Author's accepted manuscript

Warfarin versus dabigatran etexilate: an assessment of efficacy and safety in patients with atrial fibrillation.

Dzeshka MS, Lip GY

Expert Opin Drug Saf. 2015 Jan; 14(1): 45-62.

DOI: 10.1517/14740338.2015.973847

Warfarin versus dabigatran etexilate: an assessment of efficacy and safety in patients with atrial fibrillation

Abstract

Introduction Oral anticoagulation is the mainstay for stroke and thromboembolic events prevention in patients with atrial fibrillation (AF). Given limitations of warfarin therapy non-vitamin K oral anticoagulants have been developed, including direct thrombin inhibitors (i.e. dabigatran etexilate). Dabigatran etexilate has been tested thoroughly in terms of efficacy and safety in clinical trials and studies, involving 'real world' cohorts. In this review currently available evidence in patients with non-valvular AF is discussed.

Areas covered The pharmacology, efficacy and safety, and current aspects of use of dabigatran etexilate in patients with non-valvular AF are reviewed in comparative manner to warfarin both for chronic anticoagulation and in different clinical settings.

Expert opinion Dabigatran etexilate appeared to have several pharmacokinetic and pharmacodynamic advantages over warfarin as well as a favourable efficacy and safety profile being at least non-inferior and often superior to warfarin in patients with non-valvular AF. The latter was shown in the clinical trials, meta-analyses and studies with 'real world' data. Currently ongoing trials will expand the body of evidence on warfarin and will aid decision-making in currently controversial areas. Important limitations of dabigatran etexilate include contraindications for its use in patients with prosthetic heart valves and end-stage chronic kidney disease.

Key words: dabigatran etexilate, warfarin, oral anticoagulation, atrial fibrillation, efficacy, safety.

1. Introduction

Atrial fibrillation (AF) is the most prevalent sustained cardiac arrhythmia which affects approximately 1-3% of general population (i.e. aged 20 years and older).[1,2] AF is also increasing in prevalence and incidence, leading to a doubling of AF prevalence during next few decades.[1] Given that AF is frequently asymptomatic, various new screening technologies allow detection of previously undiagnosed AF in about 1.5% of individuals age ≥65 years.[3,4] Stroke is known to be the most devastating and fearing complication of AF associated with prolonged disability, increased mortality and high health care costs.[5] Moreover stroke is often the first manifestation of AF that can be diagnosed subsequently with long-term ECG monitoring.[6]

Stroke risk is not homogenous and current guidelines[7,8] focus on initial identification of low risk patients (i.e. those with lone AF and aged less than 65 years, essentially a CHA_2DS_2-VASc score of 0 [males] or 1 [females]), who do not need any antithrombotic therapy. The subsequent step is that effective stroke prevention can be offered to patients with ≥1 additional stroke risk factors in whom benefits of stroke and thromboembolic events prevention clearly outweigh risk of bleeding events.[9,10] Current guidelines use the CHA_2DS_2-VASc stroke risk assessment score whilst bleeding risk is assessed with the HAS-BLED score (Table 1).[11,12]

Effective stroke prevention means oral anticoagulation (OAC). Warfarin, the main representative of the vitamin K antagonists, was the only available option of OAC for prevention of stroke and other thromboembolic complications in AF for many years until recently. Treatment with warfarin was found to reduce stroke rate both in primary and

secondary setting by 64 % (95% [confidence interval] 49-74) and all-cause mortality by 26 % (95% CI 3–43).[12] However, a range of limitations, associated with the warfarin therapy, e.g. slow onset and offset of action, narrow therapeutic window, mandatory regular laboratory monitoring, multiple food and drug interactions, variability of response depending on genetic polymorphism and ethnicity, etc.) all triggered the development of alternative agents, the non-vitamin K OAC (NOAC) drugs as direct thrombin inhibitors (e.g. dabigatran etexilate) and factor Xa inhibitors (e.g. apixaban, rivaroxaban, edoxaban).[14-16]

The current review is focused on the pharmacology, efficacy and safety of direct thrombin inhibitor dabigatran etexilate. The latter has gained European Medicines Agency (EMA) approval for prevention of stroke and systemic embolism in patients with non-valvular AF and a risk factor for stroke; primary prevention of venous thromboembolic events (VTE) in patients undergoing elective total hip/knee replacement surgery; treatment of deep vein thrombosis (DVT) and pulmonary embolism; and the prevention of recurrent DVT and PE in adults.[17] The United States Food and Drug Administration (FDA) has approved dabigatran etexilate to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation; for the treatment of DVT and PE in patients who have been treated with a parenteral anticoagulant for 5 to 10 days; and to reduce the risk of recurrence of DVT and PE in patients who have been previously treated.[18]

Review of all available evidence on dabigatran etexilate in all approved conditions is far beyond the scope of one article. We would particularly focus on the efficacy and safety of dabigatran etexilate in different clinical situations in AF management as chronic anticoagulation in non-valvular AF, cardioversion and catheter ablation of AF, AF in patients with coronary heart disease, chronic kidney disease, obesity, etc.

2. Pharmacology of dabigatran and warfarin

Treatment with warfarin results in synthesis of vitamin K dependant coagulation factors (i.e. II, VII, IX, X, Figure 1) with decreased coagulation activity because of reduced number of carboxylated residues of glutamic acid. Carboxylated residues serve as calcium-binding domains and are essential to reach positive charge with calcium ions. Positively charged coagulation factors are then attracted to injured vessel wall with negative charge and cause downstream activation of coagulation cascade.[19] Balancing the carboxylated and decarboxylated calcium-binding domains and, hence, degree of anticoagulation depends on extent of vitamin K epoxide reductase complex subunit 1 (VKORC1) inhibition with warfarin.[19] Presence of different genetic variants of the VKORC1 as well as of cytochrome P450-2C9 [CYP2C9] and few other genes in individual determines extent and wide variability of anticoagulation effect of warfarin.[19]

On the contrary, direct thrombin inhibitors (e.g., dabigatran) bind to active catalytic site of thrombin (factor IIa, serine protease) in competitive and reversible manner and block the final stage of coagulation cascade, i.e. synthesis of fibrin from fibrinogen and its stabilization (Figure 1).[20-22] Dabigatran is capable of inhibiting both free thrombin and fibrin-bound thrombin. Because thrombin realizes multiple effects in haemostatic system, e.g. activation of coagulation factors V, VIII, XI and XIII; inhibition of fibrinolysis; platelet activation; inflammatory changes, etc., dabigatran interferes with these reactions as well.[20-22]

The drug was developed as non-active pro-drug dabigatran etexilate (drug substance is the mesilate salt of dabigatran etexilate) that is converted into dabigatran in vivo (in the gut

mucosa, liver and plasma) via non-specific ubiquitous esterases, specifically carboxylesterase-1.

The oral bioavailability of dabigatran in capsules is approximately 6.5% (ranging 3 to 7 %). It showed moderate to high intersubject variability of 31.4% and 53.5% for the area under the plasma concentration–time curve at steady state in healthy volunteers.[23] Removing the hydroxypropyl methylcellulose shell that encapsulates dabigatran etexilate and helps to stabilize the drug may significantly increase (by 75 %) dabigatran bioavailability. Food intake does not affect bioavailability of dabigatran. Formulation of dabigatran etexilate with tartaric acid allows to reduce the variability of its absorption, which is originally dependent on gastrointestinal tract acidity. For example, co-administration with pantoprazole decreases the bioavailability of dabigatran with the peak plasma concentration at steady state of approximately 28% lower with the proton pump inhibitor than without it.[24] Renal excretion is the dominant elimination pathway (up to 80%) for dabigatran applies limitations for patients with reduced glomerular filtration rate.[16,25-27] Pharmacological characteristics of dabigatran versus warfarin are summarized in table 2.

Thus, dabigatran etexilate in comparison to warfarin has range of advantages: fixed dose and no need for frequent laboratory control, more rapid onset and shorter offset of action, fewer drug and no food interactions.

3. Efficacy and safety of dabigatran in atrial fibrillation

3.1 Chronic anticoagulation in non-valvular AF

The RE-LY (Randomized Evaluation of Long-term anticoagulation therapy) trial was open-label between dose-adjusted warfarin (international normalized ratio [INR] 2.0-3.0) and dabigatran arms but double-blind between two dabigatran doses, i.e., 150 and 110 mg twice a day (Table 3).[28,29]

The efficacy analysis showed non-inferiority of dabigatran etexilate 110 mg bid (1.54 %/year) and superiority of dabigatran etexilate 150 mg bid (1.11 %/year) to warfarin (1.71 %/year) for prevention of stroke and systemic embolism.[28,29] Whilst the rate of major bleeding did not differ between warfarin (3.57 %/year) and dabigatran etexilate 150 mg bid (3.32 %/year) and was lower in dabigatran etexilate 110 mg bid arm (2.87%/year), both dosing regimens were associated with reduced risk of intracranial haemorrhage (ICH): 0.23 and 0.30 %/year in dabigatran etexilate arms, 110 mg and 150 mg bid respectively versus 0.74 %/year in warfarin arm.[28,29] Noteworthy, results on primary efficacy and safety outcome appeared to be consistent across different stroke risk strata (based on the $CHADS_2$ score).[30] However, there was an increased risk of gastrointestinal bleeding but with high dose regimen only (1.51 versus 1.02 %/year).[28]

A non-significant increase in rate of myocardial infarction (MI) was observed in both dabigatran arms. But cardio-vascular and all-cause mortality did not differ between warfarin and the dabigatran etexilate arms, and dabigatran etexilate 150 mg bid was even associated with a lower risk of cardio-vascular mortality.[28,29]

Both doses of dabigatran etexilate remained non-inferior to warfarin in patients with previous history of stroke or transient ischaemic attack.[31] In this subset of patients, treatment with dabigatran etexilate resulted in reduction of haemorrhagic stroke when compared to warfarin (relative risk [RR] 0.27, 95% CI 0.10–0.72 for dabigatran etexilate 150 mg bid; RR 0.11,

95% CI 0.03–0.47 for dabigatran etexilate 110 mg bid) and ICH (RR 0.20, 95% CI 0.08–0.47 for dabigatran etexilate 150 mg bid; RR 0.41, 95% CI 0.21–0.79 for dabigatran etexilate 110 mg bid).[31] Low dose of dabigatran was also associated with a reduced rate of death from vascular causes (RR 0.63, 95% CI 0.43–0.92) and death from any cause (RR 0.70, 95 CI% 0.53–0.94).[31]

In a modelling analysis, when hazard ratios (HR) from the RE-LY trial were applied to the high-risk (CHA_2DS_2-VASc score ≥2) population from the EuroHeart Survey on AF 34 strokes could be prevented with dabigatran etexilate 150 mg bid, and 16 strokes and 6 major bleeds could be avoided with dabigatran etexilate 110 mg bid in comparison to therapy in the study, which were warfarin, aspirin or nothing.[32] For the whole European population this would mean prevention of an additional 43 235 major cardiovascular events and deaths each year among patients with a CHA_2DS_2-VASc score ≥2 with the use of dabigatran etexilate 150 mg bid and 27 272 with the use of dabigatran etexilate 110 mg bid.[32] Another post-hoc simulation of dabigatran etexilate use based on the RE-LY trial dataset but with current European indications and dosing (Table 2) confirmed higher net clinical benefit of dabigatran etexilate administration in comparison to warfarin.[33]

Approximately half of patients under dabigatran etexilate treatment from the RE-LY trial were enrolled to the Long-term Multicenter Extension of Dabigatran Treatment in Patients with Atrial Fibrillation (RELY-ABLE) in which consistent with the RE-LY data were obtained as for the rates of major ischemic, haemorrhagic, and fatal outcomes. The only difference between low and high doses of dabigatran etexilate was the rate of major bleeding, which was higher with the 150 mg bid regime (HR 1.26; 95% CI 1.04-1.53).[34]

Given the results from the pivotal trial on dabigatran etexilate it was quite unexpected to initially get unusually high number of reports (via FDA Adverse Event Reporting System) of serious and fatal bleeding events associated with the dabigatran etexilate administration. The rate of bleeding events appeared to be even higher than amongst patients taking warfarin.[35] One explanation for this was the so-called 'Weber effect' where newly introduced drugs had an initial excess high rate of submission of adverse reports on serious bleeding driven by novelty and increased attention to the 'new' dabigatran etexilate versus the 'old' drug warfarin.[36]

In subsequent analysis undertaken by FDA on the actual rates of gastrointestinal and ICH in anticoagulation-naïve patients with AF starting dabigatran etexilate or warfarin confirmed favourable safety profile of dabigatran.[37] Data were collected from FDA's Mini-Sentinel database, pilot project of surveillance system the Sentinel Initiative, that monitors the safety of FDA-regulated medical products and included more than ten thousand records.[37] The incidence rate per 100 000 days at risk appeared to be 2.1-3.0 and 1.6-2.2 times higher in new warfarin users for intracranial and gastrointestinal haemorrhage respectively.[37] Because data were collected from insurance claims and administrative data no adjustment was performed for confounding bleeding risk factors and medical records were not reviewed for actual presence of AF and bleeding events in involved patients.[37]

Finally, the most recent analysis carried out by FDA amongst Medicare beneficiaries aged 65 years or more (>134 000 patients included and 37 500 person-years of follow-up) showed lower risk of ischaemic stroke (HR 0.80, 95% CI 0.67-0.96); ICH (HR 0.34, 95% CI 0.26-0.46) and mortality (HR 0.86, 95%CI 0.77-0.96) in AF patients taking either dabigatran etexilate 150 mg bid or 75 mg bid if dose reduction was necessary in comparison to those

taking warfarin.[38] There was higher rate of major gastrointestinal bleeding (HR 1.28, 95% CI 1.14-1.44) in patients treated with dabigatran, but no difference was observed with respect to risk of MI (HR 0.92, 95% CI 0.78-1.08).[38] Thus, apart from data on MI rate, results from Medicare database appeared to be consistent with those from the RE-LY trial.

Additional dabigatran etexilate safety and efficacy were obtained in the 'real world' Danish nationwide cohort study (Table 3).[39] The major difference from the RE-LY trial was even better safety profile of dabigatran etexilate, for example lower rate of gastrointestinal bleeding in low dose and the same rate in high dose dabigatran etexilate as well as lower risk of MI with both doses, which were attributed in part to the generally lower risk population from everyday clinical practice.[39] Interestingly, an earlier modeling analysis on patients from the Danish National Patient Registry also showed a positive net clinical benefit of dabigatran etexilate over warfarin starting from the CHA_2DS_2-VASc score of 1 regardless of risk of bleeding with the greatest benefit expected in patients with both high risk of stroke and bleeding.[40]

3.2 Impact of dabigatran exposure on its efficacy and safety

Safety and efficacy of dabigatran may be correlated to its plasma levels. Polymorphism of two genes, CES1 encoding carboxylesterase-1, and ABCB1, encoding polymorphic drug efflux transporter permeability glycoprotein (P-gp) have been shown to have impact on dabigatran concentrations.[41] In a genome-wide association study in the RE-LY participants the CES1 single-nucleotide polymorphism rs2244613 was found to be associated with both trough (15% decrease per minor allele) and peak (12% decrease per minor allele) plasma concentrations of dabigatran whilst for rs8192935 association with peak concentration (12% decrease per minor allele) was revealed.[41]

There was significantly lower risk of any bleeding in minor allele carriers (HR 0.72, 95% CI, 0.58–0.90) but only non-significant trend towards lower risk of major bleeding. No association was observed with ischemic events as well. For the CES1 single-nucleotide polymorphism rs8192935 as well as ABCB1 single-nucleotide polymorphism rs4148738 (12% increase in dabigatran peak concentration per minor allele) no associations were observed with any adverse clinical events.[41] Importantly, CES1 rs2244613 minor allele was detected in 32.8% of patients in the RE-LY trial, however there were only 3.4% of patients, who were homozygous for this allele.[41]

Overall in the RE-LY population 5.2-fold (28.2 to 155 ng/mL) and 5.5-fold (39.8 to 215 ng/mL) variability of dabigatran concentration between 10^{th} and 90^{th} percentiles was observed for 110 mg bid and 150 mg bid regimes respectively.[42] Thus, a proportion of patients appeared to have very low (and, hence, decreased stroke protection) or very high (and, hence, increased bleeding risk) plasma levels of dabigatran. Concentration-dependent increased risk of bleeding events was observed: patients with major bleeds had dabigatran concentrations (geometric mean, 10^{th}-90^{th} percentiles) of 113 (46.7-269) ng/mL versus 72.8 (30.7-175) ng/mL in patients without any bleeds.[42] On the contrary, the risk of stroke and systemic embolism was less dependent on dabigatran plasma levels: 76.6 (26.4-185) ng/mL versus 76.5 (32.1-186) ng/mL in patients with and without occurrence of events respectively.[42]

These data raised concerns about necessity of laboratory control of dabigatran concentration and appropriate dose adjustment instead of fixed dose regime in order to improve further patients outcomes, particularly, to reduce risk of bleeding complications.[43-45] An algorithm for dabigatran etexilate dose adjustment has even been proposed, that includes assessment of

dabigatran trough concentration (C_{trough}) after one week treatment with dabigatran etexilate 150 mg bid, followed by dose reduction to 75 mg bid if C_{trough} ≥140 ng/mL; 110 mg bid if C_{trough} ≥90 and <140 ng/mL; or continuation of the 150 bid regime if C_{trough} <90 ng/mL.[43] Of note, EMA published therapeutic ranges for dabigatran of 48 ng/mL (concentration below which partial loss of efficacy is very likely) to 200 ng/mL (concentration above which risk of bleeding is increased),[46] which is very close to 10^{th}-90^{th} percentile range obtained with the 150 mg bid regime in the RE-LY trial.[42]

Dose adjustment for dabigatran etexilate perhaps is reasonable in selected group of patients at higher risk (e.g., elderly and/or those with renal dysfunction). However, at a population level such an approach will eventually meet many obstacles as absence of routinely available assays for measurement of dabigatran concentration, and a considerable decrease of practicality of anticoagulation management, as well as a reduction of adherence to more complex treatment schemes, higher probability of mistakes, etc.

Also, the variability of dabigatran concentration should be perceived against the trial results, i.e. at least non-inferiority of dabigatran etexilate fixed dose approach to well-adjusted warfarin. Taken together these data indicate a wide therapeutic window of dabigatran etexilate. Moreover modelling analyses, performed by Boehringer Ingelheim, failed to predict reliably actual patients outcomes when dose adjustment strategy was applied, supporting fixed dose regime.[47]

Thus, future prospective trials are warranted to answer whether assay-guided dosing or genotyping will lead to improvement of dabigatran etexilate therapy and optimization of the balance between efficacy and safety.

3.3 Cardioversion of atrial fibrillation

Cardioversion of AF to sinus rhythm is associated with an increased risk of thromboembolic complications, therefore in patients with AF of ≥48 h or unknown duration OAC is required at least 3 weeks before and a minimum of 4 weeks after cardioversion (whether direct current or pharmacological) although OAC should be continued subsequently based on stroke risk according to CHA_2DS_2-VASc score.[7,8]

One retrospective analysis included patients who underwent cardioversion within the RE-LY trial.[48] Total of 1 983 cardioversions were performed in 1 270 patients, vast majority of which were direct current cardioversions. Numbers of patients with either left atrial (LA) thrombus (1.8% and 1.2% in low and high dose of dabigatran, respectively, versus 1.1% in warfarin arm) or left atrial spontaneous echo contrast (21.2% and 27.2% in low and high dose of dabigatran etexilate, respectively, versus 31.8 % in warfarin arm) on transoesophageal echocardiography (TOE) did not differ between three treatment groups. Analysis revealed the following rate of stroke and thromboembolic events: 0.48% and 0.46% for treatment with dabigatran etexilate (similar for both doses) and warfarin, respectively.[48] Rates of major bleeding also did not differ between groups: 2.66% in high dose dabigatran etexilate, 0.48% in low dose dabigatran etexilate, and 0.46% in warfarin.[48] Also, no complications related to cardioversion and no echocardiographic evidence of LA thrombus at a background of anticoagulation with dabigatran etexilate were observed in small retrospective study of Yadlapati et al.[49]

Transoesphageal echocardiography (TOE) is probably the most sensitive and specific technique to detect LA or LA appendage (LAA) thrombi as a potential source of systemic

embolism in AF. TOE guided cardioversion is an alternative to 3 weeks of anticoagulation prior to cardioversion.[7,8,50-52] For patients undergoing TOE-guided cardioversion who have no identifiable thrombus, cardioversion is recommended immediately after anticoagulation with heparin. If thrombus is identified, appropriate oral anticoagulation is required for at least 3 weeks, followed by a repeat TOE to ensure thrombus resolution. If thrombus resolution is evident on repeat TOE, cardioversion can be performed. If thrombus remains on repeat TOE, cardioversion is contraindicated, and alternative strategy (e.g. rate control) may be considered. LA/LAA thrombus should also be excluded before catheter ablation of AF.[7,8] Importantly, the absence of LA/LAA thrombus on TOE gives an opportunity to shorten time cardioversion but does not preclude the need for anticoagulation during (with heparin) and after cardioversion (with OAC). Thus, anticoagulation during pericardioversion period with dabigatran etexilate is a reasonable option, particularly given a more predictable anticoagulation effect.

No laboratory assays are available for routine estimation of anticoagulation intensity with dabigatran etexilate and those alternative (e.g., diluted thrombin time, or ecarin clotting time) have important limitations as availability, sensitivity, variability and lack of validation.[53-56] Thrombin time (TT) and activated partial thromboplastin time (aPTT) can be used to ensure to some extent that patient is sufficiently anticoagulated. TT was found to be sensitive to the presence of dabigatran with a level of 60 ng/mL resulting in a marked prolongation of TT (> 300 s).[55] The aPTT was correlated with the dabigatran level but showed variability of the results depending on used aPTT reagents. It was also less responsive to high dabigatran concentration (plato with supratherapeutic levels of dabigatran).[55] Moreover, both parameters are often normal despite the therapeutic dabigatran plasma levels.[56] Thus, it is also of paramount importance to emphasise patient compliance to treatment before cardioversion.

3.4 Catheter ablation of atrial fibrillation

Radiofrequency catheter ablation for AF is increasingly used procedure in patients with symptomatic recurrent AF paroxysms, which are poorly tolerated or refractory to antiarrhythmic medications.[7,8,57]

In line with pre-existed risk of thromboembolic events in patients (e.g., those incorporated into the CHA_2DS_2-VASc score) there are additional factors which contribute to development of thromboembolic complications during the ablation procedure and post-procedural period, for example presence of foreign bodies in the circulation and areas of stasis produced by catheters, sheaths, and guidewires; blood proteins denaturation, endothelium damage, atrial stunning caused by tissue heating with radiofrequency energy, etc.[58]

Historically, patient underwent bridging with heparin before and following the ablation procedure. Given the increased number of bleeding complications, recommendations on periablation anticoagulation in AF changed in favour of uninterrupted treatment with warfarin that was associated with reduction of thromboembolic events at no cost of increased bleeding.[59,60] Importantly, despite both paroxysmal and non-paroxysmal AF confers increased risk of stroke and systemic embolism, in the periablation setting non-paroxysmal AF along with warfarin discontinuation and the $CHADS_2$ score were found to be an independent predictor of thromboembolic complications after catheter ablation of AF.[60]

As in cardioversion for AF at least three weeks of systemic anticoagulation at a therapeutic level is required in case of AF duration of 48 hours or longer (or unknown) prior to ablation

procedure, but anticoagulation during minimum of two months is required following the ablation.[57]

Patients with planned ablation were excluded from the RE-LY trial.[28] Uninterrupted treatment with dabigatran etexilate (with only one dose of dabigatran on the morning of the procedure being held and resumed within 3 hours after haemostasis) resulted in a significantly higher rate of bleeding or thromboembolic complications (odds ratio [OR] 2.76, 95% CI 1.22-6.25), which was driven by bleeding complications mostly (major bleeding rate 6% versus 1%, total bleeding rate 14% versus 6%, in dabigatran and warfarin groups, respectively).[61] On the contrary, in one study with the same approach (heparin was used after ablation in few cases depending on status of femoral puncture sites) no bleeding or thromboembolic complications were observed during periprocedural period and up to one year follow-up.[62]

Plenty of studies, which tested approach with interrupted dabigatran etexilate, typically withheld 12-24 hours pre-procedure and resumed 3-4 hours after vascular haemostasis was achieved (or alternatively heparin was given after procedure and dabigatran etexilate was started the day after the intervention), yielded a comparable safety profile for dabigatran etexilate and warfarin.[63-67]

In the absence of randomised controlled trials the best available evidence is that obtained from meta-analyses of smaller studies on safety and efficacy of dabigatran etexilate versus warfarin in patients undergoing catheter ablation (Table 4).[68-73] The majority of currently published meta-analyses provides reasonable support towards the safety and efficacy of dabigatran in the setting of ablation. Meta-analyses of Sardar et al included many studies with

more than 2 doses held before ablation, i.e. longer time of anticoagulation state that might be possible explanation for higher risk of stroke and TIA in comparison to warfarin.[71]

The RE-CIRCUIT trial (Randomized Evaluation of dabigatran etexilate Compared to warfarIn in pulmonaRy vein ablation: assessment of different peri-proCedUral antIcoagulation sTrategies) has been designed to prospectively evaluate uninterrupted treatment with dabigatran etexilate compared to warfarin, in patients with paroxysmal or persistent non-valvular AF who are scheduled to undergo a first ablation procedure, and will give a final answer on safety and efficacy of dabigatran in catheter ablation of AF.[74]

3.5 Acute and chronic coronary heart disease in association with atrial fibrillation

A substantial proportion of AF patients are those with coronary heart disease.[75] and need to undergo percutaneous intervention (PCI), often with stent implantation, these patients require therefore combination of OAC and anti-platelet agents (triple therapy) to cover both activation of coagulation cascade (predominant pathway in AF) and platelet activation and aggregation (predominant pathway in coronary heart disease).[76,77]

In the RE-LY trial 32.0% of patients received combination of OAC and aspirin alone, 1.9% - OAC and clopidogrel alone and 4.5% - OAC and both aspirin and clopidogrel.[78] Not surprisingly, concomitant use of a single antiplatelet agent brought increased risk of major bleeding (HR 1.60, 95% CI, 1.42–1.82), which was even higher with dual antiplatelet therapy (HR 2.31, 95% CI 1.79–2.98).[78] However, adding antiplatelet therapy did not affect advantages of dabigatran etexilate over warfarin. Low dose dabigatran etexilate remained non-inferior to warfarin with respect to stroke and systemic embolism and superior with respect to major bleeding and ICH.[78] In high dose dabigatran etexilate adding antiplatelet

therapy was associated with partially attenuated effect on stroke and systemic embolism prevention (non-inferior to warfarin) in comparison to subgroup with no antiplatelet therapy (superior to warfarin) but the same rate of major bleeding and lower rate of ICH were observed with dabigatran etexilate irrespectively of aspirin and/or clopidogrel used concomitantly.[78]

Another important issue of dabigatran use in patients with coronary heart disease is a non-significant trend towards increased rate of MI when compared with warfarin treatment, raising concerns that dabigatran etexilate may not provide appropriate protection against MI in patients with AF and coronary heart disease.[79] Whilst there was non-significant numerical increase observed in the RE-LY trial[28,29], several meta-analyses (which included trials on dabigatran etexilate in AF, acute coronary syndrome, PE and DVT) following it found increased risk of MI to be significant.[80,81] Overall similar results (more MIs with dabigatran etexilate) were obtained when any single study (including the RE-LY trial) was excluded from the analysis.[80,81] There was no increase in MI rate observed in trials with the factor Xa inhibitors, rivaroxaban and apixaban – however, numerically more MIs was seen with low-dose edoxaban compared to warfarin in the ENGAGE-AF trial.[82-84]

Larsen et al, who reported overall lower risk of MI in the 'real world' AF population in Denmark[39], in subgroup analysis amongst anticoagulation-naïve 'starters' of dabigatran etexilate or warfarin, and VKA-experienced 'continuers' of warfarin or 'switchers' from warfarin to dabigatran etexilate distinguished the latter to be the only group, that was at increased risk of MI, and only during early period after switching (within 2 months): HR 3.01, 95% CI 1.48-6.10 for 110 mg bid dosage; HR 2.97, 95% CI 1.31-6.73 for 150 mg bid

dosage.[85] Otherwise, MI rate was broadly the same with trend to lower risk in dabigatran starters and higher rate in warfarin to dabigatran switchers (irrespectively of time).[85]

One widely accepted explanation of higher rate of MI at a background of dabigatran comes from its pharmacology. Whilst warfarin acts by suppressing the synthesis of several coagulation factors (II, VII, IX, X) dabigatran inhibits activated factor II only. Hence, with the rupture of an atherosclerotic plaque, a patient receiving warfarin would have a low factor II level and would generate fewer factor IIa. On the contrast, a patient receiving dabigatran etexilate would have normal levels of factor II and inhibitory capacity of dabigatran etexilate dose sufficient for chronic systemic anticoagulation is probably insufficient to prevent coronary thrombosis as a result of locally increased factor II concentration in acute setting.[86] Also, if to compare impact of direct thrombin inhibitors and factor Xa inhibitors on coagulation, certain differences were seen with respect to thrombin generation as assessed with calibrated automated thrombogram. Various parameters can be measured with this assay, which allow characterising of the initiation, propagation and decay phase of thrombin generation.[87,88] Direct thrombin inhibitors were found to be more active in delaying the initiation phase of thrombin generation (lag time) whilst factor Xa inhibitors exerted a greater effect on propagation phase (time to peak and endogenous thrombin potential) that eventually might also affect risk of MI development.[87,88]

Nonetheless, according to current evidence overall magnitude of reduction in stroke, ICH and cardiovascular mortality seems to overweigh moderate increase of MI risk. The RE-DUAL PCI trial has been designed to investigate the efficacy and safety of dabigatran etexilate in patients with non-valvular AF who have undergone PCI with stenting.[89]

3.6 Chronic kidney disease in association with atrial fibrillation

On the one hand chronic kidney disease is associated with an increased risk of stroke or systemic thromboembolism and bleeding among patients with AF[90-93]; on the other, up to 80% of dabigatran are excreted via kidneys. In the RE-LY trial dabigatran etexilate was contraindicated in patients with creatinine clearance below 30 mL/min. The latter was further reflected amongst range of contraindications for dabigatran etexilate in the EU label. The 75 mg bid dose was approved by the FDA in the US for patients with CrCl 15-30 mL/min based on pharmacokinetic modeling and simulation.[94] A clinical trial to evaluate safety and efficacy of the latter regime has been designed thereafter.[95] In patients with CrCl below 15 mL/min only vitamin K antagonists can be used.

Thus, OAC use with dabigatran etexilate in AF at a background of chronic kidney disease is largely challenging.[96] In the ancillary analysis of the RE-LY trial on the efficacy and safety of dabigatran etexilate in relation to baseline renal function, rates of stroke or systemic embolism, major bleeding, and all-cause mortality increased with the decreasing glomerular filtration rate.[97] In general results for both doses of dabigatran etexilate were found to be consistent with the whole RE-LY trial irrespective of renal function, i.e. 110 mg bid dose was non-inferior to warfarin in terms of stroke and systemic embolism and superior in terms of ICH as well as 150 mg bid dosage was superior to warfarin in both cases.[97] Major bleeding was best prevented with both dosages of dabigatran in comparison to warfarin in patients with CrCl $\geq$80 mL/min, however with the progression of kidney dysfunction dabigatran showed only safety comparable to warfarin.[97]

Interestingly, anticoagulation with either dose of dabigatran etexilate in AF patients appeared to have a favourable effect on kidney function deterioration over time in comparison to

warfarin. The precise mechanism is not known, however vascular calcification with warfarin is one possible explanation.[98]

Importantly, low protein binding and high water solubility of dabigatran make it appropriate for removal with haemodialysis (for example in case of acute kidney injury, overdosing or any other emergent setting). Dabigatran plasma levels can be reduced approximately by half during 4 hours haemodialysis, which is also associated with proportional reduction of its anticoagulant activity.[99-101]

3.7 Anticoagulation with dabigatran etexilate in patients with obesity

Obesity is characterised with continuously increasing prevalence. Over half of the adult population in the world is expected to be overweight or to suffer from obesity by 2030.[102] It is also considered to be one of risk factors of incident AF.[103,104]

Stroke prevention in this group of patients is challenging because increased body weight affects pharmacokinetic properties of oral anticoagulants. For example, obesity was found to result in functional and structural kidney changes which lead to increased plasma flow and glomerular hyperfiltration.[105] Glomerular hyperfiltration apparently will result into increased drug clearance (for drugs with predominantly renal clearance) and, hence, lower plasma concentration of drug with the same dose compared to normally weighted individuals. Of note, relation between body weight and drug clearance is not linear. The latter depends more from lean body weight rather than from total one.[106] Increased body weight also has impact on distribution volume.

From this point of view fixed dose regime of anticoagulation with dabigatran etexilate could provide insufficient stroke protection in obese patients with AF. Amongst patients involved in the RE-LY trial there was inverse relationship between trough plasma concentration of dabigatran and body weight.[107] Nonetheless this did not translate into poorer outcomes in terms of stroke or systemic embolism with dabigatran etexilate in patients weighed over 100 kg (approximately 17% of patients in the RE-LY trial) in comparison to those with weight of <50 kg or 50 to 99 kg. Also, no difference with respect to efficacy and safety of dabigatran etexilate was observed in patients with body mass index (BMI) >25 kg/m^2 and overall population in the pooled analysis of venous thromboembolism prevention trials.[108] The negligible impact of increased body weight on area under the plasma concentration–time curve at steady state was also shown in a pharmacokinetic study with dabigatran etexilate in patients from the RE-LY cohort. Amongst tested parameters only kidney function was found to affect dabigatran plasma level in such a degree, which eventually might require dose adjustment.[94] Thus, dabigatran etexilate can be considered effective in obese patients. Given relatively scarce evidence, degree of obesity should be considered because effect of body weight in morbidly obese patients (i.e. BMI >40 kg/m^2) on dabigatran etexilate pharmacokinetics may potentially be more profound.

3.8 Periprocedural management of dabigatran etexilate therapy

The need for surgical intervention or invasive procedure amongst patients with AF under OAC is quite common. Balancing risk of stroke and systemic embolism on the one hand and risk of major bleeding on the other in this case is even more complicated. The risk of major periprocedural bleeding with OAC depends on the type of procedure. Minimal procedures are those with little tissue trauma (superficial skin and oral mucosal surgery, including skin biopsies, wound revisions, non-extraction dental treatment). Minor procedures were

procedures with little tissue trauma, but relevant bleeding risk: transluminal interventions, pacemaker-related surgery, pleural and peritoneal puncture, eye surgery, endoscopy, laparoscopy, organ biopsies, dental extraction, etc. Major procedures include open pelvic, abdominal and thoracic surgery, brain, vascular, orthopaedic and trauma surgery, i.e. surgery associated with significant tissue trauma and high bleeding risk.[109]

As dabigatran has faster onset and offset of action, more predictable pharmacodynamics and pharmacokinetic properties and less drug interactions in comparison to warfarin, use of dabigatran etexilate in periprocedural setting seems to be advantageous. However, the absence of antidote and routine laboratory test applies limitations.

Whilst warfarin requires INR adjustment and/or temporal interruption and bridging with heparin (particularly in patients with high risk of thromboembolic events and undergoing high bleeding risk procedures)[110], dabigatran etexilate probably does not. Minimal procedures can be performed at trough concentration (but not at the peak one which is at 2 hours after ingestion) with skipping one dose of dabigatran etexilate and restarting 6 hours after procedure.[16] Minor procedures require discontinuation of dabigatran for at least 24 hours before the elective procedure in patients with CrCl>80 mL/min, 36 hours – in patients with CrCl 50-80 mL/min, and 48 hours - in patients with CrCl 30-50 mL/min.[16] In case of major procedures above mentioned time intervals should be doubled. Resuming of full dose anticoagulation is possible within the first 48–72 hours.[16]

In case of emergent surgery, anticoagulant intensity of warfarin can be easily measured by the INR, and reversed if necessary with vitamin K, fresh frozen plasma, or prothrombin complex concentrate.[111] In patients anticoagulated with dabigatran etexilate it is

recommended to postpone surgery as long as possible.[16] Also dabigatran plasma concentration can be taken into account if appropriate facilities are available. EMA and Working Group on Perioperative Haemostasis (GIHP) suggested 48 ng/ml and 30 ng/ml, respectively as cut-off levels, below which surgery might be safely performed.[112]

If bleeding developed, in line with local haemostatic measures reversal agents can be used, which currently include activated and non-activated prothrombin complex concentrate and recombinant factor VIIa, but they should be used with caution as associated with high prothrombotic risk.[112-114]

Idarucizumab, a fully humanized antibody fragment (Fab), which was developed as a specific antidote for dabigatran will be evaluated in patients with uncontrolled bleeding or requiring emergency surgery or procedures.[115]

Approximately 25% of AF patients in the RE-LY study underwent at least one invasive procedure during follow-up, most common were insertion of implantable device, dental procedures, diagnostic procedures, cataract removal, colonoscopy and joint replacement.[116] Importantly, dabigatran etexilate and warfarin were associated with similar rates of periprocedural bleeding, both in elective and urgent settings.[116] Noteworthy, treatment with dabigatran etexilate was associated with a shorter interruption of oral anticoagulation, i.e. shorter time at increased risk of stroke and thromboembolic events.[116]

3.9 Prosthetic heart valves and dabigatran etexilate

The RE-ALIGN trial (The Randomized, phase II study to evaluate the safety and pharmacokinetics of oral dabigatran etexilate in patients after heart valve replacement)

enrolled patients who underwent aortic- or mitral-valve replacement and was terminated prematurely due to excess of thromboembolic and bleeding events among patients in the dabigatran arm compared with warfarin. Mechanical prosthetic heart valves are therefore a contraindication for the use of dabigatran.[117]

4. Adherence to treatment with dabigatran etexilate

Good adherence to treatment is of paramount importance in AF patients under oral anticoagulation, either VKA (e.g. warfarin) or NOAC (e.g. dabigatran etexilate). However, because of significantly shorter half-life (Table 2) on the contrary to warfarin dabigatran etexilate does not offer persistent anticoagulation effect within several days after last dose has been taken. Hence, good adherence is even more important in case of treatment with dabigatran etexilate.

Discontinuation rates in the RE-LY trial in both dabigatran arms was approximately 20%, but rate of discontinuation due to non-adherence was not reported.[28] The proportion of patients, which were found to have inadequate adherence (assessed as proportion of days covered <80%) to treatment with dabigatran etexilate in series of observational studies, ranges between 12-39.9%.[118-121] In one study, lower adherence was associated with increased risk for combined all-cause mortality and stroke (HR 1.13, 95% CI 1.07-1.19 per 10% decrease in proportion of days covered).[120]

There were concerns that non-requirement for regular laboratory monitoring could affect adherence. Probably this is not the case since currently available laboratory techniques allow us to assess the anticoagulation effect of the last taken dose whilst INR reflects warfarin activity across a number of days prior to the measurement.

Patient education and patient-physician shared decision making with respect to oral anticoagulation have tremendous potential to improve patient adherence to treatment, whatever anticoagulant is chosen.[122-124]

5. Conclusion

In terms of efficacy and safety dabigatran is at least non-inferior to warfarin but also has important advantages which make dabigatran a favourable option for oral anticoagulation in non-valvular AF instead of less convenient warfarin. Data from large randomized clinical trials and national registries are proof for this.

Whilst currently available evidence comes from Western countries it is important to get insight into patients demography, prescribing patterns of antithrombotic therapy for stroke prevention in AF from other countries. Two large, international, observational registries, each involving >50 000 patients with newly diagnosed non-valvular AF at risk for stroke from 50 countries have been designed to investigate patient characteristics influencing choice of antithrombotic treatment of stroke prevention in patients with non-valvular AF and to collect data on outcomes of antithrombotic therapy in clinical practice: GLORIA-AF (Global Registry on Long-Term Oral Antithrombotic Treatment in Patients with Atrial Fibrillation) and GARFIELD (Global Anticoagulant Registry in the FIELD).[125,126]

6. Expert opinion

Oral anticoagulation in AF always requires balancing between risk of stroke and thromboembolic complications on the one hand and bleeding event (first of all major and life-

threatening), on the other. Given poorer outcomes of strokes (higher mortality, disability and recurrence rate) if associated with AF, intentions to prevent more strokes at cost of minor increase of bleeding seem to be reasonable[9,10] - and importantly, consistent with patients' values and preferences.[127]

Dabigatran etexilate appeared to be at least non-inferior and in several important settings (for example reduction of ICH and ischaemic stroke) superior to well-adjusted warfarin therapy as assessed in the RE-LY trial. Advantageous pharmacokinetic and pharmacodynamic profile, low drug/food interactions of dabigatran etexilate makes anticoagulation effect more stable, predictable and understandable. Notwithstanding variability of dabigatran plasma concentration with the fixed dose regime, due to wide therapeutic window it did not translated into reduction of safety and efficacy of anticoagulation with dabigatran etexilate. On the contrary, it is of paramount importance to maintain anticoagulation within narrow therapeutic window of INR 2.0-3.0 when treated with warfarin during 'good' time (65-70%), which makes anticoagulation safe and effective,[128] dabigatran etexilate gives a real alternative to patients with non-valvular AF, who experience difficulties with reaching this goal due to various reasons. Adjustment of dabigatran etexilate dose based on plasma level has been suggested recently that might result in further improvement of outcomes, particularly lower bleeding events in patients at higher risk (e.g., elderly, kidney dysfunction, etc.). However, this has to be proved with randomised controlled trials and will apparently lead to loss of simplicity and practicality of anticoagulation management that is offered by current labelling for dabigatran etexilate in comparison to warfarin. Also, this approach cannot be applied routinely in the absence of appropriate laboratory assays.

In general, patient compliance with dabigatran is less measurable. Whilst INR reflects anticoagulation effect of warfarin averaged across a number of days prior to the assessment, currently available tests for dabigatran give evidence of last taken dose only. Thus, with dabigatran etexilate as well as all other oral anticoagulants, patient education is an important means of promoting better adherence to treatment.

Importantly, consistent with the whole RE-LY trial results on dabigatran etexilate safety and efficacy were found across various subgroups of patients, e.g., patients with different stroke risk according to the $CHADS_2$ score, stage of kidney dysfunction, body mass index, prior history of stroke or transient ischaemic attack, presenting with symptomatic heart failure, VKA-experienced or naïve, with or without concurrent use of antiplatelets, etc. Only patients aged ≥75 years showed higher rate of major bleeding with dabigatran compared to those <75 years. Nonetheless it remained non-inferior to warfarin.

Of note, majority of bleeding events occurred in the RE-LY trial with dabigatran etexilate were those classed as non-major. Notwithstanding the absence of a specific antidote, which is currently under testing in an ongoing Phase 3 study (i.e. idarucizumab), activated and non-activated prothrombin complex concentrate and recombinant factor VII represent effective available options to cope with bleeding.

Available evidence from clinical trials and 'real world' data already supports use of dabigatran etexilate for effective and safe stroke prevention both for chronic anticoagulation in AF and range of clinical situations which may appear in everyday practice with two exceptions, which are end-stage chronic kidney disease (i.e. CrCl <15 mL/min) and valvular AF, broadly defined as AF at a background of prosthetic heart valves or rheumatic heart

disease (predominantly mitral stenosis). Whilst mechanical prosthetic heart valves were found to be absolute contraindication for anticoagulation with dabigatran etexilate, its use in patients with bioprosthetic heart valves is controversial because the latter are likely to be less thrombogenic than the artificial surface of the mechanical valves, which induce activation of the contact pathway of coagulation. Also, some evidence on efficacy and safety of dabigatran etexilate is based on retrospective analyses of subgroups of patients or meta-analyses of smaller studies (for example, studies on dabigatran etexilate in patients undergoing catheter ablation of AF, which were excluded from the RE-LY trial). Various patients with comorbidity (e.g. chronic kidney disease) are less represented in several analyses as well. Several ongoing trials were designed and future studies are warranted to cover these gaps.

For now, warfarin will retain its position of the most frequently used oral anticoagulant, particularly due to its 'all-purpose' applicability, e.g., in patients with valvular AF, end-stage kidney dysfunction, prosthetic mechanical valves, etc. Nonetheless, dabigatran etexilate in line with the other NOACs has changed the landscape for oral anticoagulation in AF. It provides safe and effective stroke prevention in those non-valvular AF patients, who experience difficulties with the management of warfarin therapy with respect to maintenance of high time in therapeutic range. Clinical decision making tools might aid with the selection of appropriate patients for either vitamin K antagonists or NOACs (e.g., dabigatran etexilate).[129-131]

7. Article highlights

- Patients with AF with CHA_2DS_2-VASc score ≥ 1 require oral anticoagulation either with dose-adjusted warfarin or non-vitamin K antagonist oral anticoagulants (NOAC)

- Dabigatran, a direct thrombin inhibitor, is free of major warfarin drawbacks as slow onset and offset of action, variability of anticoagulant effect, multiple food and drug interactions, necessity for regular laboratory monitoring
- Dabigatran 110 mg bid dosage is non-inferior and 150 mg bid dosage is superior to warfarin for prevention of stroke and systemic embolism, whilst 110 mg bid dosage is superior and 150 mg bid dosage is non-inferior to warfarin with respect to major bleeding events. Both dabigatran dosages are associated with lower risk of intracranial haemorrhage.
- Dabigatran found to be safe and effective for chronic anticoagulation, cardioversion and ablation of atrial fibrillation, in the periprocedural setting, in patients with concomitant chronic kidney disease up to end-stage, and in atrial fibrillation at a background of coronary heart disease.
- Ongoing trials on dabigatran will bring further data on its safety and efficacy in areas which are currently lacking evidence from randomised control trials and therefore associated with some controversy in clinical practice.

References:

1. Go AS, Hylek EM, Phillips KA, et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. JAMA 2001; 285(18):2370-5.

2. Björck S, Palaszewski B, Friberg L, et al. Atrial fibrillation, stroke risk, and warfarin therapy revisited: a population-based study. Stroke 2013;44(11):3103-8.

3. Lowres N, Neubeck L, Salkeld G, et al. Feasibility and cost-effectiveness of stroke prevention through community screening for atrial fibrillation using iPhone ECG in pharmacies. The SEARCH-AF study. Thromb Haemost 2014;111(6):1167-76. * The study investigating prevalence of asymptomatic cases of AF, and which can be diagnosed with contemporary screening technics.

4. Lowres N, Neubeck L, Redfern J, et al. Screening to identify unknown atrial fibrillation. A systematic review. Thromb Haemost 2013;110(2):213-22.

5. Lamassa M, Di Carlo A, Pracucci G, et al. Characteristics, outcome, and care of stroke associated with atrial fibrillation in Europe: data from a multicenter multinational hospital-based registry (The European Community Stroke Project). Stroke 2001;32(2):392-8.

6. Sanna T, Diener HC, Passman RS, et al; CRYSTAL AF Investigators. Cryptogenic stroke and underlying atrial fibrillation. N Engl J Med 2014;370(26):2478-86.

7. Camm AJ, Lip GY, De Caterina R, et al. 2012 focused update of the ESC guidelines for the management of atrial fibrillation: an update of the 2010 ESC guidelines for the management of atrial fibrillation. Europace 2012; 14(10): 1385–1413.

8. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: A Report of the American College of

Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. Circulation 2014. [Epub ahead of print].

9. Olesen JB, Lip GY, Lindhardsen J, et al. Risks of thromboembolism and bleeding with thromboprophylaxis in patients with atrial fibrillation: a net clinical benefit analysis using a 'real world' nationwide cohort study. Thromb Haemost 2011;106(4):739–49. ** The analysis showing positive net clinical benefit of oral anticoagulation in all AF patients with ≥1 additional stroke risk factors.

10. Friberg L, Rosenqvist M, Lip G. Net clinical benefit of warfarin in patients with atrial fibrillation: a report from the Swedish Atrial Fibrillation Cohort Study. Circulation 2012;125(19):2298–307. ** The analysis showing positive net clinical benefit of oral anticoagulation in all AF patients with ≥1 additional stroke risk factors.

11. Lip GY, Nieuwlaat R, Pisters R, et al. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the Euro Heart Survey on atrial fibrillation. Chest 2010;137(2):263–72. ** Widely accepted stroke risk stratification scheme.

12. Pisters R, Lane DA, Nieuwlaat R, et al. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. Chest 2010;138(5):1093–100. ** Widely accepted bleeding risk stratification scheme in different patient populations.

13. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Ann Intern Med 2007;146(12):857-67. ** The meta-analysis showing superiority of vitamin K antagonists over placebo and aspirin for stroke and thromboembolic event prevention in patients with non-valvular AF.

14. Potpara TS, Lip GY. Novel oral anticoagulants in non-valvular atrial fibrillation. Best Pract Res Clin Haematol. 2013; 26(2): 115-129.

15. Ahrens I, Lip GY, Peter K. New oral anticoagulant drugs in cardiovascular disease. Thromb Haemost 2010;104(1):49-60.

16. Heidbuchel H, Verhamme P, Alings M, et al. European Heart Rhythm Association Practical Guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation. Europace 2013;15(5):625–51.

17. Pradaxa: European public assessment report – product information. 03.06.2014. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000829/WC500041059.pdf. Accessed September 5, 2014.

18. Pradaxa: Prescribing information and medication guide. Revised 8/2014. Available from: http://bidocs.boehringer-ingelheim.com/BIWebAccess/ViewServlet.ser?docBase=renetnt&folderPath=/Prescribing%20Information/PIs/Pradaxa/Pradaxa.pdf. Accessed September 5, 2014.

19. De Caterina R, Husted S, Wallentin L, et al. Vitamin K antagonists in heart disease: current status and perspectives (Section III). Position paper of the ESC Working Group on Thrombosis - Task Force on Anticoagulants in Heart Disease. Thromb Haemost 2013;110(6):1087-107.

20. De Caterina R, Husted S, Wallentin L, et al. General mechanisms of coagulation and targets of anticoagulants (Section I). Position Paper of the ESC Working Group on Thrombosis - Task Force on Anticoagulants in Heart Disease. Thromb Haemost 2013;109(4):569-79.

21. Weitz JI. Factor Xa and thrombin as targets for new oral anticoagulants. Thromb Res 2011;127(Suppl 2):S5-12.

22. Esmon CT. Targeting factor Xa and thrombin: impact on coagulation and beyond. Thromb Haemost 2014;111(4):625-33.

23. Stangier J, Rathgen K, Steahle H, et al. The pharmacokinetics, pharmacodynamics and tolerability of dabigatran etexilate — a new oral direct thrombin inhibitor - in healthy male subjects. Br J Clin Pharmacol 2007;64:292–303.

24. Stangier J, Stähle H, Rathgen K, et al. Pharmacokinetics and pharmacodynamics of the direct oral thrombin inhibitor dabigatran in healthy elderly subjects. Clin Pharmacokinet 2008;47(1):47-59.

25. Scaglione F. New oral anticoagulants: comparative pharmacology with vitamin K antagonists. Clin Pharmacokinet 2013;52:69-82.

26. Hankey GJ, Eikelboom JW. Dabigatran etexilate: a new oral thrombin inhibitor. Circulation 2011;123(13):1436-50.

27. Gong IY, Kim RB. Importance of pharmacokinetic profile and variability as determinants of dose and response to dabigatran, rivaroxaban, and apixaban. Can J Cardiol. 2013; 29(7 Suppl): S24-S33.

28. Connolly SJ, Ezekowitz MD, Yusuf S, et al; RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009;361(12):1139–51. ** The pivotal phase 3 trial with dabigatran etexilate that showed noninferiority of dabigatran etexilate to adjusted warfarin therapy in patients with non-valvular AF.

29. Connolly SJ, Ezekowitz MD, Yusuf S, et al; Randomized Evaluation of Long-Term Anticoagulation Therapy Investigators. Newly identified events in the RE-LY trial. N Engl J Med 2010;363(19):1875-6.

30. Oldgren J, Alings M, Darius H, et al; RE-LY Investigators. Risks for stroke, bleeding, and death in patients with atrial fibrillation receiving dabigatran or warfarin in relation to the CHADS2 score: a subgroup analysis of the RE-LY trial. Ann Intern Med 2011;155(10):660-

7. * Subgroup analysis showing comparable to warfarin safety and efficacy of dabigatran etexilate across various stroke risk strata.

31. Diener HC, Connolly SJ, Ezekowitz MD, et al; RE-LY study group. Dabigatran compared with warfarin in patients with atrial fibrillation and previous transient ischaemic attack or stroke: a subgroup analysis of the RE-LY trial. Lancet Neurol 2010;9(12):1157-63. * Subgroup analysis showing comparable to warfarin safety and efficacy of dabigatran for secondary prevention of stroke.

32. Pisters R, Nieuwlaat R, Lane DA, et al. Potential net clinical benefit of population-wide implementation of apixaban and dabigatran among European patients with atrial fibrillation. A modelling analysis from the Euro Heart Survey. Thromb Haemost 2013;109(2):328-36.

33. Lip GY, Clemens A, Noack H, et al. Patient outcomes using the European label for dabigatran. A post-hoc analysis from the RE-LY database. Thromb Haemost 2014;111(5):933-42.

34. Connolly SJ, Wallentin L, Ezekowitz MD, et al. The long-term multicenter observational study of dabigatran treatment in patients with atrial fibrillation (RELY-ABLE) study. Circulation 2013;128(3):237-43.

35. FDA drug safety communication: safety review of post-market reports of serious bleeding events with the anticoagulant Pradaxa (dabigatran etexilate mesylate). Available from: http://www.fda.gov/drugs/drugsafety/ucm282724.htm. Accessed July 23, 2014.

36. Southworth MR, Reichman ME, Unger EF. Dabigatran and postmarketing reports of bleeding N Engl J Med 2013;368(14):1272-4.

37. FDA drug safety communication: Update on the risk for serious bleeding events with the anticoagulant Pradaxa (dabigatran). Available from: http://www.fda.gov/Drugs/DrugSafety/ucm326580.htm. Accessed July 23, 2014.

38. FDA Drug Safety Communication: FDA study of Medicare patients finds risks lower for stroke and death but higher for gastrointestinal bleeding with Pradaxa (dabigatran) compared to warfarin Available from: http://www.fda.gov/Drugs/DrugSafety/ucm396470.htm. Accessed July 23, 2014. ** An FDA analysis showing that dabigatran etexilate is associated with lower mortality and ischaemic stroke rate in large population of AF patients.

39. Larsen TB, Rasmussen LH, Skjøth F, et al. Efficacy and safety of dabigatran etexilate and warfarin in "real-world" patients with atrial fibrillation: a prospective nationwide cohort study. J Am Coll Cardiol 2013;61(22):2264-73. ** The study showing efficacy and safety of dabigatran etexilate in large 'real world' cohort of AF patients.

40. Banerjee A, Lane DA, Torp-Pedersen C, et al. Net clinical benefit of new oral anticoagulants (dabigatran, rivaroxaban, apixaban) versus no treatment in a 'real world' atrial fibrillation population: a modelling analysis based on a nationwide cohort study. Thromb Haemost. 2012;107(3):584-9. ** A modelling analysis showing positive net clinical benefit of the non-vitamin K oral anticoagulants for stroke prevention in AF.

41. Paré G, Eriksson N, Lehr T, et al. Genetic determinants of dabigatran plasma levels and their relation to bleeding. Circulation 2013;127(13):1404-12.

42. Reilly PA, Lehr T, Haertter S, et al; RE-LY Investigators. The effect of dabigatran plasma concentrations and patient characteristics on the frequency of ischemic stroke and major bleeding in atrial fibrillation patients: the RE-LY Trial (Randomized Evaluation of Long-Term Anticoagulation Therapy). J Am Coll Cardiol 2014;63(4):321-8. * An analysis highlighting variability of dabigatran plasma concentration with fixed dose regime of drug administration.

43. Cohen D. Dabigatran: how the drug company withheld important analyses. BMJ 2014; 349:g4670.

44. Charlton B, Redberg R. The trouble with dabigatran. BMJ 2014; 349:g4681.

45. Moore TJ, Cohen MR, Mattison DR. Dabigatran, bleeding, and the regulators. BMJ 2014; 349:g4517.

46. Pradaxa: CHMP assessment report. 9 June 2011. Available from: http://www.ema.europa.eu. Accessed September 5, 2014.

47. Nagarakanti R, Ezekowitz MD, Oldgren J, et al. Dabigatran versus warfarin in patients with atrial fibrillation: an analysis of patients undergoing cardioversion. Circulation. 2011;123(2):131-6. * An article on findings that dabigatran etexilate is safe and effective in AF patients undergoing cardioversion.

48. Boehringer Ingelheim. Benefits and Safety of Pradaxa® (dabigatran etexilate mesylate) Repeatedly Confirmed. British Medical Journal publishes biased article regarding PRADAXA. Press Release. July 23, 2014. Available from: http://us.boehringer-ingelheim.com/news_events/press_releases/press_release_archive/2014/07-23-14-benefits-safety-pradaxa-dabigatran-etexilate-mesylate-repeatedly-confirmed.html. Accessed August 28, 2014.

49. Yadlapati A, Groh C, Passman R. Safety of short-term use of dabigatran or rivaroxaban for direct-current cardioversion in patients with atrial fibrillation and atrial flutter. Am J Cardiol 2014;113(8):1362-3.

50. Klein AL, Grimm RA, Murray RD, et al; Assessment of Cardioversion Using Transesophageal Echocardiography Investigators. Use of transesophageal echocardiography to guide cardioversion in patients with atrial fibrillation. N Engl J Med 2001;344:1411-20.

51. Klein AL, Jasper SE, Katz WE, et al; ACUTE II Steering and Publications Committe for the ACUTE II Investigators. The use of enoxaparin compared with unfractionated heparin for short-term antithrombotic therapy in atrial fibrillation patients undergoing transoesophageal echocardiography-guided cardioversion: assessment of Cardioversion

Using Transoesophageal Echocardiography (ACUTE) II randomized multicentre study. Eur Heart J 2006;27(23):2858-65.

52. Weigner MJ, Thomas LR, Patel U, et al. Early cardioversion of atrial fibrillation facilitated by transesophageal echocardiography: short-term safety and impact on maintenance of sinus rhythm at 1 year. Am J Med 2001;110:694-702.

53. Lindahl TL, Baghaei F, Blixter IF, et al; Expert Group on Coagulation of the External Quality Assurance in Laboratory Medicine in Sweden. Effects of the oral, direct thrombin inhibitor dabigatran on five common coagulation assays. Thromb Haemost 2011;105(2):371-8.

54. Douxfils J, Mullier F, Robert S, et al. Impact of dabigatran on a large panel of routine or specific coagulation assays. Laboratory recommendations for monitoring of dabigatran etexilate. Thromb Haemost 2012;107(5):985-97. * An article discussing opportunities of laboratory monitoring of anticoagulation with dabigatran etexilate.

55. Hapgood G, Butler J, Malan E, et al. The effect of dabigatran on the activated partial thromboplastin time and thrombin time as determined by the Hemoclot thrombin inhibitor assay in patient plasma samples. Thromb Haemost 2013;110(2):308-15.

56. Hawes EM, Deal AM, Funk-Adcock D, et al. Performance of coagulation tests in patients on therapeutic doses of dabigatran: a cross-sectional pharmacodynamic study based on peak and trough plasma levels. J Thromb Haemost 2013;11:1493—502.

57. Calkins H, Kuck KH, Cappato R, et al. 2012 HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation: recommendations for patient selection, procedural techniques, patient management and follow-up, definitions, endpoints, and research trial design. Europace 2012;14(4):528-606.

58. Lee DS, Dorian P, Downar E, Burns M, Yeo EL, Gold WL, Paquette M, Lau W, Newman DM. Thrombogenicity of radiofrequency ablation procedures: what factors influence thrombin generation? Europace 2001;3(3):195-200.

59. Santangeli P, Di Biase L, Horton R, et al. Ablation of atrial fibrillation under therapeutic warfarin reduces periprocedural complications evidence from a meta-analysis. Circ Arrhythm Electrophysiol 2012;5:302-11.

60. Di Biase L, Burkhardt JD, Santangeli P, et al. Periprocedural stroke and bleeding complications in patients undergoing catheter ablation of atrial fibrillation with different anticoagulation management: results from the Role of Coumadin in Preventing Thromboembolism in Atrial Fibrillation (AF) Patients Undergoing Catheter Ablation (COMPARE) randomized trial. Circulation 2014;129(25):2638-44.

61. Lakkireddy D, Reddy YM, Di Biase L, et al. Feasibility and safety of dabigatran versus warfarin for periprocedural anticoagulation in patients undergoing radiofrequency ablation for atrial fibrillation: results from a multicenter prospective registry. J Am Coll Cardiol 2012;59(13):1168-74.

62. Eitel C, Koch J, Sommer P, et al. Novel oral anticoagulants in a real-world cohort of patients undergoing catheter ablation of atrial fibrillation. Europace 2013;15(11):1587-93.

63. Stepanyan G, Badhwar N, Lee RJ, et al. Safety of new oral anticoagulants for patients undergoing atrial fibrillation ablation. J Interv Card Electrophysiol 2014;40(1):33-8.

64. Bassiouny M, Saliba W, Rickard J, et al. Use of dabigatran for periprocedural anticoagulation in patients undergoing catheter ablation for atrial fibrillation. Circ Arrhythm Electrophysiol. 2013;6(3):460-6.

65. Haines DE, Mead-Salley M, Salazar M, et al. Dabigatran versus warfarin anticoagulation before and after catheter ablation for the treatment of atrial fibrillation. J Interv Card Electrophysiol. 2013;37(3):233-9.

66. Nin T, Sairaku A, Yoshida Y, et al. A randomized controlled trial of dabigatran versus warfarin for periablation anticoagulation in patients undergoing ablation of atrial fibrillation. Pacing Clin Electrophysiol 2013;36(2):172-9.

67. Kim JS, She F, Jongnarangsin K, et al. Dabigatran vs warfarin for radiofrequency catheter ablation of atrial fibrillation. Heart Rhythm 2013;10(4):483-9.

68. Bin Abdulhak AA, Khan AR, Tleyjeh IM, et al. Safety and efficacy of interrupted dabigatran for peri-procedural anticoagulation in catheter ablation of atrial fibrillation: a systematic review and meta-analysis. Europace. 2013;15(10):1412-20.

69. Hohnloser SH, Camm AJ. Safety and efficacy of dabigatran etexilate during catheter ablation of atrial fibrillation: a meta-analysis of the literature. Europace 2013;15(10):1407-11.

70. Providência R, Albenque JP, Combes S, et al. Safety and efficacy of dabigatran versus warfarin in patients undergoing catheter ablation of atrial fibrillation: a systematic review and meta-analysis. Heart 2014;100(4):324-35.

71. Sardar P, Nairooz R, Chatterjee S, et al. Meta-analysis of risk of stroke or transient ischemic attack with dabigatran for atrial fibrillation ablation. Am J Cardiol 2014;113(7):1173-7. * A meta-analysis showing efficacy and safety of dabigatran etexilate during periablation period.

72. Shurrab M, Morillo CA, Schulman S, et al. Safety and efficacy of dabigatran compared with warfarin for patients undergoing radiofrequency catheter ablation of atrial fibrillation: a meta-analysis. Can J Cardiol 2013;29(10):1203-10.

73. Steinberg BA, Hasselblad V, Atwater BD, Bahnson TD, Washam JB, Alexander JH, Daubert JP, Piccini JP. Dabigatran for periprocedural anticoagulation following radiofrequency ablation for atrial fibrillation: a meta-analysis of observational studies. J Interv Card Electrophysiol. 2013;37(3):213-21.

74. Boehringer Ingelheim Initiates RE-CIRCUIT™ Trial, Evaluating Pradaxa® (dabigatran etexilate mesylate) in NVAF Patients Undergoing Ablation) Press Release. June 20, 2014. Available from: http://www.us.boehringer-ingelheim.com/news_events/press_releases/press_release_archive/2014/06-20-14-boehringer-ingelheim-re-circuit-trial-pradaxa-dabigatran-etexilate-mesylate-nvaf-patients-undergoing-ablation.html. Accessed July 23, 2014.

75. Nieuwlaat R, Capucci A, Camm AJ, et al; European Heart Survey Investigators. Atrial fibrillation management: A prospective survey in ESC member countries: the Euro Heart Survey on Atrial Fibrillation. Eur Heart J 2005;26:2422-34.

76. Task Force Members, Lip GY, Windecker S, Huber K, et al. Management of antithrombotic therapy in atrial fibrillation patients presenting with acute coronary syndrome and/or undergoing percutaneous coronary or valve interventions: a joint consensus document of the European Society of Cardiology Working Group on Thrombosis, European Heart Rhythm Association (EHRA), European Association of Percutaneous Cardiovascular Interventions (EAPCI) and European Association of Acute Cardiac Care (ACCA) endorsed by the Heart Rhythm Society (HRS) and Asia-Pacific Heart Rhythm Society (APHRS). Eur Heart J 2014. doi: 10.1093/eurheartj/ehu298 [Epub ahead of print].

77. Depta JP, Bhatt DL. Atherothrombosis and atrial fibrillation: Important and often overlapping clinical syndromes. Thromb Haemost 2010;104(4): 657-63.

78. Dans AL, Connolly SJ, Wallentin L, et al. Concomitant use of antiplatelet therapy with dabigatran or warfarin in the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial. Circulation 2013;127(5):634-40.

79. Lip GY, Lane DA. Does warfarin for stroke thromboprophylaxis protect against MI in atrial fibrillation patients? Am J Med 2010;123(9):785-9.

80. Sipahi I, Celik S, Akyol A. Letter to the editor: Efficacy and safety of dabigatran etexilate and warfarin in "real-world" patients with atrial fibrillation by Larsen et al. J Am Coll Cardiol 2013;62(10):945-6.

81. Douxfils J, Buckinx F, Mullier F, et al. Dabigatran etexilate and risk of myocardial infarction, other cardiovascular events, major bleeding, and all-cause mortality: a systematic review and meta-analysis of randomized controlled trials. J Am Heart Assoc 2014;3(3):e000515. * A meta-analysis providing evidence that dabigatran etexilate is associated with a significantly increased risk of myocardial infarction.

82. Patel MR, Mahaffey KW, Garg J, et al; ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011; 365(10): 883–91.

83. Granger CB, Alexander JH, McMurray JJ, et al; ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2011; 365(11): 981–92.

84. Giugliano RP1, Ruff CT, Braunwald E, et al; ENGAGE AF-TIMI 48 Investigators. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2013; 369(22): 2093-104.

85. Larsen TB, Rasmussen LH, Gorst-Rasmussen A, et al. Myocardial ischemic events in 'real world' patients with atrial fibrillation treated with dabigatran or warfarin. Am J Med 2014;127(4):329-336.e4. * An article investigating risk of myocardial infarction with dabigatran etexilate in ‘real world’ cohort of AF patients.

86. Dale B, Eikelboom JW, Weitz JI, et al. Dabigatran attenuates thrombin generation to a lesser extent than warfarin: could this explain their differential effects on intracranial hemorrhage and myocardial infarction? J Thromb Thrombolysis. 2013;35:295-301.

87. Samama MM, Le Flem L, Guinet C, et al. Three different patterns of calibrated automated thrombogram obtained with six different anticoagulants. J Thromb Haemost 2007;5(12):2554-6.

88. Gerotziafas GT, Elalamy I, Depasse F, et al. In vitro inhibition of thrombin generation, after tissue factor pathway activation, by the oral, direct factor Xa inhibitor rivaroxaban. J Thromb Haemost 2007;5(4):886-8.

89. Boehringer Ingelheim Planning to Initiate Two New Global Clinical Trials of Pradaxa® (dabigatran etexilate mesylate). Press Release. November 19, 2013. Available from: http://us.boehringer-ingelheim.com/news_events/press_releases/press_release_archive/2013/11-19-2013-boehringer-ingelheim-global-clinical-trials-pradaxa-dabigatran-etexilate-mesylate.html. Accessed July 23, 2014.

90. Banerjee A, Fauchier L, Vourc'h P,et al. A prospective study of estimated glomerular filtration rate and outcomes in patients with atrial fibrillation: the Loire Valley Atrial Fibrillation Project. Chest. 2014;145(6):1370-82.

91. Apostolakis S, Guo Y, Lane DA, et al. Renal function and outcomes in anticoagulated patients with non-valvular atrial fibrillation: the AMADEUS trial. Eur Heart J 2013;34(46):3572-9.

92. Roldán V, Marín F, Manzano-Fernandez S, et al. Does chronic kidney disease improve the predictive value of the CHADS2 and CHA2DS2-VASc stroke stratification risk scores for atrial fibrillation? Thromb Haemost 2013;109(5):956-60.

93. Olesen JB, Lip GY, Kamper AL, et al. Stroke and bleeding in atrial fibrillation with chronic kidney disease. N Engl J Med 2012;367(7):625-35.

94. Liesenfeld KH, Lehr T, Dansirikul C, et al. Population pharmacokinetic analysis of the oral thrombin inhibitor dabigatran etexilate in patients with non-valvular atrial fibrillation from the RE-LY trial. J Thromb Haemost 2011;9(11):2168-75.

95. Boehringer Ingelheim. Pradaxa study in non-valvular atrial fibrillation patients with severely impaired renal function. 2013. NLM Identifier: NCT01896297. Available from: http://www.clinicaltrials.gov/show/NCT01896297. Accessed July 23, 2014.

96. Poulsen BK, Grove EL, Husted SE. New oral anticoagulants: a review of the literature with particular emphasis on patients with impaired renal function. Drugs 2012;72(13):1739-53.

97. Hijazi Z, Hohnloser SH, Oldgren J, et al. Efficacy and safety of dabigatran compared with warfarin in relation to baseline renal function in patients with atrial fibrillation: a RE-LY (Randomized Evaluation of Long-term Anticoagulation Therapy) trial analysis. Circulation 2014;129(9):961-70. * An analysis showing consistency of safety and efficacy profile of dabigatran etexilate with the whole RE-LY trial across patient subgroups with different degree of kidney dysfunction.

98. Boehringer Ingelheim. ESC Congress 2014 Hot Line Session: Favourable effect of Pradaxa® on kidney function over time compared to warfarin. Press release archive: SPAF. 02 September 2014. Available from: http://www.boehringer-ingelheim.com/news/news_releases/press_releases/2014/02_september_2014_dabigatranetexilate.html. Accessed September 5, 2014.

99. Singh T, Maw TT, Henry BL, et al. Extracorporeal therapy for dabigatran removal in the treatment of acute bleeding: a single center experience. Clin J Am Soc Nephrol 2013;8(9):1533-9.

100. Chang DN, Dager WE, Chin AI. Removal of dabigatran by hemodialysis. Am J Kidney Dis 2013;61(3):487-9.

101. Khadzhynov D, Wagner F, Formella S, et al. Effective elimination of dabigatran by haemodialysis. A phase I single-centre study in patients with end-stage renal disease. Thromb Haemost 2013;109(4):596-605.

102. Kelly T, Yang W, Chen CS, et al. Global burden of obesity in 2005 and projections to 2030. Int J Obes (Lond) 2008;32(9):1431-7.

103. Wang TJ, Parise H, Levy D, et al. Obesity and the risk of new-onset atrial fibrillation. JAMA. 2004;292(20):2471-7.

104. Huxley RR, Misialek JR, Agarwal SK, et al. Physical activity, obesity, weight change, and risk of atrial fibrillation: the atherosclerosis risk in communities study. Circ Arrhythm Electrophysiol 2014;7(4):620-5.

105. Chagnac A, Weinstein T, Korzets A, et al. Glomerular hemodynamics in severe obesity. Am J Physiol Renal Physiol 2000;278(5):F817-22.

106. Han PY, Duffull SB, Kirkpatrick CMJ, et al. Dosing in obesity: a simple solution to a big problem. Clin Pharmacol Ther 2007;82(5):505-8.

107. Patel JP, Roberts LN, Arya R. Anticoagulating obese patients in the modern era. Br J Haematol 2011;155(2):137-49.

108. Eriksson BI, Dahl OE, Feuring M, et al. Dabigatran is effective with a favourable safety profile in normal and overweight patients undergoing major orthopaedic surgery: a pooled analysis. Thromb Res 2012;130(5):818-20.

109. Beyer-Westendorf J, Gelbricht V, Förster K, et al. Peri-interventional management of novel oral anticoagulants in daily care: results from the prospective Dresden NOAC registry. Eur Heart J 2014;35(28):1888-96.

110. Douketis JD, Spyropoulos AC, Spencer FA, et al. Perioperative management of antithrombotic therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed:

American College of Chest Physicians Evidence‑Based Clinical Practice Guidelines. Chest 2012; 141: e326S‑350S.

111. Nitzki-George D, Wozniak I, Caprini JA. Current state of knowledge on oral anticoagulant reversal using procoagulant factors. Ann Pharmacother 2013;47(6):841-55.

112. Pernod G, Albaladejo P, Godier A, et al. Management of major bleeding complications and emergency surgery in patients on long-term treatment with direct oral anticoagulants, thrombin or factor-Xa inhibitors: proposals of the working group on perioperative haemostasis (GIHP) - March 2013. Arch Cardiovasc Dis 2013;106(6-7):382-93.

113. Dickneite G, Hoffman M. Reversing the new oral anticoagulants with prothrombin complex concentrates (PCCs): what is the evidence? Thromb Haemost 2014;111(2):189-98.

114. Miesbach W, Seifried E. New direct oral anticoagulants--current therapeutic options and treatment recommendations for bleeding complications. Thromb Haemost 2012;108(4):625-32.

115. Boehringer Ingelheim. Reversal of Dabigatran Anticoagulant Effect With Idarucizumab. 2014. NLM Identifier: NCT02104947. Available from: http://clinicaltrials.gov/show/NCT02104947. Accessed July 23, 2014.

116. Healey JS, Eikelboom J, Douketis J, et al; RE-LY Investigators. Periprocedural bleeding and thromboembolic events with dabigatran compared with warfarin: results from the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) randomized trial. Circulation 2012;126(3):343-8. * An analysis showing comparable to warfarin safety and efficacy of dabigatran etexilate in case of periprocedural anticoagulation but with shorter interruption time.

117. Eikelboom JW, Connolly SJ, Brueckmann M, et al; RE-ALIGN Investigators. Dabigatran versus warfarin in patients with mechanical heart valves. N Engl J Med. 2013;369(13):1206-14. * A recent trial showing higher rate of thromboembolic and bleeding

events in AF patients with prosthetic mechanical valves in dabigatran etexilate arm in comparison to warfarin arm.

118. Thorne K, Jayathissa S, Dee S, et al. Adherence and outcomes of patients prescribed dabigatran (Pradaxa) in routine clinical practice. Intern Med J 2014;44(3):261-5.

119. Schulman S, Shortt B, Robinson M, et al. Adherence to anticoagulant treatment with dabigatran in a real-world setting. J Thromb Haemost 2013;11(7):1295-9.

120. Shore S, Carey EP, Turakhia MP, et al. Adherence to dabigatran therapy and longitudinal patient outcomes: insights from the veterans health administration. Am Heart J 2014;167(6):810-7.

121. Tsai K, Erickson SC, Yang J, et al. Adherence, persistence, and switching patterns of dabigatran etexilate. Am J Manag Care 2013;19(9):e325-32.

122. Barker RV, Lip GY, Lane DA. Best practice for atrial fibrillation patient education. Curr Pharm Des 2014. [Epub ahead of print].

123. Clarkesmith DE, Pattison HM, Lane DA. Educational and behavioural interventions for anticoagulant therapy in patients with atrial fibrillation. Cochrane Database Syst Rev 2013;6:CD008600.

124. Clarkesmith DE, Pattison HM, Lip GY, et al. Educational intervention improves anticoagulation control in atrial fibrillation patients: the TREAT randomised trial. PLoS One 2013;8(9):e74037.

125. Huisman MV, Lip GY, Diener HC, et al. Design and rationale of Global Registry on Long-Term Oral Antithrombotic Treatment in Patients with Atrial Fibrillation: a global registry program on long-term oral antithrombotic treatment in patients with atrial fibrillation. Am Heart J 2014;167(3):329-34.

126. Kakkar AK, Mueller I, Bassand JP, et al. International longitudinal registry of patients with atrial fibrillation at risk of stroke: Global Anticoagulant Registry in the FIELD (GARFIELD). Am Heart J 2012;163(1):13-19.e1.

127. Lahaye S, Regpala S, Lacombe S, et al. Evaluation of patients' attitudes towards stroke prevention and bleeding risk in atrial fibrillation. Thromb Haemost 2014;111(3):465-73. * An article on findings that AF patients would be willing to tolerate approximately four major bleeds in order to prevent one stroke.

128. Gallagher AM, Setakis E, Plumb JM, et al. Risks of stroke and mortality associated with suboptimal anticoagulation in atrial fibrillation patients. Thromb Haemost 2011;106(5):968-77.

129. Apostolakis S, Sullivan RM, Olshansky B, et al. Factors affecting quality of anticoagulation control among patients with atrial fibrillation on warfarin: the SAMe-TT2R2 score. Chest 2013;144(5):1555-63. ** An useful scoring tool to identify those patients with AF who would do well on vitamin K antagonists.

130. Poli D, Antonucci E, Testa S, et al. A prospective validation of the SAME-TT2R2 score: how to identify atrial fibrillation patients who will have good anticoagulation control on warfarin. Intern Emerg Med 2014;9(4):443-7.

131. Lip GY, Haguenoer K, Saint-Etienne C, et al. Relationship of the SAME-TT2R2 score to poor quality anticoagulation, stroke, clinically relevant bleeding and mortality in patients with atrial fibrillation. Chest 2014. doi: 10.1378/chest.13-2976. [Epub ahead of print].

132. Hoffman M, Monroe DM. Coagulation 2006: a modern view of hemostasis. Hematol Oncol Clin North Am. 2007;21(1):1-11.

Table 1. Stroke and bleeding risk stratification with the CHA_2DS_2-VASc[11] and HAS-BLED[12] scores

CHA_2DS_2-VASc	Score	HAS-BLED	Score
Congestive heart failure/LV dysfunction	1	Hypertension (systolic blood pressure >160 mmHg)	1
Hypertension	1	Abnormal renal or liver function	1 or 2
Age ≥75 years	2	Stroke	1
Diabetes mellitus	1	Bleeding tendency or predisposition	1
Stroke/TIA/TE	2	Labile INRs (if on warfarin)	1
Vascular disease (prior MI, PAD, or aortic plaque)	1	Age (e.g., >65, frail condition)	1
Aged 65–74 years	1	Drugs (e.g., concomitant antiplatelet or NSAIDs) or alcohol excess/abuse	1 or 2
Sex category (i.e. female gender)	1		
Maximum score	9		9

CHA_2DS_2-VASc: heart failure [moderate-to-severe left ventricular systolic dysfunction refer to left ventricular ejection fraction ≤40% or recent decompensated heart failure requiring hospitalization], hypertension, age ≥75, diabetes, stroke/transient ischaemic attack [TIA], vascular disease [specifically, MI, complex aortic plaque and peripheral artery disease], age 65–74 years, female sex.

HAS-BLED: uncontrolled hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio [INR], elderly [e.g. age >65, frail condition], drugs [e.g., antiplatelet, non-steroidal anti-inflammatory drugs]/excessive alcohol.

INR, international normalized ratio; LV, left ventricular; MI, myocardial infarction; NSAIDs, non-steroidal anti-inflammatory drugs; TIA/TE, transient ischemic attack/thromboembolism; PAD, peripheral artery disease.

Table 2. Pharmacological characteristics of warfarin and dabigatran[16,25-27]

Parameter	Warfarin	Dabigatran
Mechanism of action	Inhibition of VKORC1	Direct thrombin inhibitor (free or bound), reversible
Onset of action	Slow, indirect inhibition of clotting factor synthesis	Fast
Offset of action	Long	Short
Absorption	Rapid	Rapid, acid-dependent
Bioavailability, %	>95	6.5
T_{max}, hour	2.0-4.0	1.0-3.0
V_d, L	10	60-70
Protein binding, %	99	35
$T_{1/2\beta}$, hour	40	12-17
Renal clearance	None	80
Non-renal clearance	None	20
CL/F, L/hour	0.35	70-140
Accumulation in plasma	Dependent on CYP2C9 metabolic efficiency	None
Food effect	No effect on absorption; dietary vitamin K influence on pharmacodynamics	Delayed absorption with food with no influence on bioavailability
Age	Yes, lower CL/F as age increases	Yes, lower CL/F as age increases
Body weight	Yes, higher dose for	None

	increased weight	
Sex	Yes, lower CL/F in women	Yes, lower CL/F in women
Ethnicity	Lower dose in Asian patients; higher dose in African-American patients	None
Drug transporter	None	P-gp
CYP-mediated metabolism	CYP2C9, CYP3A4, CYP2C19, CYP1A2	None
Drug-drug interactions*	Numerous	Potent P-gp inhibitors (verapamil, reduce dose; dronedarone: avoid) and inducers (avoid)
Coagulation measurement	INR	TT, dTT, aPTT, ECA
Reversal agents	Vitamin K (slow reversal, prolonged inhibition), FFP or PCCs (rapid reversal)	Activated charcoal or haemodialysis (overdose); PCCs or recombinant FVII (uncontrolled bleeding)
Dosing for AF	Individualised for each patient according to INR response (0.5-16 mg qd)	150 mg, 110 mg, 75 mg bid†

AF, atrial fibrillation; aPTT, activated partial thromboplastin test; BCRP, breast cancer resistance protein; bid, twice daily; CL/F, apparent clearance; CrCl, creatinine clearance; CYP, cytochrom P450 isozymes; dTT, diluted thrombin test; ECT, ecarin chromogenic assay; F, factor; FFP, fresh frozen plasma; INR, international normalized ratio; qd, once daily; PCC, prothrombin complex concentrate; P-gp, Permeability glycoprotein; PT, prothrombin time;

T_{max}, time to maximum plasma concentration; TT, thrombin time; $T_{1/2\beta}$, terminal half-life, V_d, volume of distribution; VKORC1, vitamin K epoxide reductase enzyme subunit 1.

* Potent inhibitors of CYP3A4 include antifungals (e.g., ketoconazole, intraconazole, voriconazole, posaconazole), chloramphenicol, clarithromycin, and protease inhibitors (e.g., ritonavir, atanazavir). P-gp inhibitors include verapamil, amiodarone, quinidine, and clarithromycin. P-gp inducers include rifampicin, St. John's wort (Hypericum perforatum), carbamazepine, and phenytoin. Potent CYP3A4 inducers include phenytoin, carbamazepine, phenobarbital, and St. John's wort.

† 110 mg bid is recommended in Europe for patients aged 80 years or above; concomitantly with verapamil; can be considered in patients aged 75-80 years and high risk of bleeding; in patients with gastritis, oesophagitis, or gastroesophageal reflux; in patients with moderate renal impairment (CrCl 30-50 mL/min) and high risk of bleeding; contraindicated if CrCl < 30 mL/min. 75 mg bid is recommended in the US in patients with CrCl 15-30 mL/min

Table 3. Summary on efficacy and safety of dabigatran in pivotal RE-LY trial[28,29] and 'real world' Danish Nationwide cohort study[39] in patients with non-valvular AF

Clinical trial	RE-LY		Danish Nationwide Cohort Study	
Patients	18113		14267	
Age, years	71.8		70.8	
Male gender, %	63.6		56.5	
Median duration of follow-up	2.0 years		10.5 months	
Mean $CHADS_2$ score	2.13		1.16	
Dabigatran dosing arm	110 mg bid	150 mg bid	110 mg bid	150 mg bid
Prior vitamin K antagonist treatment, %	50.1	50.2	warfarin-naïve patients	
Prior stroke/TIA/systemic embolism, %	20.0		16.1	
Mean TTR, warfarin arm; %	64		NA*	
Stroke/systemic embolism	0.90 (0.74–1.10)	0.65 (0.52-0.81)	0.73 (0.53-1.00) / 0.60 (0.19-1.60)	1.18 (0.85-1.64) / 1.00 (0.26-3.35)
Death	0.91 (0.80-1.03)	0.88 (0.77-1.00)	0.79 (0.65-0.95)	0.57 (0.40-0.80)
Myocardial infarction	1.29 (0.96-1.75)	1.27 (0.94-1.71)	0.30 (0.18-0.49)	0.40 (0.21-0.70)
Pulmonary embolism	1.26 (0.57-2.78)	1.61 (0.76-3.42)	0.33 (0.12-0.74)	0.24 (0.06-0.72)
Major bleeding	0.80(0.70-	0.93 (0.81-	0.82 (0.59-	0.77 (0.51-1.13)

	0.93)	1.07)	1.12)	
Intracranial hemorrhage	0.30 (0.19-0.45)	0.41 (0.28-0.60)	0.24 (0.08-0.56)	0.08 (0.01-0.40)
Gastrointestinal bleeding	1.09 (0.85-1.39)	1.49 (1.19-1.88)	0.60 (0.37-0.93)	1.12 (0.67-1.83)
Hospitalisation	0.92 (0.87-0.97)	0.97 (0.92-1.03)	0.53 (0.49-0.57)	0.86 (0.79-0.93)

* Mean TTR in Denmark during the RE-LY study was at 72% and has been reported to be >65% in both hospitals and in general practice

NA, not available

Table 4. Summary of meta-analyses on dabigatran safety and efficacy in patients with non-valvular AF undergoing catheter ablation

References	Number of studies included	Number of participants involved*	Thrombo-embolic event rate, %*	Risk of thromboembolic complications, OR, 95% CI	Major bleeding rate, %*	Risk of major bleeding, OR, 95% CI
Bin Abdulhak et al[68]	9	1073/1963	0.4/0.1	2.15 (0.58-7.98)	5.4/5.2†	0.92 (0.55-1.45)
Hohnloser et al[69]	10	1407/2241	0.64/0.13	2.38 (0.82-6.85)	1.71/1.56	1.05 (0.62-1.80)
Providência et al[70]	14	1823/2959	0.55/0.17	1.78 (0.66-4.80)	1.48/1.35	1.07 (0.51-2.26)
Sardar et al[71]	18	2137/3376	0.74/0.21	2.81 (1.23-6.45)	1.54/1.57	0.99 (0.55-1.78)
Shurrab et al[72]	11	1463/2378	0.6/0.1	2.51 (0.78-8.11)	1.9/1.6	1.04 (0.51-2.13)
Steinberg et al[73]	10	1501 /2356	0.7/0.2	0.0047 (0.0007-0.0099)‡	1.6/1.7	−0.0010 (−0.0090-0.0076) ‡

* dabigatran/warfarin

† total bleeding

‡ estimated absolute risk difference

OR, odds ratio; CI, confidence interval

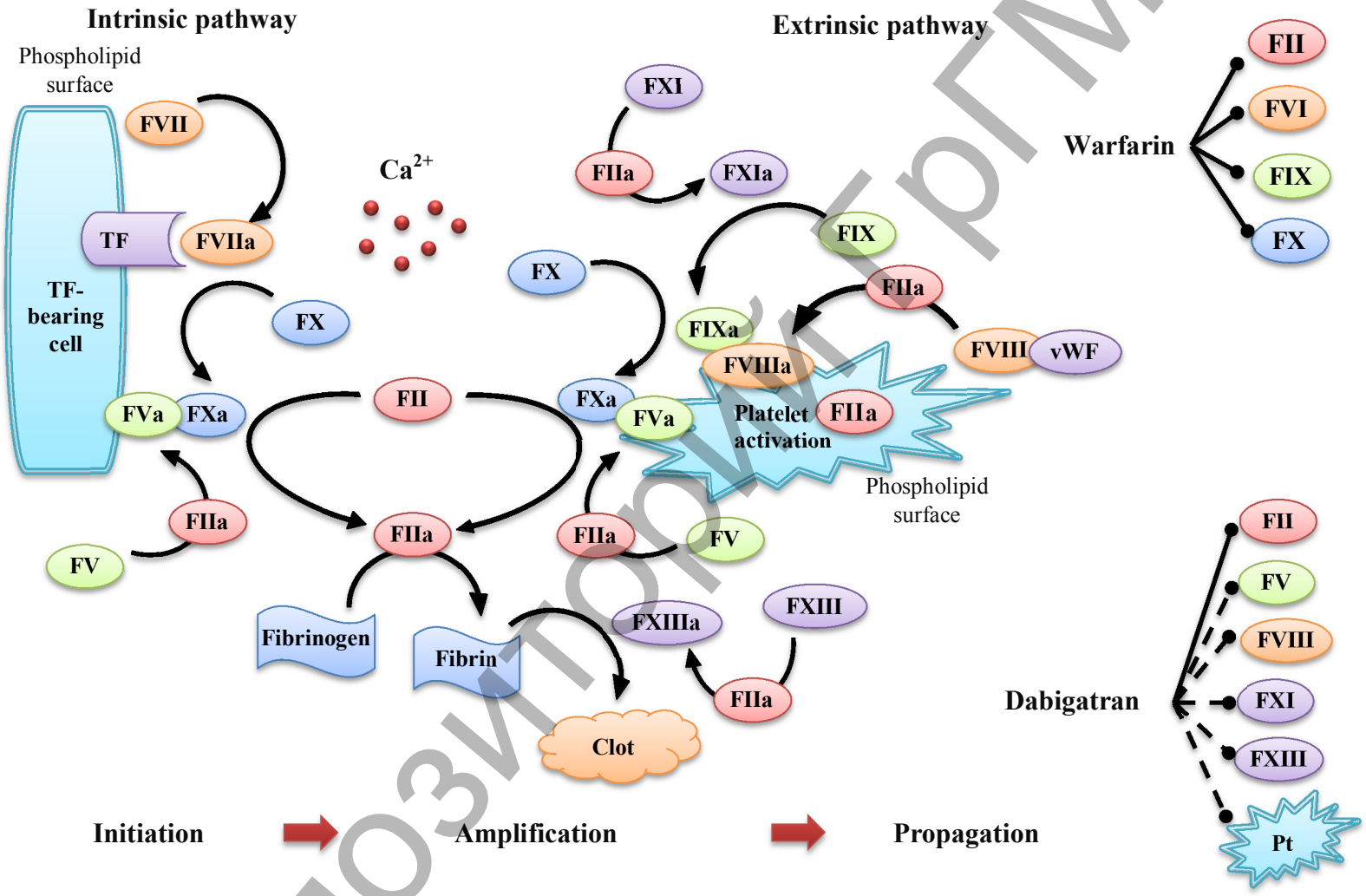

Figure 1. Coagulation cascade and application points for dabigatran and warfarin[132]

Solid line, affects synthesis in direct way; dashed line, affects activation via thrombin inhibition; F, factor; Pt, platelet; TF, tissue factor