No NOAC use	98 885 (80.1%)	32 802 (87.1%)	131 687 (81.7%)
Chronic NOAC users	20 194 (16.4%)	2 830 (7.5%)	23 024 (14.3%)
NOAC use but not chronic	4 380 (3.5%)	2 025 (5.4%)	6 405 (4.0%)

10.4.2.8 Persistence

The compliance to the medication is not an easy measure to compute through administrative data and even more to interpret in term of comparison between treatments. The defined daily dose (DDD) used in this measure is usually the dose recommended in a standard case. Therefore, we decided to work on a measure that estimated the persistence to treatment. Mainly, we consider that the patient is persistent to the treatment if there is no gap of more than 6 months between 2 prescriptions delivered in a pharmacy (i.e. that the treatment is not discontinued more than maximum 6 months). As shown in Figure 32, there are around 20% of patients starting a VKA between 2005 and 2011 that “discontinued” their treatment at least 6-months. For patients starting the anticoagulant treatment between 2012 and 2014, the percentage was of 25% to 29%, respectively for VKA and NOAC chronic users. We need more perspective on the data for the new users in order to interpret those last results cautiously. Our data correspond with the proportion of patients discontinuing oral anticoagulation as reported in the pivotal NOAC trials.

Figure 32 − Percentage of patients with a gap of at least 6-months between 2 prescriptions by period of first prescription (Chronic users – 2005-2014)



	1-year	2-year	3-year	4-year	5-year	6-year	7-year
Period 2006-2008 VKA	20.4%	29.6%	33.6%	35.9%	37.8%	39.5%	42.3%
Period 2009-2011 VKA	21.4%	30.6%	34.9%	40.0%			
Period 2012-2014 VKA	25.6%						
Period 2012-2014 NOAC	28.7%						

Source: IMA – AIM database

10.5 Discussion

Anticoagulants have been increasingly prescribed since the early 2000s. The number of patients prescribed with an anticoagulant more than doubled between 2004 (n=130,000) and 2014 (n=260,000). Since the introduction of NOACs on the Belgian market, they have gradually replaced VKAs, reaching a share of 40% of newly anticoagulated patients in 2012-2014 with an increasing trend towards more NOAC.

While rivaroxaban and apixaban became reimbursed for AF in 2012, apixaban was reimbursed in 2013. Sales took off sharply after their introduction. Dabigatran sales levelled from 2013 on, while those of apixaban and rivaroxaban continued to increase. In 2014 the Belgian market share of rivaroxaban was more than twice that of apixaban and dabigatran. Sixty percent of the patients under a NOACs in 2014 took at least rivaroxaban, 16% apixaban and 24% dabigatran. The fact that rivaroxaban is more often prescribed is probably at least partly due to the fact that it is the only NOAC that needs to be taken only once a day.

In order to identify patients with AF in whom lifelong treatment was anticipated (defined here as “chronic AF user”), we considered patients taking an anticoagulant for at least 1 year as having AF. Obviously this is an overestimation since there are other clinical indications for lifelong anticoagulation such as mechanical heart valves, recurrent venous thromboembolic disease, and some rare coagulation disorders. We could not find reliable numbers on this, but assume that about 80% of our “chronic AF users” are in fact patients with AF.

We analysed the dose of any anticoagulant at the moment of its first prescription and considered – at least for NOACs – that this dose was prescribed long term (Figure 26). NOACs are available in different doses (low, medium and high) as discussed in a previous chapter (Table 11). Dabigatran is available in 75, 110 and 150 mg, rivaroxaban in 10, 15 and 20 mg and apixaban in 2.5 and 5 mg. The lowest dose of dabigatran (75 mg) and rivaroxaban (10 mg) is available only for short-term postoperative prevention of VTE. The other doses, further designated as standard and reduced dose, can be prescribed in both AF and VTE disease. In both clinical indications, dose reductions apply, depending on age (80+ require reduced dose) and reduced renal function (clearance 15-30 mL/min). From our data it appears that in many patients (43% of NOAC users), the reduced dose of NOAC is prescribed: 58% dabigatran-110, 42% rivaroxaban-15, and 24% apixaban-2.5. These proportions are far higher than those reported in the NOAC RCTs, although they are often induced by Belgian reimbursement rules or safety warnings in guidelines. In the pivotal dabigatran trial, patients were equally randomised to the 110 and 150 mg doses.[54] In the rivaroxaban trial, 20.7% of patients received the low dose (15 mg).[19] In the pivotal apixaban study, 4.7% received the low dose of apixaban (2.5 mg).[60] If we analyse the proportion of reduced-dose prescription by age, for patients of 80+years, those percentages raise to respectively, 49.7% for apixaban 2.5mg, 96.6% for dabigatran 110mg and 66.3% for rivaroxaban 15mg. Of note, in RCTs, age was not a criterium for dose reduction, except in the ARISTOTLE trial in which apixaban dose was reduced to 2.5-mg twice a day in a subset of patients with two or more of the following criteria: an age of at least 80 years, a body weight of no more than 60 kg, or a serum creatinine level of 1.5 mg/dL or more.[60]

Similar observations from real world data have been published by other authors. In a Danish study, 55% of patients that were on dabigatran received the lower dose, similar to our data[165] In the XANTUS registry, 20.8% of rivaroxaban users were treated with the lower dose, similar to our data.[166] Data from the REVISIT-US study showed that the lower dose of apixaban was used in 15.5% of patients, about three times more often than in its pivotal clinical trial and somewhat less than in our data.[m] It is reported that current global prescription data of apixaban indicate that the reduced dose is used in at least in 25% of patients.[111] One of the reasons that physicians tend to prescribe the lower dose of a NOAC may be explained by their fear of bleeding, and the absence of a means to monitor the appropriateness of the prescribed dose. The use of the reduced NOAC doses that have not been adequately tested in RCTs may have important consequences.

In order to estimate the prescription of anticoagulants by baseline stroke risk, we estimated CHA2DS2-VASc scores from age, gender and pharmaceutical data. In our most conservative approach (all beta blockers indicating associated cardiovascular disease), we see in the period 2005-2011 6.7% score=0 and 11% score=1, versus 4.1% and 7.7% in 2012-2014,

[m] http://www.medpagetoday.com/cardiology/prevention/57483

respectively. In absolute terms, this corresponds to 4,000 to 5,400 patients. From a more liberal approach (all beta blockers used for rate control), the following proportions emerge: in the period 2005-2011 8.4% score=0 and 47.2% score=1, versus 5.5% and 54.6% in 2012-2014, respectively. In absolute terms, this corresponds to 7,600 to 53,800 patients.

The use of antiplatelets differed across the two study periods. Patients in whom an OAC was started in the period 2005-2011, were treated with an antiplatelet in the preceding year in 20.1% of cases. After the initiation of the OAC, the proportion of antiplatelet users dropped to 16.9%. In the period 2012-2014, a much higher proportion was previously treated with an antiplatelet (36.5%), dropping to 18.1% after the initiation of the OAC. In recent years, it has been stressed that this practice may lead to an increase of (intracranial) bleeding, at least in patients on VKA. The combined use of an oral anticoagulant and an antiplatelet is estimated to be appropriate in 10 to 15% of patients.[17, 164]

Since their introduction, NOACs have been promoted because of the absence of the need for regular monitoring, and the consequential potential for better adherence to treatment. Therefore, we assessed the use of laboratory tests and physician visits in our database. Patients on VKA on median have each year 17 GP visits, 3 specialist visits and 19 INR laboratory controls. Patients on NOAC have on median per year 8 GP visits, 2 specialist visits and 2 renal tests.

There were 14% of patients under VKA switching to NOAC after its reimbursement in 2012. Unfortunately, due to data restriction, we cannot assess the reasons for this switch.

After 1-year, there are around 20% to 30% of OAC users who discontinued the treatment more than 6-months. Due to short follow-up time in our data, we cannot see clear differences between types of OACs.

Key points

- **Reimbursement of NOACs for AF has been introduced in Belgium in 2012 and is dependent on patient characteristics (Chapter IV).**
- **The percentage of patients with a low risk of stroke (CHA_2DS_2-VASc score=0) and inappropriately taking OACs has decreased over the years.**
- **In the absence of clinical diagnoses, our IMA data do not allow to critically appraise anticoagulant treatment in patients with a CHA2DS2-VASc risk scores >1.**
- **There are 36.5% patients taking antiplatelets before their first OACs intake, and 18% in the 2 years afterwards. This suggests that in most cases antiplatelets are correctly stopped once an OAC is started, although the proportion of patients remaing on dual therapy remains somewhat high.**
- **The number of general practitioners visits for VKA users is higher than for NOAC users (median of 17 visits for VKA versus 8 visits for NOAC) and can be explained by the need for regular blood sampling. The median number of INR test in VKA users is 19 (versus 1 test for NOAC users).**
- **Persistence rate (no gap in prescriptions of more than 6-months) at one-year ranges between 70% and 80%.**
- **A high proportion (43% of all users) of NOAC users is prescribed the reduced dose of NOACs.**
- **Around 15% of VKA chronic users switch to a NOAC.**

11 FINAL CONCLUSION

11.1 To anticoagulate or not?

11.1.1 Risk of stroke risk associated with non-valvular AF

Atrial fibrillation (AF) is a common heart rhythm disorder with a prevalence of 1.5-2.0% in the general population. It is diagnosed in 5 to 15% of people aged 80 years or older. The most dreaded complications of AF are thromboembolic events, particularly ischemic stroke. This is most commonly seen in people over the age of 65, or in people suffering from an underlying clinical condition.

In untreated patients with AF, the risk of stroke ranges from 0% to more than 10%.[4, 22, 27, 100] The CHA2DS2-VASc score is used to estimate this risk and to guide a physician for prescribing an anticoagulant. In this score, points are attributed to any of the following characteristics: congestive heart failure (C), hypertension (H), age (A), diabetes mellitus (D), history of stroke (S), vascular disease (VA) and female gender (sex category: Sc). Previous stroke and age >74 years are attributed 2 points, age 64-74 years and the other items are counted as 1 point. In women in whom "sex category" is the single risk factor, it is not taken into account for assessing risk.

The absolute risk of stroke for any given CHA2DS2-VASc score is not exactly known and estimates are derived from cohorts of hospitalised not-anticoagulated patients. With a score=0, the yearly stroke risk is close to zero, whereas a score ≥2 indicates a risk of 2% or more.[5] In patients with a CHA2DS2-VASc=1, large differences in the estimates of stroke risk have been reported. In a recent meta-analysis the pooled yearly risk of stroke was 1.61% (95%CI: 0% - 3.23%).[9] There was however a considerable heterogeneity among studies, with a particularly high risk of stroke in Asian populations. Whereas the risk of stroke in Asian populations was 2.22% (95%CI: 0.84% - 3.59%) it was 0.56% (95%CI: 0.08% - 1.03%) in Western cohorts.

11.1.2 Net clinical benefit of anticoagulants

Anticoagulants reduce the risk of stroke by more than 60%. However, anticoagulants also increase the risk of major bleeding, particularly haemorrhagic stroke. In older VKA trials, this risk ranged from 0.30 to 0.60% per year.[27, 33, 34] In the more recent pivotal NOAC trials, the risk of haemorrhagic stroke in the VKA arm of the trials was higher (0.38 to 0.70%), whereas it was lower in the respective NOAC arms (0.10 to 0.50%) (Table 7).

The concept of "net clinical benefit" of anticoagulation has been introduced to estimate the real benefit a patient derives from treatment. It is the rate of ischemic strokes prevented by anticoagulation, minus the rate of hemorrhagic stroke they induce. Since the risk for haemorrhagic stroke induced by anticoagulants is fairly constant over the CHA2DS2-VASc risk spectrum, the net clinical benefit largely depends on the baseline stroke risk.

Practice guidelines strongly recommend to prescribe anticoagulation therapy in patients with a CHA2DS2-VASc score ≥2 in men or ≥3 in women, and not to prescribe them in those with a CHA2DS2-VASc score of 0. For patients with a CHA2DS2-VASc=1 in men or 2 in women, there is no clear consensus among experts about the indication for anticoagulants. Given a yearly risk of ischemic stroke of 0.56% (0.08% - 1.03%) in Western populations, and an overlapping range of risk of intracranial bleeding induced by anticoagulants (0.10 - 0.80%), the net clinical benefit in patients with only 1 cardiovascular risk factor is not always positive and may even be negative.

11.1.3 Overdiagnosis and oveartreatment

Several patient registries across the world indicate that a substantial proportion of high risk patients are not treated, and a substantial proportion of low risk patients are. In clinical medicine this is a widespread phenomenon known as the risk-treatment paradox.[167]

Overtreatment can be defined as treating patients in whom there is consensus among experts that they should not be treated. In case of patients with AF, this is those with a CHA2DS2-VASc score=0. Overtreatment of AF patients with anticoagulants is a well-known problem worldwide, and suggests that prescribing physicians may not be fully aware of the potential risks associated with anticoagulation, or of the particularly low risk of stroke in some patients with AF.[75, 168] Flemish INTEGO data suggest that in recent years (2013-2014) 15% of patients with a CHA2DS2-VASc=0 score received long term anticoagulation. Although the absolute number of those patients in this database is low, the available data suggest that there might be a favourable trend for fewer anticoagulation prescription in them. Estimates from IMA data also suggest a lowering trend for prescribing anticoagulants in such patients. Because of the very small number of patients involved, no firm conclusions can be drawn here.

Current ESC guidelines promulgate that anticoagulation "should be considered" in AF patients with a CHA2DS2-VASc=1 in men and 2 in women.[17] We have argued that there is no hard evidence for a net benefit of anticoagulation in those patients. Anticoagulation in AF is a purely preventive action, and one may wonder if it can be justified to consider the initiation of a potential harmful treatment in patients in whom it is not sure that those harms are outweighed by the benefits.[169] Flemish INTEGO data suggest that in recent years long term anticoagulant treatment was prescribed in 40% of patients with a CHA2DS2-VASc=1 score. Belgian IMA data do not contain diagnostic information, and hence they do not allow to correctly determine a patient's CHA2DS2-VASc score. Therefore, it is hard to formulate reliable estimates of the number of CHA2DS2-VASc=1 patients that are treated with an anticoagulant in Belgium.

11.1.4 Undertreatment

Undertreatment can be defined as the practice in which patients who should be prescribed a given treatment, are not receiving it. Considering that anticoagulation may be contraindicated in 15% of AF patients, undertreatment can be suspected if less than 85% of a cohort of patients with an indication for anticoagulation are not treated. Traditionally, undertreatment is explained by physicians being reluctant to prescribe anticoagulants in elderly people because of their old age per se, or because they are more prone to be involved in falls.[10] It has however been shown that elderly AF patients may derive a larger net benefit from anticoagulation than younger individuals.[101] Undertreatment can also result from patients refusing treatment, or inappropriately stopping it. Furthermore, a gap in the evidence base may also have a role since elderly people (85+) are poorly represented in RCTs.

INTEGO data suggest that in recent years (2013-2014) an anticoagulant was initiated in 74.5% of patients with a CHA2DS2-VASc ≥2 score. In a previous analysis of INTEGO data (2002-2011), 50% of patients at high risk (then defined as a CHADS2 ≥ 2) of stroke were initiated an anticoagulant.[103] These data suggest that physicians nowadays are more inclined to appropriately start anticoagulation. However, long term data indicate that 50% of patients inadequately stop treatment after 6 to 12 months for reasons that cannot be identified from our data. Similar observations were made in the IMA data that showed an increased use of anticoagulants in elderly patients since the introduction of NOACs. The proportion of patients aged ≥80 yrs. treated with any anticoagulant was 29.6% in the period 2005-2011, whereas it was 35.6% in the period 2012-2014. Among those, the proportion of patients taking a VKA remained essentially the same over the two time periods: 29.6% and 30.7% respectively.

A hopeful observation from the INTEGO data is that in recent years the delay for starting chronic anticoagulation treatment shortened dramatically. In 2007-2009 it took 8 years before 50% of patients with a CHA2DS2-VASc≥2 score were chronically treated, in 2010-2012, it took 4 years, and in 2013-2014 it took only 1 year.

With the introduction of NOACs in clinical practice, a worrying phenomenon that may lead to undertreatment has entered anticoagulation practice. The physician who prescribes a NOAC has to make a choice between the

standard and the reduced dose of the drug. Since monitoring of the effect of a NOAC is not needed – and in routine practice is even not possible – the prescriber is left unaware if a patient is taking the most appropriate NOAC dose. Recent data from UK, France and Germany indicate that the reduced dose of NOACs in real world is used more often than in the pivotal RCTs. This holds true for Belgium as well: IMA data show that the reduced dose of NOACs is prescribed in 43% of patients. This practice may be induced by several mechanisms: formal recommendations in the Summary of Product Characteristics (SmPC) issued by the European Medicines Agency (EMA), recommendations by international practice guidelines and reimbursement conditions. Undoubtedly there is also fear of the physician of inducing bleeding by a drug of which he does not know or cannot measure its action.[95] The problem here is that the efficacy and safety outcomes derived from RCTs may not be applicable in real world conditions where on average lower doses of the drugs are used than in the RCTs.[7]

11.2 VKA or NOAC?

11.2.1 Advantages of NOACs versus VKAs

As compared to VKAs, NOACs can be considered equivalent in terms of ischemic stroke prevention. In absolute terms, differences in harms induced by the drugs are expressed in tenths of a percent. NOACs have a somewhat lower risk of inducing haemorrhagic stroke (-0.25% per year) but a somewhat higher risk of gastrointestinal bleeding (+0.25% per year at the standard dose and non-significantly different at the reduced dose).[48, 170]

The extrapolation of RCT data over a lifetime for a Belgian patient results in an estimated gain ranging from 1 to 4 quality adjusted life-months.[115-117] Most international economic evaluations found a net favourable effectiveness of NOACs versus VKAs. Since extrapolated total lifetime cost estimations in most of these studies indicate that costs associated with NOACs are only slightly higher than for VKAs, NOACs are considered cost-effective against VKAs. In Belgian studies, ICER estimates ranging between €2807 and €13,564 were calculated.[115-117] In the present report, we did not include a home-made economic evaluation since the available administrative data on oral anticoagulants were considered inappropriate to feed an economic model.

In contrast to VKAs, that require monthly blood sampling, monitoring of haemostasis for patients on NOACs is not needed. However, follow-up of renal function is necessary because of the significant renal clearance of these drugs. Follow-up visits of NOAC patients are indicated with a frequency of 2 to 4 times per year in order to check drug adherence, side effects, co-medication and blood sampling.[1] Belgian IMA data show that patients on NOACs had an annual median of 8 (IQR: 5-13) GP visits, compared to 17 (IQR: 9-24) for patients on VKAs. Regarding specialist visits, patients on NOACs had an annual median of 2 (IQR: 1-4), versus 3 (IQR: 1-5) for patients on VKAs.

In addition to medical visits, Belgian data confirmed a difference in blood sampling frequency, with patients on NOACs having a median of 1 (IQR: 0-2) INR controls per year, versus 19 (IQR: 14-27) for patients on VKAs. There was also a difference in renal test checks, with patients on NOACs having a median of 2 (IQR: 1-5) versus 3 (IQR: 1-7) in patients on VKAs. Despite the fact that the Belgian economic evaluations included in this review appeared to have used optimistic assumptions with regard to the annual frequency of GP visits/controls required for patients on NOACs versus those on VKAs (a reduction of 13 GP visits assumed in Kleintjens et al.[116] and of 14 in Wouters et al;[117], versus a reduction of 9 GP visits reflected in the present IMA administrative data), the potential to reduce the frequency of controls and visits in clinical practice appears non-negligible. More so if we take into consideration that patients on NOACs captured in the IMA data appeared to be slightly sicker and older than those treated with VKAs.

11.2.2 Disadvantages of NOACs versus VKAs

Each of the NOACs have been studied in only one RCT, and with a median follow-up of 1.8 to 2.8 years. The long term effects of NOACs are not known. This is at present a major disadvantage of NOACs against VKAs, since anticoagulants in AF are intended to be used for up to 10-20 years or even more.

A daily dose of a NOACs presently costs 10 times as much as a VKA: 2.85€ versus 0.28€ per day (2016 price; source: Riziv/Inami). Although NOACs are considered cost-effective against VKAs in most economic evaluations, the published estimations may be overoptimistic. We have argued that there is a substantial risk of bias in the pivotal RCTs in favour of NOACs above VKAs. The economic studies may also overestimate the incremental effect

of NOACs by their assumptions regarding quality of care, the adherence to treatment in real-world conditions, and because of unknown long-term efficacy and safety effects. Moreover, most economic studies were funded by grants from the pharmaceutical industry which may introduce bias by itself. The real impact of these limitations is not exactly known but even if it is low in absolute terms, it may be pertinent given the fact that differences in benefit and harm of NOACs over VKAs are also low, and expressed in tenths of a percent.

The short half-life of NOACs makes that strict drug compliance is more critical than with VKAs. Missing even one dose of a NOAC can result in a period without protection from thromboembolism.[25] This is in contrast to the days-long half-life of VKAs, ensuring some residual anticoagulant effect up to 72h following the last dose.[104] The shorter half-life of NOACs may be an advantage in case of bleeding or when surgery is needed. In emergency situations the action of VKAs can be antagonised with vitamin K, at a cost of about €10 per treatment. Specific reversal agents for NOACs have only recently been developed and presently only idarucizumab (Praxbind) is available in Belgium to antagonise the action of dabigatran. The drug is used at a dose of 5 gram, and comes at a RIZIV/INAMI cost of €2 687 per treatment.

It has been suggested that the absence of a need for regular blood testing would lead to a better acceptance of NOACs, and a better persistence/compliance of patients. However, drug discontinuation rates for NOACs and VKAs appear to be similar. In the Belgian IMA data, in which we considered lack of persistence if there was a gap of more than 6-months between 2 prescriptions, 20 to 30% of patients were non-adherent, with no clear difference between VKAs and NOACs. As argued above, the absence of monitoring may lead to a clinical disadvantage for NOACs since it makes the prescribing physician unaware if a patient is taking the most appropriate NOAC dose.

The unstable and unpredictable action of VKAs reflected in a low “time in therapeutic range” (TTR) has been a major argument in favour of NOACs which reportedly have predictable plasma concentrations. However, drug monitoring data from the RE-LY trial suggest that up to 20% of patients fall outside the optimal concentration range of 35 to 300 ng/mL.[93, 171] Adding this element to the observation that a higher than expected proportion of patients is prescribed the reduced dose of a NOAC, makes that patients on a NOAC may - in terms of TTR - not perform better than those on a VKA.

11.2.3 VKA or NOAC: KCE’s conclusion

Our analysis shows that in optimal trial conditions, NOACs perform only slightly better than VKAs in terms of benefit and harm. NOACs have an important advantage over VKAs in that haemostasis monitoring is not needed, rendering them more acceptable to both patients and physicians. It has been anticipated that the absence of a need for monitoring would increase patient compliance. This promise however has not been fulfilled. It gave rise to an unexpected adverse effect since it made physicians - being reluctant of inducing bleeding – prescribe too low a dose of these drugs, the absence of monitoring leaving them unaware that a patient was insufficiently protected against stroke. Based on this observation, it might be that the slight benefit of NOACs as demonstrated in clinical trials disappears in real world practice, making substantial additional costs for the purchase of these drugs hard to defend.

NOACs are an appropriate choice for patients on a VKA in whom no stable INR values can be reached, or those in whom regular blood sampling is problematic, provided that they are prescribed the appropriate dose of the NOAC and that they are strictly compliant with (once or twice) daily intake.

11.3 Trends in anticoagulant prescription

Since the early 2000s, anticoagulants have been increasingly prescribed in patients with AF. Presently, almost 2.5% of the overall Belgian population is prescribed an anticoagulant. After the introduction of NOACs for AF on the Belgian market, the increasing trend in anticoagulation use became steeper, and 3 years later, 60% of the newly prescribed anticoagulants for long-term use were NOACs. In 2014, only a few years following their introduction, NOACs generated combined global sales of $5.8 billion. In Belgium, the increasing use of anticoagulants with a growing share of NOACs, can be expected to lead to an extra yearly cost for drugs of 100 million euros in the years to come (if one does not take secret refunds to the Riziv/Inami into consideration).

Our data suggest a number of positive trends in anticoagulation practice in Belgium. In recent years deficiencies in overtreating low risk patients and undertreating high risk patients have at least partly been corrected, although there remains room for improvement in this respect. In addition, it appears that Belgian physicians appropriately limit the combined prescription of anticoagulants with antiplatelets.

The increasing use of NOACs, in Belgium and abroad, is noteworthy. International practice guidelines most probably have been a major driver for the growing use of anticoagulants by progressively increasing the indications for anticoagulation, by lowering the stroke risk threshold from which to start anticoagulation, and by promoting the use of NOACs. Furthermore, the introduction of NOACs has been supported (and still is) by worldwide major marketing efforts from pharmaceutical industry.

The anticoagulation practice in patients treated with a NOAC in real world differs from the protocol used in the pivotal RCTs. A substantially higher proportion of patients than in the pivotal RCTs are treated with the reduced dose of the drug. The absence of monitoring leaves the physician unaware for this. Furthermore, there is no way for checking a patient's compliance of these drugs, which is particularly important for NOACs that have a rapid offset of action. The 2016 US Clinical Performance Measure stipulates that missing even 1 dose of a NOAC could result in a period without protection from thromboembolism.

Therefore, we would like to encourage prescribing physicians to critically consider the pros and cons of NOACs, and to discuss with their patients the uncertainties surrounding their benefit/harm balance before systematically prescribing them.[172]

APPENDICES

APPENDIX 1. RCTS COMPARING NOACS WITH VKA IN NON-VALVULAR AF

Author	Year	Acronym	Study phase	Status	Brand name
Direct thrombin inhibitors					
Dabigatran					Pradaxa
Connolly	2009	RE-LY	phase 3	Reimbursed in Belgium	
Ezekowitz	2007	PETRO	phase 2		
NCT00448214	2010		phase 2		
NCT01136408	2010		phase 2		
Ximelagatran					
Albers	2005	SPORTIF V	phase 3	Withdrawn from the market due to liver toxicity	
NCT00206063	2006		phase 2		
Olsson	2003	SPORTIF III	phase 3		
AZD0837					
Lip	2009		phase 2	Under investigation	
Olsson	2010		phase 2		
Direct Factor Xa inhibitors					
Rivaroxaban					Xarelto
Hori	2012	J-ROCKET AF	phase 3	Reimbursed in Belgium	
NCT00973323	2008		phase 2		
NCT00973245	2008		phase 2		
Patel	2011	ROCKET-AF	phase 3		
Apixaban					Eliquis
Granger	2011	ARISTOTLE	phase 3	Reimbursed in Belgium	
Ogawa	2011	ARISTOTLE-J	phase 2		
Edoxaban					Lixiana
Chung	2011		phase 2	EMEA and FDA approval 2015. Not reimbursed in Belgium.	
Weitz	2010		phase 2		
Yamashita	2012		phase 2		
Giugliano	2013	ENGAGE-AF	phase 3		
Betrixaban					
Connolly	2013	EXPLORE Xa	phase 2	Under investigation	
Darexaban					
Lip	2015	OPAL-2	phase 2	Under investigation	

Source: Liu et al.46

APPENDIX 2. LITERATURE SEARCH FOR EFFICACY OF NOAC

Appendix 2.1. Medline (Ovid) search string used for Systematic Reviews

#	Searches	Results
1	exp Anticoagulants/	93658
2	exp Dabigatran/	1534
3	apixapan.mp	1085
4	edoxaban.mp	332
5	exp Rivaroxaban/	1219
6	exp Atrial Fibrillation/	30550
7	1 or 2 or 3 or 4 or 5	93730
8	6 and 7	5774
9	limit 8 to ("review articles" and yr="2014-Current")	242

Appendix 2.2. SRs selected on title and abstract

#	FIRST AUTHOR	TITLE	COMMENT
1	Acharya T	An evidence-based review of edoxaban and its role in stroke prevention in patients with non-valvular atrial fibrillation.	Edoxaban only
2	Arbit B	Non-Vitamin K Antagonist Oral Anticoagulant Use in Patients With Atrial Fibrillation and Associated Intracranial Hemorrhage: A Focused Review.	Patient subgroup
3	Aryal M	Meta-analysis of efficacy and safety of rivaroxaban compared with warfarin or dabigatran in patients undergoing catheter ablation for atrial fibrillation.	Ablation
4	Bloom B	Meta-analysis of randomized controlled trials on the risk of bleeding with dabigatran.	Dabigatran only
5	CADTH	Apixaban and rivaroxaban for stroke prevention in atrial fibrillation: safety	Apixaban and rivaroxaban only

6	Caldeira D	Tolerability and Acceptability of Non-Vitamin K Antagonist Oral Anticoagulants in Atrial Fibrillation: Systematic Review and Meta-Analysis.	Not available in our bib
7	Dogliotti	Current and new oral antithrombotics in non-valvular atrial fibrillation: a network meta-analysis of 79 808 patients	Network meta-analysis
8	Fauchier	Efficacy of new oral anticoagulants in patients with atrial fibrillation previously treated with warfarin: a meta-analysis of randomized controlled trials	Letter
9	Lin L	Clinical and Safety Outcomes of Oral Antithrombotics for Stroke Prevention in Atrial Fibrillation: A Systematic Review and Network Meta-analysis.	Not available in our bib
10	Lin L	Clinical and Safety Outcomes of Oral Antithrombotics for Stroke Prevention in Atrial Fibrillation: A Systematic Review and Network Meta-analysis.	Not available in our bib
11	Lip G	Stroke prevention in atrial fibrillation: a systematic review.	No SR of NOACs
12	Salazar C	Direct thrombin inhibitors versus vitamin K antagonists for preventing cerebral or systemic embolism in people with non-valvular atrial fibrillation.	Meta-analysis includes phase 2 studies and ximelagatran
13	Caldeira D	Systematic review with meta-analysis: the risk of major gastrointestinal bleeding with non-vitamin K antagonist oral anticoagulants.	Limited to adverse effects
14	Albert N	Use of novel oral anticoagulants for patients with atrial fibrillation: systematic review and clinical implications.	Narrative review
15	Bentz B	Non-vitamin K antagonist oral anticoagulants in everyday practice: Stroke prevention in atrial fibrillation and treatment of venous thromboembolism.	Narrative review
16	Cameron C	Systematic review and network meta-analysis comparing antithrombotic agents for the prevention of stroke and major bleeding in patients with atrial fibrillation.	Network meta-analysis. To be compared with Fu et al.
17	Chai	Mortality outcomes in patients receiving direct oral anticoagulants: a systematic review and meta-analysis of randomized controlled trials	Combines AF and DVT
18	Ezekowitz M	Stroke prevention in atrial fibrillation: established oral anticoagulants versus novel anticoagulants-translating clinical trial data into practice.	Narrative review
19	Fu W	Relative efficacy and safety of direct oral anticoagulants in patients with atrial fibrillation by network meta-analysis.	Network meta-analysis
20	Jalota A	Novel anticoagulants for stroke prevention in patients with atrial fibrillation.	Narrative review

21	Liu G	The efficacy and safety of novel oral anticoagulants for the preventive treatment in atrial fibrillation patients: a systematic review and meta-analysis.	Selected
22	Liew A	Comparing mortality in patients with atrial fibrillation who are receiving a direct-acting oral anticoagulant or warfarin: a meta-analysis of randomized trials	Selected
23	Providencia R	A meta-analysis of phase 3 randomized controlled trials with novel oral anticoagulants in atrial fibrillation: comparisons between direct thrombin inhibitors vs. factor Xa inhibitors and different dosing regimens.	Selected
24	Ruff C	Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials	Selected
25	Senoo K	Oral anticoagulants for stroke prevention in atrial fibrillation.	Narrative review
26	Jia B	Meta-analysis of efficacy and safety of the new anticoagulants versus warfarin in patients with atrial fibrillation	Selected

Appendix 2.3. Systematic reviews selected for the present report

FIRST AUTHOR	TITLE	CONTENT	SEARCH UNTIL	AMSTAR SCORE
Providencia	A meta-analysis of phase III randomized controlled trials with novel oral anticoagulants in atrial fibrillation: comparisons between direct thrombin inhibitors vs. factor Xa inhibitors and different dosing regimens.	Meta-analysis of 7 phase 3 studies. Focus on comparing direct thrombin inhibitors and Factor Xa inhibitors.	Nov 2013	6
Jia B	Meta-analysis of efficacy and safety of the new anticoagulants versus warfarin in patients with atrial fibrillation.	Meta-analysis of 5 phase 3 studies.	Dec 2013	7
Ruff C	Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials.	Meta-analysis of 4 phase 3 studies. Includes secondary endpoints and subgroup analyses.	Nov 2013	3

References: Jia et al.45, Providencia et al.47, Ruff et al.48 The AMSTAR score is a measurement tool to assess the methodological quality of systematic reviews.173

APPENDIX 3. SUMMARY OF FINDINGS TABLES

Stroke prevention with ximelagatran vs warfarin in nonvalvular AF. Olsson et al. Lancet 2003;362:1691-98.		
Sponsor: AstraZeneca. ClinicalTrials.gov Identifier: 0. Acronym: SPORTIF III. 259 centres, 23 countries.		
Non-inferiority RCT. Recruitment started August, 2000. Total n=3410. Mean follow-up: 17.4 months.		
Patients: Any AF + at least one risk factor for stroke. Mean age 70.2 yrs. Concomitant aspirin 20%.		
Intervention: Open label ximelagatran 36 mg twice daily. Drop out: 18%.		
Control: Unblinded Warfarin (INR 2-3). Drop out: 14% in VKA and 18% in ximelagatran group. TTR: 66%.		
Outcomes (ITT)	**Ximelagatran**	**Warfarin**
	n=1704	n=1703
Primary study outcome: stroke or systemic embolism	40	56
Absolute Risk (% per year)	1.6	2.3
Absolute Risk Reduction Ximelagatran vs. Warfarin (% per year)	0.7 (1.4 to -0.1)	
Relative Risk, Ximelagatran vs. Warfarin (% per year; 95%CI)	0.71 (0.48-1.07)	
Major bleeding (On Treatment)	29	41
Absolute Risk (% per year)	1.3	1.8
Absolute Risk Reduction Ximelagatran vs. Warfarin (% per year)	0.5	
Relative Risk, Ximelagatran vs. Warfarin (% per year; 95%CI)	0.71 (0.44-1.13)	
Haemorrhagic stroke (ITT)	4	9
Absolute Risk (% per year)	0.2	0.4
Absolute Risk Reduction Ximelagatran vs. Warfarin (% per year)	0.2	
Relative Risk, Ximelagatran vs. Warfarin (% per year; 95%CI)	0.44 (0.13-1.44)	
Ischaemic stroke (ITT)	32	46
Absolute Risk (% per year)	1.3	1.9
Absolute Risk Reduction Ximelagatran vs. Warfarin (% per year)	0.6	
Relative Risk, Ximelagatran vs. Warfarin (% per year; 95%CI)	0.70 (0.44-1.09)	
Gastrointestinal bleeding	15	15
Absolute Risk (% over follow-up)	0.9	0.9
Absolute Risk Reduction Ximelagatran vs. Warfarin (% per year)	0	
Relative Risk, Ximelagatran vs. Warfarin (% per year; 95%CI)	1.0 (0.49-2.03)	
All-cause mortality (ITT)	78	79
Absolute Risk (% per year)	3.2	3.2
Absolute Risk Reduction Ximelagatran vs. Warfarin (% per year)	0	
Relative Risk, Ximelagatran vs. Warfarin (% per year; 95%CI)	0.99 (0.72-1.33)	
All-cause mortality (ITT)	85	82
Relative Risk, Ximelagatran vs. Warfarin (% per year; 95%CI)	0.88 (0.65-1.18)	

Ximelagatran vs warfarin for stroke prevention in nonvalvular AF. Albers et al. JAMA 2005;293:690-698.		
Sponsor: AstraZeneca. ClinicalTrials.gov Identifier: 0. Acronym: SPORTIF V. 409 centres in US and Canada.		
Non-inferiority RCT. Recruitment started August 2, 2000. Total n=3922. Mean follow-up: 20 months.		
Patients: Any AF + at least one risk factor for stroke. Mean age 71.6 yrs. Concomitant aspirin 18%.		
Intervention: Blinded ximelagatran 36 mg twice daily. Drop out: 37%.		
Control: Blinded Warfarin (INR 2-3). Drop out: 33% in warfarin and 37% in ximelagatran group. TTR: 68%.		
Outcomes (ITT)	**Ximelagatran**	**Warfarin**
	n=1960	n=1962
Primary study outcome: stroke or systemic embolism	51	37
Absolute Risk (% per year)	1.6	1.2
Absolute Risk Reduction Ximelagatran vs. Warfarin (% per year)	-0.4	
Relative Risk, Ximelagatran vs. Warfarin (% per year; 95%CI)	1.37 (0.90-2.10)	
Major extracerebral bleeding (On Treatment)	63	84
Absolute Risk (% per year)	2.4	3.1
Absolute Risk Reduction Ximelagatran vs. Warfarin (% per year)	0.7	
Relative Risk, Ximelagatran vs. Warfarin (% per year; 95%CI)	0.75 (0.54-1.03)	
Haemorrhagic stroke (ITT)	2	2
Absolute Risk (% per year)	0.1	0.1
Absolute Risk Reduction Ximelagatran vs. Warfarin (% per year)	0	
Relative Risk, Ximelagatran vs. Warfarin (% per year; 95%CI)	1.00	
Ischaemic stroke (ITT)	45	36
Absolute Risk (% per year)	1.4	1.1
Absolute Risk Reduction Ximelagatran vs. Warfarin (% per year)	-0.3	
Relative Risk, Ximelagatran vs. Warfarin (% per year; 95%CI)	1.25 (0.81-1.93)	
Gastrointestinal bleeding	NA	NA
Absolute Risk (% over follow-up)		
Absolute Risk Reduction Ximelagatran vs. Warfarin (% per year)		
Relative Risk, Ximelagatran vs. Warfarin (% per year; 95%CI)		
All-cause mortality (ITT)	116	123
Absolute Risk (% per year)	3.6	3.8
Absolute Risk Reduction Ximelagatran vs. Warfarin (% per year)	0.2	
Relative Risk, Ximelagatran vs. Warfarin (% per year; 95%CI)	0.94 (0.73-1.21)	

Dabigatran versus Warfarin in Patients with Atrial Fibrillation. Connolly et al. N Engl J Med 2009;361:1139-51.			
Sponsor: Boehringer Ingelheim. ClinicalTrials.gov Identifier: NCT00262600. Acronym: RE-LY. 951 centres, 44 countries,			
Non-inferiority RCT. Recruitment started Dec 15, 2008. Total n=18,113. Median follow-up: 2.0 years.			
Patients: Any AF + at least one risk factor for stroke. Mean age 71.5 yrs. CHADS2 score 0 or 1: 32%. Concomitant aspirin 40%.			
Intervention: 1:1:1 design: Blinded dabigatran 110 or 150 mg twice daily. Drop out: 110 mg: 20,7%, 150 mg: 21.2%.			
Control: Unblinded Warfarin (INR 2-3). Drop out: 16.6%. TTR: 64%.			
Outcomes (all ITT)	**Dabigatran 110 mg**	**Dabigatran 150 mg**	**Warfarin**
	n=6015	n=6076	n=6022
Primary study outcome: stroke or systemic embolism - corr. 2014	183	135	203
Absolute Risk (% per year)	1.54	1.12	1.72
Absolute Risk Reduction Dabigatran vs. Warfarin (% per year)	0.18	0.60	
Relative Risk, Dabigatran vs. Warfarin (% per year; 95%CI)	0.89 (0.73–1.09)	0.65 (0.52–0.81)	
Major bleeding - corr. 2014	347	409	426
Absolute Risk (% per year)	2.92	3.40	3.61
Absolute Risk Reduction Dabigatran vs. Warfarin (% per year)	0.69	0.21	
Relative Risk, Dabigatran vs. Warfarin (% per year; 95%CI)	0.80 (0.70–0.93)	0.94 (0.82–1.08)	
Haemorrhagic stroke	14	12	45
Absolute Risk (% per year)	0.12	0.10	0.38
Absolute Risk Reduction Dabigatran vs. Warfarin (% per year)	0.26	0.28	
Relative Risk, Dabigatran vs. Warfarin (% per year; 95%CI)	0.31 (0.17–0.56)	0.26 (0.14–0.49)	
Ischaemic or unspecified stroke	159	111	142
Absolute Risk (% per year)	1.34	0.92	1.20
Absolute Risk Reduction Dabigatran vs. Warfarin (% per year)	-0.14	0.28	
Relative Risk, Dabigatran vs. Warfarin (% per year; 95%CI)	1.11 (0.89-1.40)	0.76 (0.60-0.98)	
Gastrointestinal bleeding	133	182	120
Absolute Risk (% per year)	1.12	1.51	1.02
Absolute Risk Reduction Dabigatran vs. Warfarin (% per year)	-0.10	-0.49	
Relative Risk, Dabigatran vs. Warfarin (% per year; 95%CI)	1.10 (0.86–1.41)	1.50 (1.19–1.89)	
All-cause mortality	446	438	487
Absolute Risk (% per year)	3.75	3.64	4.13
Absolute Risk Reduction Dabigatran vs. Warfarin (% per year)	0.38	0.49	
Relative Risk, Dabigatran vs. Warfarin (% per year; 95%CI)	0.91 (0.80–1.03)	0.88 (0.77–1.00)	

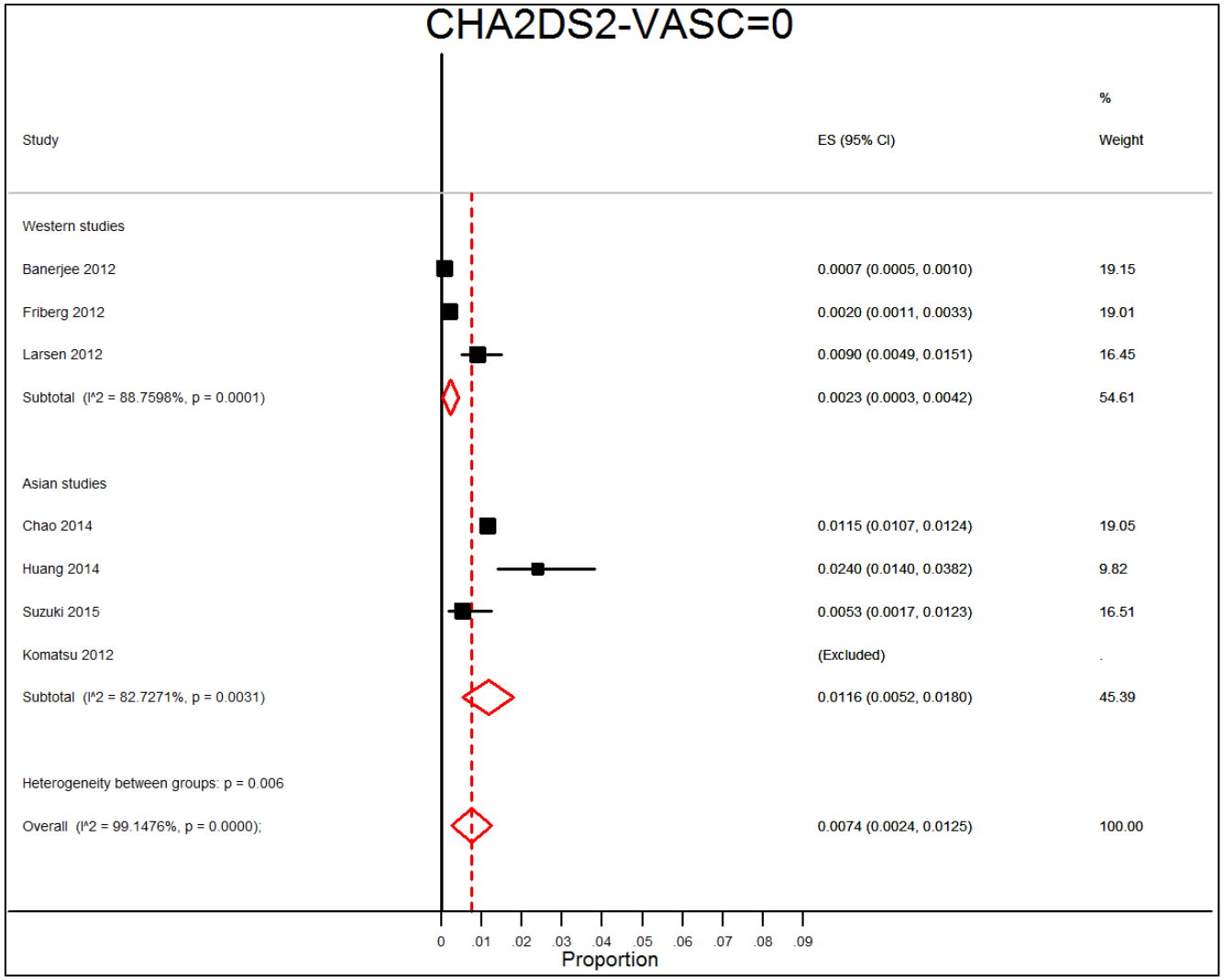
Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation. Patel et al. N Engl J Med 2011;365:883-91.		
Sponsor: Johnson & Johnson and Bayer HealthCare. ClinicalTrials.gov Identifier: NCT00403767. Acronym: ROCKET-AF. 1178 centres, 45 countries.		
Non-inferiority RCT. Recruitment started Dec 18, 2006. Total n=14,264. Median follow-up: 707 days (=1.94 yrs).		
Patients: Any AF + CHADS2 score of 2 or more. Median age 73 yrs. CHADS2 score 0 or 1: 0%. Concomitant aspirin 35%.		
Intervention: Blinded Dabigatran 20 or 15 (clearance 30-49 ml/min) mg. Drop out: 23.7%.		
Control: Blinded Warfarin (INR 2-3). Drop out: 23,7% in the rivaroxaban and 22.2% in the warfarin group. TTR: 55%.		
Outcomes	**Rivaroxaban (20 or 15 mg)**	**Warfarin**
	(n=7131)	(n=7133)
Primary study outcome: stroke or systemic embolism (ITT)	269	306
Absolute Risk (% per year)	2.10	2.40
Absolute Risk Reduction Rivaroxaban vs. Warfarin (% per year)	0.30	
Hazard ratio, Rivaroxaban vs. Warfarin (% per year; 95%CI)	0.88 (0.75-1.03)	
Major bleeding (per protocol)	395	386
Absolute Risk (% per year)	3.6	3.4
Absolute Risk Reduction Rivaroxaban vs. Warfarin (% per year)	-0.2	
Hazard ratio, Rivaroxaban vs. Warfarin (% per year; 95%CI)	1.04 (0.90-1.20)	
Intracranial haemorrhage	55	84
Absolute Risk (% per year)	0.5	0.7
Absolute Risk Reduction Rivaroxaban vs. Warfarin (% per year)	0.2	
Hazard ratio, Rivaroxaban vs. Warfarin (% per year; 95%CI)	0.67 (0.47-0.93)	
Ischaemic stroke (Safety-on-treatment population)	149	161
Absolute Risk (% per year)	1.34	1.42
Absolute Risk Reduction Dabigatran vs. Warfarin (% per year)	0.08	
Relative Risk, Dabigatran vs. Warfarin (% per year; 95%CI)	0.94 (0.75, 1.17)	
Gastrointestinal bleeding	224 on 7111	154 on 7125
Absolute Risk (% per year)	1.62	1.11
Absolute Risk Reduction Rivaroxaban vs. Warfarin (% per year)	-0.51	
Relative risk, Rivaroxaban vs. Warfarin (% per year; 95%CI)	1.54 (1.19-1.78)	
All cause mortality (ITT)	582	632
Absolute Risk (% per year)	4.5	4.9
Absolute Risk Reduction Rivaroxaban vs. Warfarin (% per year)	0.40	
Hazard ratio, Rivaroxaban vs. Warfarin (% per year; 95%CI)	0.92 (0.82-1.03)	

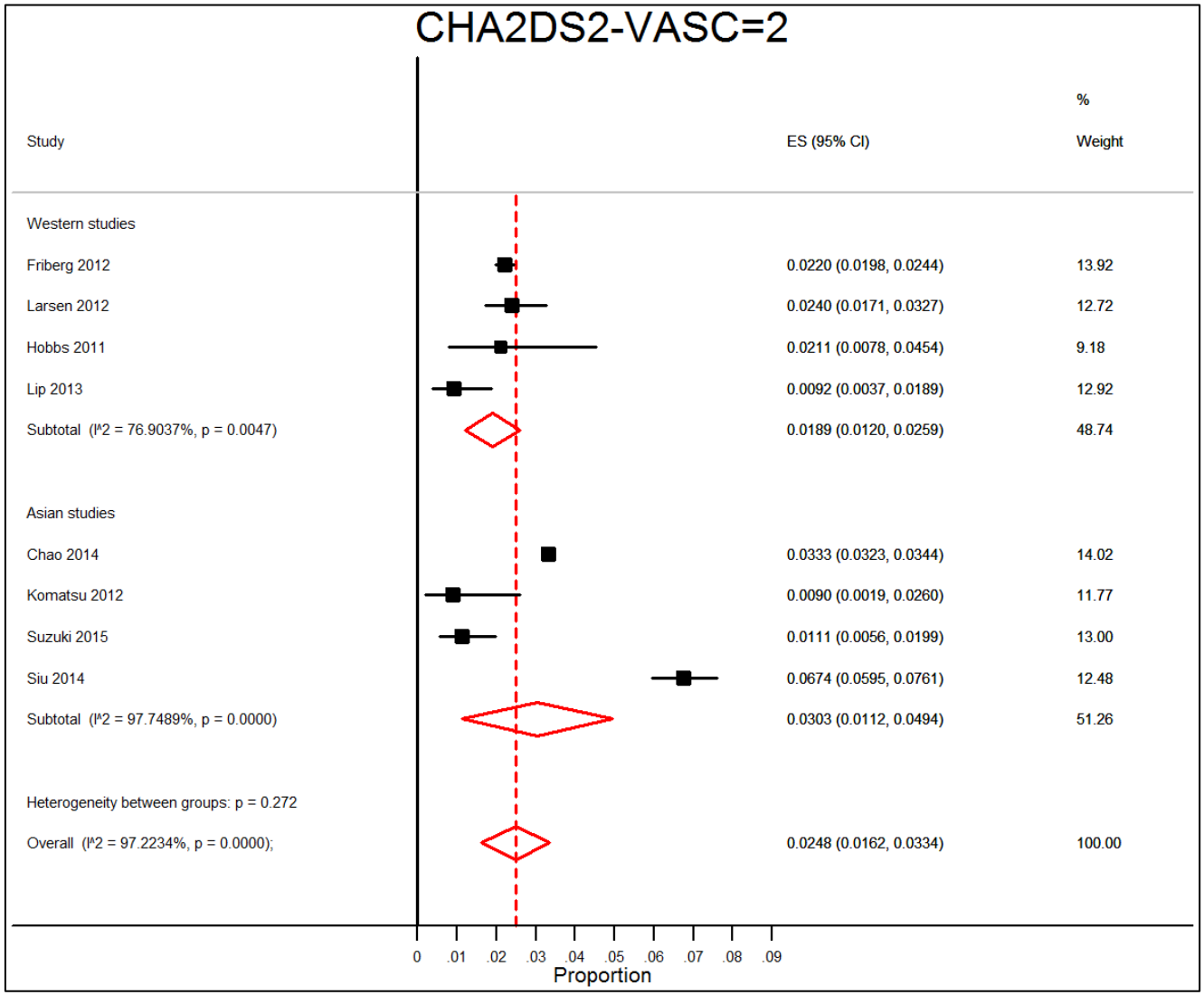
Apixaban versus Warfarin in Patients with Atrial Fibrillation. Granger et al. N Engl J Med 2011;365:981-92.		
Sponsor: Bristol-Meyers Squibb and Pfizer. ClinicalTrials.gov Identifier: NCT00412984. Acronym: ARISTOTLE. 1034 sites, 39 countries.		
Non-inferiority RCT. Recruitment started Dec 19, 2006. Total n=18,201. Median follow-up: 1.8 yrs.		
Patients: Any AF + at least one risk factor for stroke. Median age 70 yrs. CHADS2 score 0 or 1: 34%. Concomitant aspirin 31%.		
Intervention: Blinded Apixaban 5 mg twice per day [or 2.5 mg twice if two or more of the following: age of at least 80 years, body weight of no more than 60 kg, or serum creatinine level of 1.5 mg/dL or more]. Drop out: 25.3%.		
Control: Blinded Warfarin (INR 2-3). Drop out: 25.3% in the apixaban and 27.5% in the warfarin group. TTR: 66.0/62.2%.		
Outcomes (ITT)	**Apixaban**	**Warfarin**
	n=9120	n=9081
Primary study outcome: stroke or systemic embolism	212	265
Absolute Risk (% per year)	1.27	1.60
Absolute Risk Reduction, Apixaban vs. Warfarin (% per year)	0.33	
Hazard ratio, Rivaroxaban vs. Warfarin (% per year; 95%CI)	0.79 (0.66-0.95)	
Major bleeding	327	462
Absolute Risk (% per year)	2.13	3.09
Absolute Risk Reduction, Apixaban vs. Warfarin (% per year)	0.96	
Hazard ratio, Apixaban vs. Warfarin (% per year; 95%CI)	0.69 (0.60-0.80)	
Haemorrhagic stroke	40	78
Absolute Risk (% per year)	0.24	0.47
Absolute Risk Reduction, Apixaban vs. Warfarin (% per year)	0.23	
Hazard ratio, Apixaban vs. Warfarin (% per year; 95%CI)	0.51 (0.35-0.75)	
Ischaemic or uncertain stroke	162	175
Absolute Risk (% per year)	0.97	1.05
Absolute Risk Reduction Apixaban vs. Warfarin (% per year)	0.08	
Relative Risk, Apixaban vs. Warfarin (% per year; 95%CI)	0.92 (0.74-1.13)	
Gastrointestinal bleeding	105	119
Absolute Risk (% per year)	0.76	0.86
Absolute Risk Reduction, Apixaban vs. Warfarin (% per year)	0.10	
Hazard ratio, Apixaban vs. Warfarin (% per year; 95%CI)	0.89 (0.70-1.15)	
All cause mortality	(331)	(349)
Absolute Risk (% per year)	3.52	3.94
Absolute Risk Reduction, Apixaban vs. Warfarin (% per year)	0.42	
Hazard ratio, Apixaban vs. Warfarin (% per year; 95%CI)	0.89 (0.80-0.99)	

Rivaroxaban vs Warfarin in Japanese Patients with Atrial Fibrillation. Hori et al. Circ J 2012;76:2104-2111.		
Sponsor: Janssen Pharmaceuticals and Bayer HealthCare. ClinicalTrials.gov Identifier: NCT00494871. Acronym: J-ROCKET-AF. Japan.		
Non-inferiority RCT. Recruitment started June 8, 2007. Total n=1,280. Median follow-up: ?		
Patients: Any AF + CHADS2≥2. Median age 71.1 yrs. Concomitant aspirin ?%.		
Intervention: Blinded rivaroxaban 15 mg once (or 10 mg in case of renal failure). Drop out: 0%?		
Control: Blinded Warfarin (INR 2-3; 1.6-2.6 in case of renal failure). Drop out: %. TTR: 65%.		
Outcomes	**Rivaroxaban**	**Warfarin**
	n=639	n=639
Primary study outcome: stroke or systemic embolism (ITT)	22	26
Absolute Risk (% per year)	2.38	2.91
Absolute Risk Reduction rivaroxaban vs. Warfarin (% per year)	0.53	
Hazard ratio, rivaroxaban vs. Warfarin (% per year; 95%CI)	0.82 (0.46-1.45)	
Major bleeding		
Absolute Risk (% per year)	3.00	3.59
Absolute Risk Reduction rivaroxaban vs. Warfarin (% per year)	0.59	
Hazard ratio, rivaroxaban vs. Warfarin (% per year; 95%CI)	0.85 (0.50-1.43)	
Haemorrhagic stroke	3	4
Absolute Risk (% per year)		
Absolute Risk Reduction rivaroxaban vs. Warfarin (% per year)		
Hazard ratio, rivaroxaban vs. Warfarin (% per year; 95%CI)	0.73 (0.16-3.25)	
Ischemic stroke	7	17
Absolute Risk (% per year)		
Absolute Risk Reduction rivaroxaban vs. Warfarin (% per year)		
Hazard ratio, rivaroxaban vs. Warfarin (% per year; 95%CI)	0.40 (0.17-0.95)	
All cause mortality	7	5
Absolute Risk (% per year)		
Absolute Risk Reduction rivaroxaban vs. Warfarin (% per year)		
Hazard ratio, rivaroxaban vs. Warfarin (% per year; 95%CI)		

Edoxaban versus Warfarin in Patients with Atrial Fibrillation. Giugliano et al. N Engl J Med 2013;369:2093-104.			
Sponsor: Daiichi Sankyo Pharma. ClinicalTrials.gov Identifier: NCT00781391. Acronym: ENGAGE AF-TIMI 48. 1393 centres, 46 countries.			
Non-inferiority RCT. Recruitment started ?. Total n=21,105. Median follow-up: 2.8 yrs.			
Patients: Any AF + CHADS2≥2. CHADS2 score 0 or 1: 0%. Median age 72 yrs. Concomitant aspirin 29%.			
Intervention: 1:1:1 design: Blinded edoxaban twice 30 or 60 mg per day. In either group, dose was halved depending on renal function, body weight, co-medication). Drop out: warfarin: 34,5%, 60 mg apixaban: 34%, 30 mg apixaban: 33.0%.			
Control: Blinded Warfarin (INR 2-3). Drop out: 34.5%. TTR: 68.4%.			
Outcomes	**Edoxaban high**	**Edoxaban low**	**Warfarin**
	n=7035	n=7034	n=7036
Primary study outcome: stroke or systemic embolism (ITT)	182	253	232
Absolute Risk (% per year)	1.18	1.61	1.50
Absolute Risk Reduction Edoxaban vs. Warfarin (% per year)	0.32	-0.11	
Hazard ratio, Edoxaban vs. Warfarin (% per year; 95%CI)	0.79 (0.63–0.99)	1.07 (0.87–1.31)	
Major bleeding	418	254	524
Absolute Risk (% per year)	2.75	1.61	3.43
Absolute Risk Reduction Edoxaban vs. Warfarin (% per year)	0.68	1.82	
Hazard ratio, Edoxaban vs. Warfarin (% per year; 95%CI)	0.80 (0.71–0.91)	0.47 (0.41–0.55)	
Haemorrhagic stroke	49	30	90
Absolute Risk (% per year)	0.26	0.16	0.47
Absolute Risk Reduction Edoxaban vs. Warfarin (% per year)	0.21	0.31	
Hazard ratio, Edoxaban vs. Warfarin (% per year; 95%CI)	0.54 (0.38–0.77)	0.33 (0.22–0.50)	
Ischemic stroke	236	333	235
Absolute Risk (% per year)	1.25	1.77	1.25
Absolute Risk Reduction Edoxaban vs. Warfarin (% per year)	0	-0.22	
Hazard ratio, Edoxaban vs. Warfarin (% per year; 95%CI)	1.00 (0.83–1.19)	1.41 (1.19–1.67)	
Gastrointestinal bleeding	232	129	190
Absolute Risk (% per year)	1.51	0.82	1.23
Absolute Risk Reduction Edoxaban vs. Warfarin (% per year)	-0.28	0.41	
Hazard ratio, Edoxaban vs. Warfarin (% per year; 95%CI)	1.23 (1.02–1.50)	0.67 (0.53–0.83)	
All cause mortality	773	737	839
Absolute Risk (% per year)	3.99	3.80	4.35
Absolute Risk Reduction Edoxaban vs. Warfarin (% per year)	0.36	0.55	
Hazard ratio, Edoxaban vs. Warfarin (% per year; 95%CI)	0.92 (0.83–1.01)	0.87 (0.79–0.96)	

APPENDIX 4. META-ANALYSES OF ISCHEMIC STROKE RISK BY CHA2DS2-VASC SCORE





Source: Data extracted from Joundi et al.[9] are categorised into Asian and Western populations. Meta-analysis according to Nyaga et al.[14]

APPENDIX 5. SYSTEMATIC REVIEWS ON INAPPROPRIATE USE OF ORAL ANTICOAGULANTS

Appendix 1.1. Cochrane Database of Systematic Reviews

Date	**18/07/16 10:54:40.534**	
Database	Cochrane Database of Systematic Reviews	
Search strategy		
#1	[mh "Atrial Fibrillation"]	3140
#2	"atrial fibrillation":ab,ti	5776
#3	"auricular fibrillation":ab,ti	11
#4	#1 or #2 or #3	6012
#5	[mh "Prescription Drug Misuse"]	112
#6	[mh "Inappropriate Prescribing"]	71
#7	[mh "medication errors"]	331
#8	[mh "medical overuse"]	127
#9	[mh "health services misuse"]	209
#10	"inappropriate use":ab,ti	113
#11	overtreat*:ab,ti	176
#12	overdos*:ab,ti	493
#13	undertreat*:ab,ti	257
#14	overus*:ab,ti	377
#15	underus*:ab,ti	230
#16	over-treat*:ab,ti	262
#17	under-treat*:ab,ti	683

#18	[mh "drug overdose"]	84
#19	misus*:ab,ti	681
#20	CHA2DS2*:ab,ti	55
#21	#5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20	3778
#22	#4 and #21	85
#23	apixaban:ab,ti	259
#24	dabigatran:ab,ti	354
#25	rivaroxaban:ab,ti	453
#26	edoxaban:ab,ti	108
#27	eliquis:ab,ti	1
#28	pradaxa:ab,ti	8
#29	xarelto:ab,ti	7
#30	#23 or #24 or #25 or #26 or #27 or #28 or #29	1009
#31	#22 and #30	17
#32	[mh Anticoagulants]	4437
#33	[mh "administration, oral"]	21519
#34	#32 and #33	507
#35	(oral near/3 anticoag*):ab,ti	1165
#36	#34 or #35	1385
#37	#22 and #36	21
#38	[mh Rivaroxaban]	133
#39	[mh Dabigatran]	90
#40	#38 or #39	210

#41	#22 and #40	2
#42	#31 or #37 or #41	34
Notes	No systematic reviews found. The 34 hits were from CENTRAL.	

Appendix 5.1. Embase

Date	**2016-07-18**	
Database	Embase	
Search strategy		
1	'atrial fibrillation'/exp	105191
2	'atrial fibrillation':ab,ti	81199
3	'auricular fibrillation':ab,ti	912
4	#1 OR #2 OR #3	112956
5	'prescription drug misuse'/exp	6137
6	'inappropriate prescribing'/exp	2269
7	'medication errors'/exp	14644
8	'medical overuse':ab,ti	16
9	'health services misuse':ab,ti	2
10	'inappropriate use':ab,ti	3736
11	overtreat*:ab,ti	4664
12	overdos*:ab,ti	23617
13	undertreat*:ab,ti	6488
14	overus*:ab,ti	10567
15	underus*:ab,ti	5879
16	'over treat*':ab,ti	2539

17	'under treat*':ab,ti	11638
18	'drug overdose'/exp	18583
19	misus*:ab,ti	18471
20	cha2ds2*:ab,ti	1603
21	#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20	112991
22	#4 AND #21	2860
23	apixaban:tn,rn,ab,ti	2682
24	dabigatran:tn,rn,ab,ti	5267
25	rivaroxaban:tn,rn,ab,ti	4663
26	edoxaban:tn,rn,ab,ti	814
27	eliquis:tn,rn,ab,ti	347
28	pradaxa:tn,rn,ab,ti	837
29	xarelto:tn,rn,ab,ti	728
30	#23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29	8932
31	#22 AND #30	420
32	'anticoagulants'/exp	556146
33	'administration, oral'/exp	385535
34	#32 AND #33	25858
35	(oral NEAR/3 anticoag*):ab,ti	17498
36	#34 OR #35	41734
37	#22 AND #36	960
38	'rivaroxaban'/exp	8027
39	'dabigatran'/exp	7337

40	'apixaban'/exp	5094
41	'edoxaban'/exp	1700
42	#38 OR #39 OR #40 OR #41	12198
43	#22 AND #42	473
44	#31 OR #37 OR #43	1141
45	'meta-analysis'/exp OR 'meta-analysis' OR 'systematic review'/exp OR 'systematic review'	248465
46	#44 AND #45	39
47	#46 NOT [medline]/lim	23
Notes	Systematic filter adapted from Wilczynski NL, 2007	

Appendix 5.2. Medline OvidSP

Date	**2016-07-18**	
Database	Medline OvidSP	
Search strategy		
1	Atrial Fibrillation/	41180
2	"atrial fibrillation".ab,ti,kw.	49476
3	"auricular fibrillation".ab,ti,kw.	1346
4	1 or 2 or 3	59427
5	exp Prescription Drug Misuse/	9498
6	Inappropriate Prescribing/	1457
7	exp medication errors/	13085
8	exp medical overuse/	4669
9	exp health services misuse/	8630

10	"inappropriate use".ab,ti,kw.	2728
11	overtreat*.ab,ti,kw.	3345
12	overdos*.ab,ti,kw.	17280
13	undertreat*.ab,ti,kw.	4789
14	overus*.ab,ti,kw.	8101
15	underus*.ab,ti,kw.	4671
16	over-treat*.ab,ti,kw.	1611
17	under-treat*.ab,ti,kw.	7054
18	drug overdose/	8684
19	misus*.ab,ti,kw.	14539
20	CHA2DS2*.ab,ti,kw.	846
21	5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20	85610
22	4 and 21	1425
23	limit 22 to systematic reviews	51
24	apixaban.ab,ti,kw,nm,rn.	1706
25	dabigatran.ab,ti,kw,nm,rn.	3209
26	rivaroxaban.ab,ti,kw,nm,rn.	2743
27	edoxaban.ab,ti,kw,nm,rn.	626
28	eliquis.ab,ti,kw,nm,rn.	35
29	pradaxa.ab,ti,kw,nm,rn.	110
30	xarelto.ab,ti,kw,nm,rn.	95
31	24 or 25 or 26 or 27 or 28 or 29 or 30	5011
32	22 and 31	170

33	exp Anticoagulants/	193755
34	exp administration, oral/	127335
35	33 and 34	5409
36	(oral adj3 anticoag*).ab,ti,kw.	11126
37	35 or 36	13374
38	22 and 37	510
39	Rivaroxaban/	1417
40	Dabigatran/	1764
41	39 or 40	2541
42	22 and 41	81
43	32 or 38 or 42	576
44	limit 43 to systematic reviews	23
Notes	Systematic review filter is adapted from NLM filter by Ovid.	

APPENDIX 6. SEARCH STRATEGIES FOR C-E CHAPTER

Appendix 6.1. Embase.com search strategy

(Embase.com includes both MEDLINE and Embase databases)

#22 #13 AND #21

#21 #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20

#20 'quality-adjusted life-year':ab,ti OR qaly:ab,ti

#19 incremental:ab,ti OR icer:ab,ti

#18 cost:ab,ti OR 'cost effective*':ab,ti OR economic*:ab,ti

#17 'cost minimization analysis'/de

#16 'cost utility analysis'/de

#15 'cost effectiveness analysis'/de

#14 'cost benefit analysis'/de

#13 #4 AND #12

#12 #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11

#11 'edoxaban'/de

#10 'apixaban'/de

#9 'rivaroxaban'/de

#8 'dabigatran etexilate'/de

#7 'dabigatran'/de

#6 pradaxa:ab,ti OR dabigatran:ab,ti OR xarelto:ab,ti OR rivaroxaban:ab,ti OR eliquis:ab,ti OR apixaban:ab,ti OR savaysa:ab,ti OR edoxaban:ab,ti

#5 anticoagulant*:ab,ti OR anticoagulation:ab,ti OR noac*:ab,ti

#4 #1 OR #2 OR #3

#3 (atrial OR atrium OR auricular) NEXT/1 (fibrillation OR flutter)

#2 'heart atrium flutter'/de

#1 'atrial fibrillation'/exp

Appendix 6.2. Cochrane Library search strategy

#1 MeSH descriptor: [Atrial Fibrillation] this term only

#2 MeSH descriptor: [Atrial Flutter] this term only

#3 ((atrial or atrium or auricular) next (fibrillation or flutter)):ti,ab,kw

#4 #1 or #2 or #3

#5 (anticoagulant* or anticoagulation or noac*):ti,ab,kw

#6 (pradaxa or dabigatran or xarelto or rivaroxaban or eliquis or apixaban or savaysa or edoxaban):ti,ab,kw

#7 MeSH descriptor: [Dabigatran] this term only

#8 MeSH descriptor: [Rivaroxaban] this term only

#9	#5 or #6 or #7 or #8
#10	#4 and #9

Appendix 6.3. CRD search strategy

1	MeSH DESCRIPTOR atrial fibrillation EXPLODE ALL TREES IN HTA
2	MeSH DESCRIPTOR atrial flutter EXPLODE ALL TREES IN HTA
3	("atrial fibrillation" OR "auricular fibrillation"):TI OR ("atrial flutter" OR "auricular flutter"):TI IN HTA
4	#1 OR #2 OR #3
5	(anticoagulant* OR anticoagulation OR noac*) IN HTA
6	(pradaxa OR dabigatran OR xarelto OR rivaroxaban OR eliquis OR apixaban OR savaysa OR edoxaban) IN HTA
7	#5 OR #6
8	#4 AND #7

APPENDIX 7. APPENDICES TO FLEMISH GPS' DATA

Appendix 7.1. Characteristics of patients with an OAC prescribed between 2009 and 2015 and without any chronic prescription of OACs

Approximately 45% of patients with no chronic prescription of OAC had an OAC prescribed only once during their FUP (n=975/2 168), 20% two times (n=432/2 168), and 12.9% three times (n=279/2 168). All in all, 22.1% of the patients had ≥4 prescriptions of an OAC during their FUP.

Almost all people had an OAC prescribed in only one year (n=2 016/2 168, 93.0%).

Variables	One year* with prescription(s) of OAC (N=2 016) median [P_{25}; P_{75}]	Two years* with prescription(s) of OAC (N=129) median [P_{25}; P_{75}]	Three years* with prescription(s) of OAC (N=22) median [P_{25}; P_{75}]	Four years* with prescription(s) of OAC (N=1) median [P_{25}; P_{75}]
Number of days between the first and last prescription of OAC	1 [1; 100]	637 [471; 883]	1 108 [830; 1 434]	1656
Mean number of OAC prescriptions per year	2.0 [1.0; 3.0]	1.5 [1.0; 2.0]	1.3 [1.1; 2.0]	1.5
Total number of OAC prescriptions during the FUP	2.0 [1.0; 3.0]	3.0 [2.0; 4.0]	4.0 [3.25; 6.0]	6
Length of FUP since the day first prescription of OAC until the end of FUP, in years	1.23 [0.56; 2.60]	3.22 [2.36; 4.46]	4.10 [2.97; 4.88]	5.04

Number of years with ≥1 prescription of OAC, since the day of the first prescription of OAC

Appendix 7.2. Comparison of patients' characteristics at $T0_{OAC}$ according to the first OAC prescribed between 2009 and 2015*

Variables	Total (N=1 312) Median [P_{25}; P_{75}] or n (%)	VKA as first OAC prescribed (N=904) Median [P_{25}; P_{75}] or n (%)	NOAC as first OAC prescribed (N=408) Median [P_{25}; P_{75}] or n (%)	p-value**
Patients' characteristics at $T0_{OAC}$				
Age, years	73 [66; 80]	72 [64; 79]	76 [70; 81]	<0.001
Age group				<0.001[a]
<65 years	287 (21.9)	251 (27.8)	36 (8.8)	
65-74 years	422 (32.2)	282 (31.2)	140 (34.3)	
≥75 years	603 (46.0)	371 (41.0)	232 (56.9)	
Females	559 (42.6)	377 (41.7)	182 (44.6)	0.325 [a]
Indication for an OAC prescription at $T0_{OAC}$				
Atrial fibrillation	771 (58.8)	481 (53.2)	290 (71.1)	<0.001 [a]
Deep vein thrombosis	76 (5.8)	65 (7.2)	11 (2.7)	<0.001 [a]
Lung embolism	68 (5.2)	63 (7.0)	5 (1.2)	<0.001 [a]
Valve problems	165 (12.6)	122 (13.5)	43 (10.5)	0.135 [a]
No indication recorded	373 (28.4)	270 (29.9)	103 (25.2)	0.306 [a]
Comorbidities included in CHA_2DS_2-VASc and $CHADS_2$ scores at $T0_{OAC}$				
Heart failure	103 (7.9)	74 (8.2)	29 (7.1)	0.502 [a]
Hypertension	570 (43.4)	374 (41.4)	196 (48.0)	0.024 [a]

Diabetes	284 (21.6)	196 (21.7)	88 (21.6)	0.963 [a]
Thromboembolic event				
Stroke	126 (9.6)	83 (9.2)	43 (10.5)	0.440 [a]
TIA	88 (6.7)	51 (5.6)	37 (9.1)	0.022 [a]
Stroke and/or TIA	200 (15.2)	126 (13.9)	74 (18.1)	0.050 [a]
Vascular disease				
Myocardial infarction	89 (6.8)	59 (6.5)	30 (7.4)	0.582 [a]
Peripheral arterial disease	110 (8.4)	79 (8.7)	31 (7.6)	0.490 [a]
MI and/or PAD	184 (14.0)	128 (14.2)	56 (13.7)	0.834 [a]
CHA_2DS_2-VASc score	3 [2; 4]	3 [1; 4]	3 [2; 4]	<0.001 [a]
0	*88 (6.7)*	*84 (9.3)*	*4 (1.0)*	
1	*195 (14.9)*	*155 (17.1)*	*40 (9.8)*	
≥2	*1 029 (78.4)*	*665 (73.6)*	*364 (89.2)*	
$CHADS_2$ score	1 [1; 2]	1 [0; 2]	1.5 [1; 2]	<0.001 [a]
0	*306 (23.3)*	*250 (27.7)*	*56 (13.7)*	
≥1	*1 006 (76.7)*	*654 (72.3)*	*352 (86.3)*	
Medications in the year before $T0_{OAC}$ (≥2 prescriptions)				
Diuretics	272 (20.7)	182 (20.1)	90 (22.1)	0.426 [a]
ACE inhibitors	305 (23.2)	192 (21.2)	113 (27.7)	0.010 [a]
ATII antagonists	184 (14.0)	121 (13.4)	63 (15.4)	0.321 [a]
Dihydropyridine	172 (13.1)	118 (13.1)	54 (13.2)	0.928 [a]
Verapamil	13 (1.0)	9 (1.0)	4 (1.0)	0.999 [b]
Diltiazem	24 (1.8)	14 (1.5)	10 (2.5)	0.259 [a]

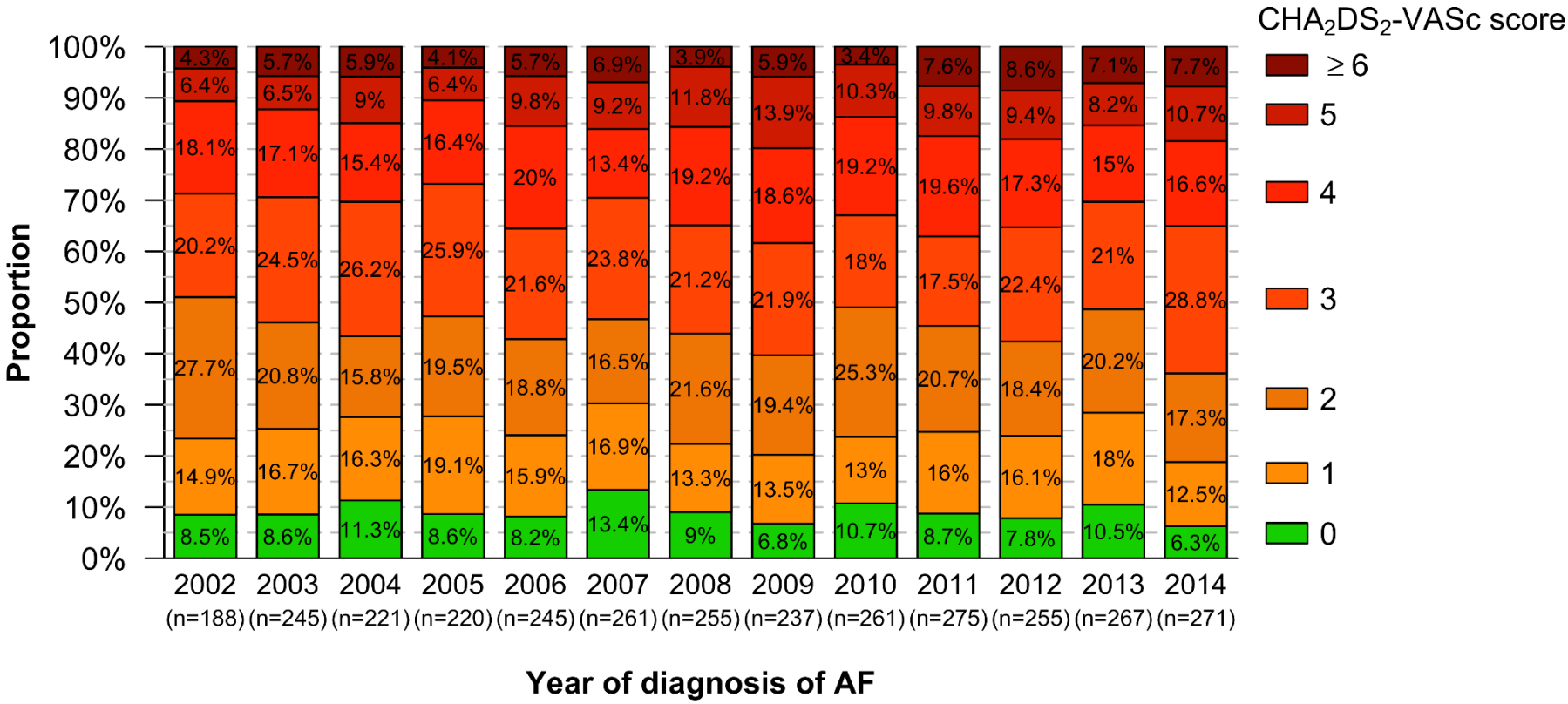
Beta-blockers	497 (37.9)	327 (36.2)	170 (41.7)	0.058 [a]
Anti-diabetics	190 (14.5)	127 (14.0)	63 (15.4)	0.507 [a]
Proxies for the CHA_2DS_2-VASc and $CHADS_2$ scores at $T0_{OAC}$				
Proxy for the CHA_2DS_2-VASc score				<0.001 [a]
0	87 (6.6)	82 (9.1)	5 (1.2)	
1	168 (12.8)	136 (15.0)	32 (7.8)	
≥2	1 057 (80.6)	686 (75.9)	371 (90.9)	
Chads2 to be added 0 or ≥1 (high risk)				<0.001 [a]
0	265 (20.2)	220 (24.3)	45 (11.0)	
≥1	1 047 (79.8)	684 (75.7)	363 (89.0)	

** Patients included in this table had the required FUP period*

*** Continuous variables were compared between the 2 groups using the Mann-Whitney U test; categorical variables were compared between the 2 groups using Pearson's chi-squared test (a) or Pearson's chi-squared test with Yates continuity correction (b) according to the conditions of validity.*

TIA: transient ischemic attack, MI: myocardial infarction; PAD: peripheral arterial disease

Appendix 7.3. CHA_2DS_2-VASc score at $T0_{AF}$ among patients* diagnosed with AF between 2002 and 2014



** Patients included in this figure had ≥ 1 year of FUP after $T0_{AF}$*

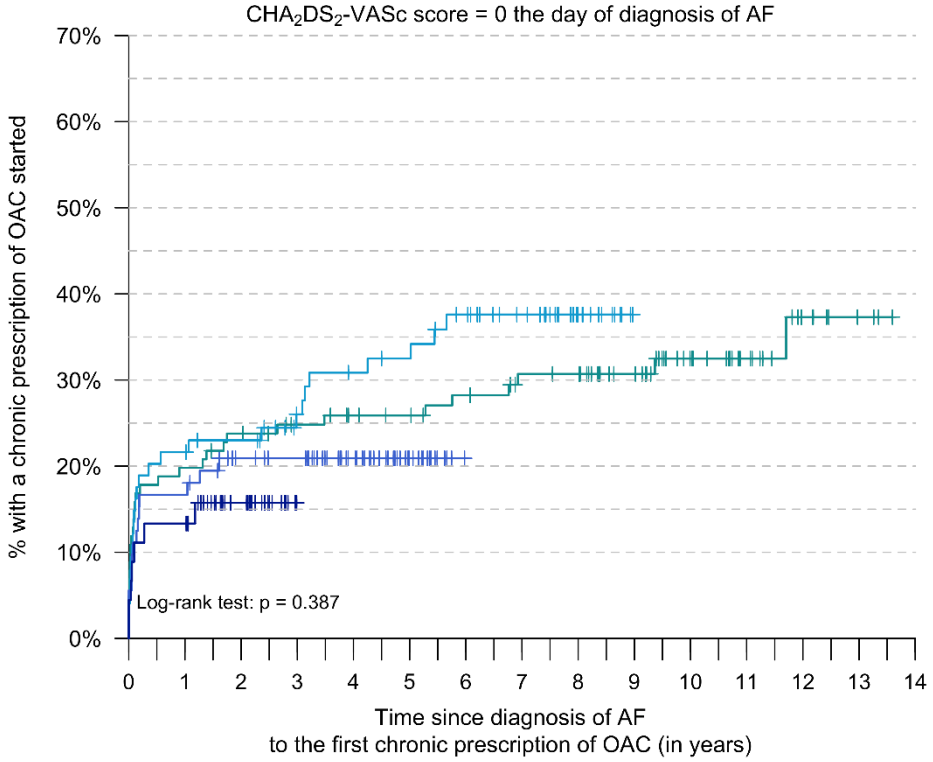
Appendix 7.4. Proportion of OAC prescriptions in AF patients* with a CHA_2DS_2-VASc score of 0 at $T0_{AF}$, 6 months to 3 years after $T0_{AF}$

Variable	Total	Diagnosis of AF between 2002 and 2006	Diagnosis of AF between 2007 and 2009	Diagnosis of AF between 2010 and 2012	Diagnosis of AF between 2013 and 2014	Log-rank test: p-value
Number of people at $T0_{AF}$	292	101	74	72	45	
Oral anticoagulation at 6 months						0.807
Number of people anticoagulated	51	18	15	12	6	
Proportion of people anticoagulated (95%CI)	0.175 (0.136-0.223)	0.178 (0.116-0.268)	0.203 (0.128-0.314)	0.167 (0.098-0.275)	0.133 (0.062-0.273)	
Oral anticoagulation at 1 year						0.672
Number of people anticoagulated	54	20	16	12	6	
Proportion of people anticoagulated (95%CI)	0.185 (0.145-0.234)	0.198 (0.133-0.29)	0.216 (0.138-0.328)	0.167 (0.098-0.275)	0.133 (0.062-0.273)	
Oral anticoagulation at 2 years						0.716
Number of people anticoagulated	63	24	17	15	7	
Proportion of people anticoagulated (95%CI)	0.216 (0.173-0.268)	0.238 (0.166-0.333)	0.230 (0.15-0.343)	0.208 (0.131-0.322)	0.156 (0.077-0.299)	
Oral anticoagulation at 3 years						0.559
Number of people anticoagulated	66	25	19	15	7	
Proportion of people anticoagulated (95%CI)	0.226 (0.182-0.278)	0.248 (0.175-0.344)	0.257 (0.172-0.372)	0.208 (0.131-0.322)	0.156 (0.077-0.299)	

** Patients included in this table had ≥ 1 year of FUP after $T0_{AF}$*

95%CI: 95% confidence interval

Appendix 7.5. Time to the first chronic prescription of OAC in AF patients* with a CHA_2DS_2-VASc score of 0 at $T0_{AF}$



Year of AF diagnosis	Number of people not anticoagulated at time t														
2002-2006	101	81	76	71	67	65	61	55	54	44	30	19	8	3	/
2007-2009	74	58	55	46	42	40	35	27	12	/	/	/	/	/	/
2010-2012	72	60	51	48	32	14	/	/	/	/	/	/	/	/	/
2013-2014	45	39	22	/	/	/	/	/	/	/	/	/	/	/	/

** Patients included in this figure had ≥ 1 year of FUP after $T0_{AF}$*

The log-rank test was computed for the whole FUP period

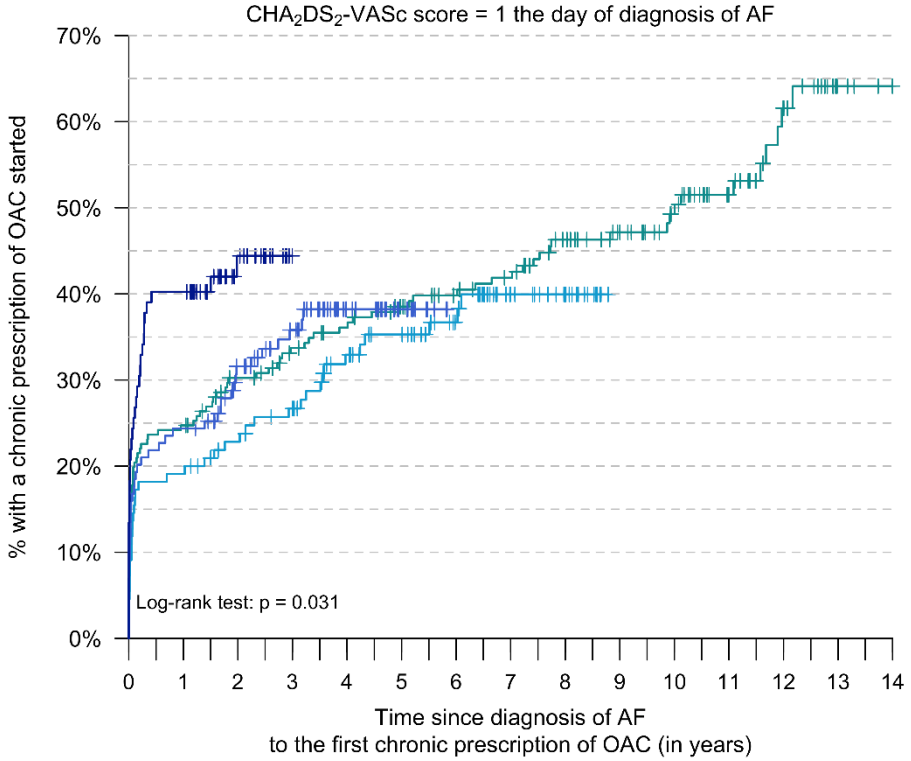
Appendix 7.6. Proportion of OAC prescriptions in AF patients* with a CHA_2DS_2-VASc score of 1 at $T0_{AF}$, 6 months to 3 years after $T0_{AF}$

Variable	Total	Diagnosis of AF between 2002 and 2006	Diagnosis of AF between 2007 and 2009	Diagnosis of AF between 2010 and 2012	Diagnosis of AF between 2013 and 2014	Log-rank test: p-value
Number of people at $T0_{AF}$	497	186	110	119	82	0.003
Oral anticoagulation at 6 months						
Number of people anticoagulated	123	44	20	26	33	
Proportion of people anticoagulated (95%CI)	0.247 (0.212-0.288)	0.237 (0.182-0.304)	0.182 (0.121-0.267)	0.218 (0.154-0.304)	0.402 (0.306-0.517)	
Oral anticoagulation at 1 year						0.009
Number of people anticoagulated	129	46	21	29	33	
Proportion of people anticoagulated (95%CI)	0.260 (0.223-0.300)	0.247 (0.192-0.316)	0.191 (0.129-0.278)	0.244 (0.176-0.331)	0.402 (0.306-0.517)	
Oral anticoagulation at 2 years						0.032
Number of people anticoagulated	153	56	25	37	35	
Proportion of people anticoagulated (95%CI)	0.308 (0.269-0.350)	0.301 (0.241-0.373)	0.227 (0.16-0.317)	0.311 (0.236-0.402)	0.427 (0.328-0.541)	
Oral anticoagulation at 3 years						0.130
Number of people anticoagulated	167	62	29	41	35	
Proportion of people anticoagulated (95%CI)	0.336 (0.296-0.379)	0.333 (0.271-0.406)	0.264 (0.191-0.357)	0.345 (0.267-0.437)	0.427 (0.328-0.541)	

** Patients included in this table had ≥ 1 year of FUP after $T0_{AF}$*

95%CI: 95% confidence interval

Appendix 7.7. Time to the first chronic prescription of OAC in AF patients* with a CHA_2DS_2-VASc score of 1 at $T0_{AF}$



Year of AF diagnosis	Number of people not anticoagulated at time t														
2002-2006	186	140	124	113	106	97	89	83	69	58	46	30	17	4	/
2007-2009	110	89	81	75	61	52	40	21	13	/	/	/	/	/	/
2010-2012	119	90	72	58	32	12	/	/	/	/	/	/	/	/	/
2013-2014	82	49	23	/	/	/	/	/	/	/	/	/	/	/	/

** Patients included in this figure had ≥ 1 year of FUP after $T0_{AF}$*

The log-rank test was computed for the whole FUP period

APPENDIX 8. APPENDICES TO BELGIAN IMA DATA

Appendix 8.1. Number of INR tests performed in the year following the first OAC prescription – Chronic AF users

		VKA	NOAC	All
Period 2005-2011		**N=154 015**	**N=139**	**N=154 154**
	0 test	5 001 (3.2%)	18 (12.9%)	5 019 (3.3%)
	1-2 tests	5 589 (3.6%)	98 (70.5%)	5 687 (3.7%)
	3-5 tests	6 528 (4.2%)	22 (15.8%)	6 550 (4.2%)
	6-10 tests	13 519 (8.8%)	1 (0.7%)	13 520 (8.8%)
	11+ tests	123 378 (80.1%)	0 (0.0%)	123 378 (80.0%)
Period 2012-2014		**N=39 424**	**N=59095**	**N=98 519**
	0 test	1 009 (2.6%)	29461 (49.9%)	30 470 (30.9%)
	1-2 tests	0 798 (2.0%)	19561 (33.1%)	20 359 (20.7%)
	3-5 tests	0 882 (2.2%)	6532 (11.1%)	7 414 (7.5%)
	6-10 tests	2 574 (6.5%)	2358 (4.0%)	4 932 (5.0%)
	11+ tests	34 161 (86.7%)	1183 (2.0%)	35 344 (35.9%)

Source: IMA – AIM database. Nomenclature codes 554573 & 554584.

Appendix 8.2. Number of Renal tests performed in the year following the first OAC prescription – Chronic AF users

		VKA	NOAC	All
Period 2005-2011		**N=154 015**	**N=139**	**N=154 154**
	0 test	23 489 (15.3%)	2 (1.4%)	23 491 (15.2%)
	1-2 tests	52 704 (34.2%)	39 (28.1%)	52 743 (34.2%)
	3-5 tests	35 467 (23.0%)	74 (53.2%)	35 541 (23.1%)
	6-10 tests	21 547 (14.0%)	23 (16.5%)	21 570 (14.0%)
	11+ tests	20 808 (13.5%)	1 (0.7%)	20 809 (13.5%)
Period 2012-2014		**N=39 424**	**N=59095**	**N=98 519**
	0 test	4 141 (10.5%)	6752 (11.4%)	10 893 (11.1%)
	1-2 tests	12 467 (31.6%)	25390 (43.0%)	37 857 (38.4%)
	3-5 tests	9 788 (24.8%)	15187 (25.7%)	24 975 (25.4%)
	6-10 tests	6 088 (15.4%)	6883 (11.6%)	12 971 (13.2%)
	11+ tests	6 940 (17.6%)	4883 (8.3%)	11 823 (12.0%)

Source: IMA – AIM database. Nomenclature codes: 540330 & 540341.

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