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REVIEW ARTICLE

Benefit–Risk Assessment of Dabigatran in the Treatment of Stroke Prevention in Non-Valvular Atrial Fibrillation

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Abstract Non-valvular atrial fibrillation (NVAF) is the most common clinically significant cardiac arrhythmia and is a common cause of stroke. The direct thrombin inhibitor dabigatran etexilate is approved for a variety of indications requiring anticoagulation, including stroke prevention in NVAF. Dabigatran does not require routine monitoring and exhibits only a few drug–drug interactions; however, impaired renal function needs observation. The Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) study comprised about 18,000 patients with NVAF who received dabigatran 110 mg twice daily or 150 mg twice daily, or dose adjusted warfarin. Compared with warfarin, dabigatran 110 mg twice daily was associated with similar rates of stroke and systemic embolism, and lower rates of haemorrhage. Dabigatran 150 mg twice daily was associated with lower rates of stroke and systemic embolism but similar rates of haemorrhage. The rate of intracerebral haemorrhage (ICH) was significantly lower in both dabigatran arms. Basing on the results of the RE-LY study, the net clinical benefit balancing stroke against ICH has been estimated with various settings (study data, registry patients). In patients with low stroke risk but at high risk of bleeding, only dabigatran 110 mg twice daily had a positive net clinical benefit when compared with warfarin. In patients with higher stroke risks, both doses of dabigatran (110 and 150 mg twice daily) had a positive net clinical benefit even if the bleeding risk was high. Registry data after approval of dabigatran indicate similar stroke/systemic embolism and major bleeding rates with dabigatran (both doses) compared with warfarin. Pharmacovigilance sources prove the anticipated bleeding risk, but a refined analysis of such data showed that bleeding rates associated with dabigatran use did not appear to be higher than those associated with warfarin. Dabigatran confers an advantage over warfarin regarding stoke prevention without the burden of the surveillance of vitamin K antagonists, especially in patients with high stroke risk. However, in elderly patients with impaired renal function or considerable bleeding risks, label advice regarding dosing needs strict observation.

Key Points

In the pivotal Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) study, dabigatran at a dose of 150 mg twice daily was superior to dose-adjusted warfarin regarding the primary efficacy endpoint of stroke and systemic embolism, with no significant difference in the primary safety endpoint of major bleeding. A dose of dabigatran 110 mg twice daily was non-inferior to warfarin, with 20 % fewer major bleeds

So far, observational data from registries are grossly consistent with the findings of the RE-LY data, and currently available pharmacovigilance data do not indicate an excess of bleeding events or myocardial infarction among dabigatran-treated patients

The current appraisal of dabigatran benefit–risk relationship is that it does confer an advantage over warfarin regarding stoke prevention, especially in patients with high stroke risk

Labelling advice regarding dabigatran dosing needs strict observation, especially in elderly patients with impaired renal function or considerable bleeding risk

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1 Epidemiology of Non-Valvular Atrial Fibrillation (NVAF)

Atrial fibrillation (AF) affects 1–2 % of the population, and this figure is likely to increase in the next 50 years [1]. AF may long remain undiagnosed (silent AF), and many patients with AF will never present to hospital. Hence, the 'true' prevalence of AF is probably closer to 2 % of the population [2]. The prevalence of AF increases with age, from 0.5 % at 40–50 years, to 5–15 % at 80 years [3]. Men are more often affected than women. The lifetime risk of developing AF is 25 % in those who have reached the age of 40 years [4]. The incidence of AF appears to be increasing (13 % in the past two decades) [3]. The most common form of AF—separating from mitral stenosis—is non-valvular AF (NVAF). Death rates are doubled by NVAF, independently of other known predictors of mortality [1]. Stroke in NVAF is often severe and results in long-term disability or death. Approximately every fifth stroke is due to NVAF; furthermore, undiagnosed 'silent AF' is a likely cause of some 'cryptogenic' strokes [2, 3]. Paroxysmal NVAF carries the same stroke risk as permanent or persistent AF [5]. Hospitalizations due to NVAF account for one-third of all admissions for cardiac arrhythmias. Acute coronary syndrome (ACS), aggravation of heart failure, thromboembolic complications, and acute arrhythmia management are the main causes of hospitalization [3]. Quality of life and exercise capacity are impaired in patients with AF. Patients with AF have a significantly poorer quality of life compared with healthy controls, the general population, or patients with coronary heart disease in sinus rhythm. Stroke risk in NVAF populations is usually determined by the $CHADS_2$ [3, 6] score or the more recently introduced CHA_2DS_2-VASc score [5, 7], with treatment recommendations in all patients with a score ≥ 1 [3, 5]. Bleeding risk can be categorized using the HAS-BLED score [8].

2 Treatment of NVAF

Before the advent of direct oral anticoagulants (DOACs) [i.e. dabigatran, rivaroxaban, apixaban and edoxaban], vitamin K antagonists (VKAs) have been the main agents used in AF [9], and in patients where satisfying dose adjustment failed, or in those not tolerating or denying (e.g. due to inconvenience) VKA, or those having a $CHADS_2$ score of 1, aspirin has been used. Several large randomized trials evaluated dose-adjusted VKA for the primary prevention of thromboembolism in patients with NVAF or in secondary prevention among patients who had survived non-disabling stroke or transient ischaemic attack (TIA). In a meta-analysis, the relative risk reduction (RRR) with VKA was highly significant and amounted to an absolute annual risk reduction in all strokes of 2.7 % [10]. This reduction was similar for both primary and secondary prevention, and for both disabling and non-disabling strokes. All-cause mortality was significantly reduced (RRR 26 %) by adjusted-dose VKA versus control. However, before the introduction of the newer DOACs, epidemiological data indicated a proportion of about 40 % of NVAF patients were required to have oral anticoagulation but were not receiving it [11–13]. In a multinational, worldwide cohort established before the advent of dabigatran and other DOACs, overall 38.0 % of patients with a $CHADS_2$ score ≥ 2 did not receive any anticoagulant therapy, whereas about 42 % with a $CHADS_2$ score of 0 did receive VKAs. These data indicate VKA overuse in patients at low risk, and underuse in those at high risk, of stroke [14].

Supported by the results of the trials with VKA and now also with DOACs, oral anticoagulation is generally considered for patients with AF with ≥ 1 stroke risk factor(s) provided there are no contraindications, especially with careful assessment of the benefit–risk ratio and an appreciation of the patient's values and preferences. However, conventional anticoagulant therapy with VKAs is associated with various pharmacological and practical limitations, e.g. multiple food and drug interactions and necessity of coagulation monitoring [15, 16]. The clinical burden of thromboembolic diseases, especially the undertreatment resulting from the VKA limitations [11–13], have prompted the development of new anticoagulant agents that directly target a single enzyme in the coagulation cascade (i.e. Factor Xa or thrombin) [17]; in the past few years the DOACs rivaroxaban [18], apixaban [19], and dabigatran etexilate [20] have undergone extensive evaluation and gained approval for use in several indications, notably for NVAF. Edoxaban [21] is awaiting approval for NVAF in late 2014. Guidelines from the American College of Chest Physicians [22] or the European Society of Cardiology [23] now recommend oral anticoagulation, preferably with one of the DOACs in patients with AF, paroxysmal AF, or atrial flutter who have an intermediate to high risk of stroke (CHA_2DS_2-VASc score of 1 or higher). Aspirin is no longer recommended. Patients undergoing cardioversion should receive anticoagulation for at least 4 weeks after the procedure, and patients with AF with a duration of greater than 48 h should receive anticoagulation for at least 3 weeks prior to the procedure [23].

3 Dabigatran in NVAF

3.1 Pharmacokinetics of Dabigatran

The direct, reversible thrombin inhibitor dabigatran binds to thrombin with high affinity and specificity [24], inactivating both fibrin-bound as well as unbound thrombin [25].

Dabigatran etexilate is an oral prodrug that is absorbed rapidly and hydrolyzed completely to the active molecule, dabigatran [25]. The dominant elimination pathway of dabigatran is renal excretion, which accounts for approximately 80 % of systemically available dabigatran [26]. The plasma concentrations and anticoagulant effects of dabigatran are dose-dependent and peak within 2 h of oral administration [27, 28]. Dabigatran, in its clinically used dose range, exhibits linear pharmacokinetics [25], and steady-state dabigatran concentration is achieved approximately 3 days after multiple-dose administration in healthy volunteers [28]. The mean terminal half-life of dabigatran after oral administration is approximately 8 h after a single dose, and increases to 12–14 h with multiple dosing [25]. The half-life increases to >24 h in patients with creatinine clearance (CrCl) <30 mL/min [29] and is independent of dose [20]. Dabigatran effects on coagulation can be measured by several coagulation tests (e.g. ecarin time), and calibrated assays are available [30].

3.2 Approval of Dabigatran and Exposure to Dabigatran

In Europe, on 1 August 2011, the European Medicines Agency (EMA) granted marketing authorization for dabigatran for the prevention of strokes and systemic embolism in adult patients with NVAF and at least one risk factor for stroke. The US FDA approved dabigatran in the same indication on 19 October 2011, as did Canada on 27 October 2011; Australia followed in April 2012. 1–2 years preceding approval in NVAF, dabigatran was already approved in most of the above-mentioned countries for the prevention of thromboembolic disease following hip or knee replacement surgery. In NVAF, the normal dose recommendation is 150 mg twice daily. The EMA label currently recommends the use of dabigatran 150 mg twice daily in NVAF patients who are aged <80 years without an increased risk for bleeding (e.g. HAS-BLED score <3) and not on concomitant verapamil. The EMA label advises use of a lower dose of 110 mg twice daily in patients with impaired renal function, aged between 75 and 80 years, and prompts use of 110 mg twice daily if aged >80 years [31]. For these patients, in the US, a dose of 75 mg twice daily is advised (instead of 110 mg twice daily recommended by the EMA [32] (Table 1).

From the time when the FDA approved dabigatran in October 2011 through August 2012, approximately 3.7 million prescriptions for dabigatran were dispensed, and approximately 725,000 patients received a dispensed prescription from US outpatient retail pharmacies during that period. Actual sales figures are available for the US, and show a quarterly delivery of about 900,000 package units between 2011 and the end of 2013 [33], which should approximate the same number of patients.

In the Danish National Patient Register, between August (market entry of dabigatran) and 31 December 2011, a total of 52,366 Danish residents registered with a diagnosis of AF (International Classification of Diseases, Tenth Revision [ICD-10] code I48) claimed a prescription for oral anticoagulation. Of these, 1,612 (3.1 %) and 1,114 (2.1 %) patients were treated with dabigatran 110 or 150 mg twice daily, respectively, and 49,640 (94.8 %) were treated with VKAs [34]. However, 2 years after market entry, in July 2013, the number of dabigatran users increased to 8,197 versus 58,001 warfarin users, generating a share of about 14 %. In the cohort of new anticoagulant users, the share of dabigatran users was actually about 60 % [35]. In 2010–2011, the US-based Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) enrolled about 10,000 patients with AF from 174 community-based outpatient practices in the US, from whom about 7,500 received oral anticoagulation with either warfarin or dabigatran. The rate of dabigatran uses in this cohort was 5 % [36]; a later communication of this cohort indicated a frequency use of 12 % [37]. These numbers show that dabigatran was well received in the treatment of AF patients in Western societies; however, the actual share of dabigatran in NVAF patients under oral anticoagulation is not reported. Since in the meantime other DOACs (anti-FXa-inhibitors, e.g. rivaroxaban or apixaban) have also been approved, dabigatran faces considerable competition, and an increase in the recent figures of the market share of dabigatran of about 10 % of all NVAF patients seems unlikely.

4 Benefit–Risk Evaluation of Dabigatran

Data available for benefit–risk analysis of dabigatran currently come mainly from controlled trials preceding the drug approval, notably one large pivotal trial, the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) [20, 38]. Since the approval for NVAF was quite recent, further real-life data, e.g. from registries, are limited at the time of this evaluation, but a growing number of representative observational data on bleeding and thromboembolic event complications in dabigatran patients are available, e.g. the Danish National Patient Register with about 5–10 % of all patients with NVAF treated with dabigatran [35, 39]. Several post-marketing evaluations (e.g. NCT01491178, NCT01588119) or registry trials (e.g. Huisman et al. [40]) are ongoing.

5 Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY)

The RE-LY trial was a 2-year, randomized, prospective, non-inferiority trial ($n = 18{,}113$) in patients with non-

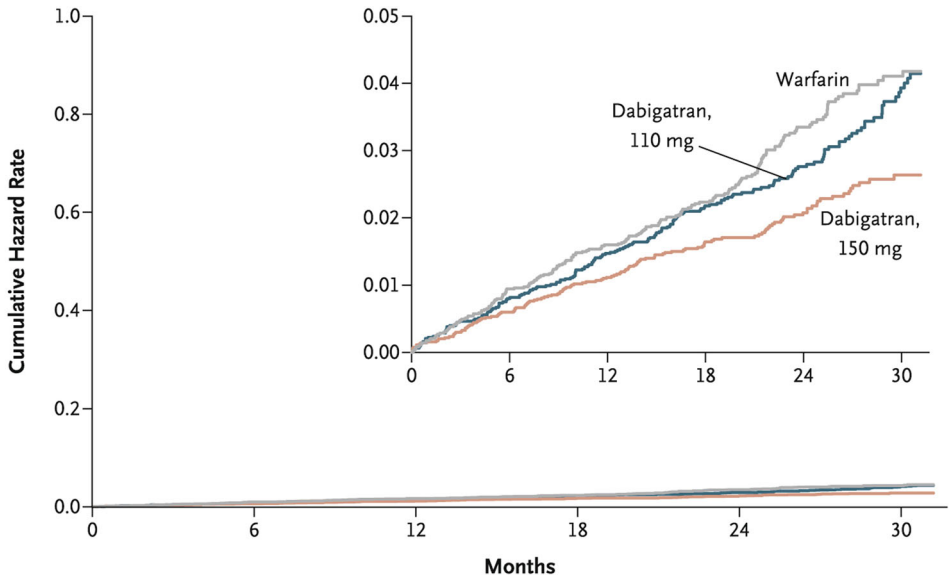
Table 1 Dosing recommendations for dabigatran [31]. Stroke prevention in patients with AF (EMA labelling advice[a])

Patients characteristics	Standard dose 150 mg twice daily
Bleeding risk	No dose adjustment (but use with caution in conditions with increased bleeding risk)
	Excessive dabigatran exposure and high bleeding risk: 110 mg twice daily
Bodyweight	No dose adjustment (but close surveillance when <50 kg)
Elderly patients	Age 75–80 years: 150 mg twice daily or 110 mg twice daily depending on individual thromboembolic and bleeding risk
Gastric conditions: gastritis, esophagitis, gastroesophageal reflux	110 mg twice daily
Renal impairment	
Mild (CrCl 50–80 mL/min)	No dose adjustment
Moderate (CrCl 30–49 mL/min)	150 mg twice daily or 110 mg twice daily depending on individual thromboembolic and bleeding risk
Severe (CrCl 15–29 mL/min)	Contraindicated (US label[a] allows 75 mg twice daily)
ESRD	Contraindicated
Concomitant medication	Verapamil: 110 mg twice daily

AF atrial fibrillation, *EMA* European Medicines Agency, *CrCl* creatinine clearance (estimated according to the Cockroft–Gault formula [31], *ESRD* end stage renal disease (dialysis), *NVAF* non-valvular atrial fibrillation

[a] The US label for the use of dabigatran in NVAF is widely in agreement with the EMA label, but advises 75 mg twice daily in all cases, whereas the EMA label quotes 110 mg twice daily [32]

valvular, persistent, paroxysmal, or permanent AF. In this trial, dabigatran 110 mg twice daily was as effective as warfarin in preventing stroke and systemic embolism with lower occurrence of major haemorrhage, while 150 mg twice daily was more effective than warfarin at preventing stroke and systemic embolism with similar occurrence of major haemorrhage. Patients (mean age 71 years, 64 % males) diagnosed with AF and at risk of stroke were randomized to receive dabigatran either 110 or 150 mg twice daily or dose-adjusted warfarin (target International Normalized Ratio [INR] of 2–3). Exclusion criteria included CrCl <30 mL/min and active liver disease. The $CHADS_2$ score of the treatment cohorts ranged from 2.1 to 2.2 (mean values). The primary outcome of stroke or systemic embolism occurred at a rate of 1.54 % per year in the dabigatran 110 mg group, 1.11 % per year in the dabigatran 150 mg group, and 1.71 % per year in the warfarin group. Compared with warfarin, the 110 mg dose of dabigatran was associated with a relative risk (RR) of 0.90 (95 % confidence interval [CI] 0.74–1.10; $p < 0.001$ for non-inferiority; $p = 0.34$ for superiority), and the 150 mg dose of dabigatran was associated with an RR of 0.65 (95 % CI 0.52–0.81; $p < 0.001$ for non-inferiority and superiority; number needed to treat [NNT] per treatment year = 167). Major bleeding occurred at a rate of 2.87 % per year for the dabigatran 110 mg dose, 3.32 % per year for the dabigatran 150 mg dose, and 3.57 % per year with warfarin. The RR for major bleeding was 0.80 (95 % CI 0.70–0.93; $p = 0.003$) for the dabigatran 110 mg dose (NNT to prevent one major bleeding 143) and 0.93 (95 % CI 0.81–1.07; $p = 0.31$) for the dabigatran 150 mg dose. Intracerebral haemorrhage (ICH) occurred less often under both doses of dabigatran (0.23 and 0.32 vs. 0.76 %) as under warfarin, and the NNT of preventing one ICH was 189 for dabigatran 110 mg twice daily and 227 for dabigatran 150 mg twice daily. The composite net clinical benefit outcome of systemic embolism, stroke, myocardial infarction (MI), pulmonary embolism, death or major bleeding was 7.34 % per year for the dabigatran 110 mg dose (RR 0.92; 95 % CI 0.84–1.01; $p = 0.09$), 7.11 % per year for the dabigatran 150 mg dose (RR 0.90; 95 % CI 0.82–0.99; $p = 0.02$; NNT = 125), and 7.91 % per year for warfarin [20, 41] (Fig. 1). The rate of all-cause mortality was 3.75 % per year for patients who received dabigatran 110 mg and 3.64 % per year for patients who received dabigatran 150 mg compared with 4.1 % for patients who received warfarin. There was a non-significant increase in MI with dabigatran compared with warfarin in the first RE-LY report [20], but other myocardial ischaemic events were not increased. Additionally, the rate of vascular death was 2.3 % for dabigatran compared with 2.7 % for warfarin; non-vascular death rates were similar in both groups. The only adverse effect significantly more common with dabigatran use was dyspepsia, occurring in 11.8 % of the dabigatran 110 mg group, 11.3 % in the dabigatran 150 mg group, and 5.8 % in the warfarin group ($p < 0.001$) [20]. Discontinuation of treatment over the entire treatment period had occurred in 21 % of patients randomized to dabigatran, and 17 % of those randomized to warfarin. However, subsequent analysis of the RE-LY data showed that dabigatran was associated with a 30 % increased odds of major gastrointestinal bleeding compared with adjusted-dose VKA (odds ratio [OR] 1.30; 95 % CI 1.06–1.59; number needed to harm [NNH] = 204) [42]. Further subanalysis of the RE-LY trial found that the risk of major bleeding was significantly



No. at Risk						
Warfarin	6022	5862	5718	4593	2890	1322
Dabigatran, 110 mg	6015	5862	5710	4593	2945	1385
Dabigatran, 150 mg	6076	5939	5779	4682	3044	1429

Fig. 1 Cumulative hazard rates for the primary outcome of stroke or systemic embolism, according to treatment group. Reproduced with permission [20]

associated with increasing age, with patients aged ≥75 years having the highest risk [43]. The risk of major bleeding was also increased with decreasing CrCl [43], which comes not unexpected because of the renal excretion of dabigatran. Indeed stroke and bleeding outcomes were correlated with dabigatran plasma concentrations, and age (with declining renal function) was the most important covariate for enhanced plasma levels [44].

5.1 Follow-Up for RE-LY (RELY-ABLE)

In the follow-up study RELY-ABLE [38], patients randomly assigned to dabigatran in RE-LY who had not permanently discontinued study medication at the time of their final study visit, continued to receive their double-blind dabigatran dose for up to 28 months of follow-up after RE-LY (median follow-up 2.3 years). There were 5,851 patients enrolled, representing 48 % of patients originally randomly assigned to receive dabigatran in RE-LY. Rates of stroke or systemic embolism were 1.46 and 1.60 % per year on dabigatran 150 and 110 mg twice daily, respectively (RR 0.91; 95 % CI 0.69–1.20). Rates of major haemorrhage were 3.74 and 2.99 % per year on dabigatran 150 and 110 mg (RR 1.26; 95 % CI 1.04–1.53). Rates of death were 3.02 and 3.10 % per year (RR 0.97; 95 % CI 0.80–1.19). Rates of haemorrhagic stroke were 0.13 and 0.14 % per year. The rates of outcome of the RE-LY study and the follow-up data are summarized in Table 2.

5.2 Benefit–Risk Assessment Based on RE-LY Cohorts

In AF, the prevention of embolism is closely connected with the risk of bleeding. Both endpoints, embolism and bleeding, are potentially lethal. Therefore, and more than in other therapeutic areas, risks and benefits of anticoagulant treatment deserve an integrated and multilevel analysis. (1) To adjust for the negative consequences of bleeding, especially intracranial bleeding, the approach of a 'net clinical benefit' has been employed [45–47]. Since the relative importance of thrombotic and bleeding events for patients is not equivalent, weighting of events according to their measured clinical importance might be advantageous [45]. (2) Given the fact that large numbers of patients with NVAF are not treated (due to preferences and bleeding risks), a benefit–risk evaluation of a new anticoagulant might consider both the figures from the comparator (e.g. warfarin) as well as the figures of no treatment [46, 48]. (3) The risk of getting a stroke or a bleeding event varies with demographic factors and comorbidities, as assessed by the CHA_2DS_2-VASc score and the HAS-BLED score [46]. Based on the RE-LY data, several benefit–risk analyses of dabigatran have been published [45, 46, 48]. Estimates of the effects of 'no treatment', and the effects of aspirin, warfarin and dabigatran 150 mg twice daily on the number of deaths, strokes and bleeds in a theoretical population of 100,000 NVAF patients followed for 1 year have been provided by Eikelboom et al [48]. Estimates were derived from contemporary global randomized controlled trials of

Table 2 Rates of outcome (%/year) in RE-LY versus RELY-ABLE (according to Connolly et al. [20, 38, 41])

	Dabigatran		Warfarin	Dabigatran 110 mg vs. warfarin		Dabigatran 150 mg vs. warfarin		Dabigatran 110 mg vs. dabigatran 150 mg	
	110 mg	150 mg		RR 95 % (CI)	*p*-value	RR 95 % (CI)	*p*-value	RR 95 % (CI)	*p*-value
Stroke or systemic embolism									
RE-LY	1.54	1.11	1.71	0.90 (0.74–1.10)	0.29	0.65 (0.52–0.81)	<0.001	0.72 (0.58–0.90)	0.004
RELY-ABLE	1.60	1.46						0.91 (0.69–1.20)	NA
Major bleeding									
RE-LY	2.87	3.32	3.57	0.80 (0.70–0.93)	0.003	0.93 (0.81–1.07)	0.31	1.16 (1.00–1.34)	0.04
RELY-ABLE	2.99	3.74						1.26 (1.04–1.53)	NA
Intracranial bleeding									
RE-LY	0.23	0.32	0.76	0.31 (0.20–0.47)	<0.001	0.40 (0.27–0.60)	<0.001	1.39 (0.85–2.28)	0.19
RELY-ABLE	0.25	0.33						1.31 (1.68–2.51)	NA
Gastrointestinal haemorrhage									
RE-LY	1.15	1.56	1.07	1.08 (0.85–1.38)	0.52	1.48 (1.18–1.85)	0.001	1.36 (1.09–1.70)	0.006
RELY-ABLE	1.56	1.54						0.99 (0.75–1.31)	NA
Myocardial infarction									
RE-LY	0.82	0.81	0.64	1.29 (0.96–1.75)	0.09	1.27 (0.94–1.71)	0.12	0.98 (0.74–1.30)	0.88
RELY-ABLE	0.72	0.69						0.96 (0.63–1.45)	NA
All-cause mortality									
RE-LY	3.57	3.64	4.13	0.91 (0.80–1.03)	0.13	0.88 (0.77–1.00)	0.051	0.97 (0.85–1.11)	0.66
RELY-ABLE	3.10	3.02						0.97 (0.80–1.19)	NA

RE-LY Randomized Evaluation of Long-Term Anticoagulation Therapy, *RELY-ABLE* follow-up study to RE-LY, *RR* relative risk, *CI* confidence interval, *NA* not available

aspirin, warfarin and dabigatran, and from a meta-analysis [10] of randomized controlled trials of aspirin or warfarin compared with placebo/no treatment in patients with NVAF. If no antithrombotic treatments were used there would be 6,664 deaths and 5,998 strokes over a 1-year period. Compared with no treatment, aspirin would prevent 492 deaths and 2,582 strokes, warfarin would prevent 2,629 deaths and 4,458 strokes, and dabigatran 150 mg twice daily would prevent 3,024 deaths and 4,988 strokes for every 100,000 patients treated for 1 year. To achieve these benefits, dabigatran compared with no treatment would be associated with an increase of 164 intracranial haemorrhages (ICH) and 77 fatal bleeds. If dabigatran 150 mg twice daily was given instead of warfarin, 318 ICHs, 99 fatal bleeds and 395 deaths would be saved.

The same authors provided a study that compared the net clinical benefit of dabigatran 110 mg twice daily and 150 mg twice daily with that of warfarin in patients with NVAF [45]. Using the data of the 18,113 patients in the RE-LY trial, a previously developed method [49] for integrating ischaemic and bleeding events as 'ischaemic stroke equivalents' in order to compare a weighted benefit of two doses of dabigatran with each other and with that of warfarin, has been applied. Compared with warfarin, there was a significant decrease in ischaemic stroke equivalents with both dabigatran doses: −0.92 per 100 patient years (95 % CI −1.74 to −0.21; $p = 0.02$) with dabigatran 110 mg twice daily, and −1.08 (95 % CI −1.86 to −0.34; $p = 0.01$) with dabigatran 150 mg twice daily. There was no significant difference in ischaemic stroke equivalents between the two doses: −0.16 (95 % CI −0.80 to 0.43) comparing dabigatran 150 mg twice daily with 110 mg twice daily. When including death in the weighted benefit calculations, the results were similar. On a group level, both doses of dabigatran, compared with warfarin, have similar benefits when considering a weighted estimate including both efficacy and safety (see Fig. 2). The authors concluded that the similar overall benefits of the two doses of dabigatran versus warfarin support individualizing the dose based on patient characteristics (e.g. renal function, age, bleeding risks) and physician and patient preferences.

Banerjee et al. [46] sought to combine the 'real-world' pattern of stroke and bleeding risk obtained from a Danish patient registry with the outcome data from the RE-LY trial and other trials with other direct anticoagulants (apixaban, rivaroxaban) and applied them to a representative cohort of patients. The event rates per 100 person-years for ischaemic stroke and ICH were calculated using data from the Danish study population for patients receiving 'no treatment' and receiving warfarin, stratified by stroke risk as predicted by the $CHADS_2$ and CHA_2DS_2-VASc scores,

Fig. 2 Weighted net clinical benefit of dabigatran 110 mg twice daily compared with warfarin, dabigatran 150 mg twice daily compared with warfarin, and dabigatran 150 mg twice daily compared with Dabigatran 110 mg twice daily. Results are expressed as ischaemic stroke equivalents per 100 patient years. Reproduced with permission [45]. *CI* confidence interval

and the bleeding risk as predicted by the HAS-BLED score. Using data from recent trials of the DOACs, the event rates per 100 person-years for ischaemic stroke and ICH were calculated using these RRs, and stratified by stroke risk as predicted by the $CHADS_2$ and CHA_2DS_2-VASc scores. From these data it was concluded that in patients with $CHADS_2$ or CHA_2DS_2-VASc = 0, but at high bleeding risk (HAS-BLED $\geq$3), apixaban and dabigatran 110 mg twice daily have a positive net clinical benefit compared with warfarin. At CHA_2DS_2-VASc = 1, apixaban and both doses of dabigatran (110 and 150 mg twice daily) have a positive net clinical benefit. In patients with a $CHADS_2$ score $\geq$1 or CHA_2DS_2-VASc $\geq$2, the three new OACs (dabigatran, rivaroxaban and apixaban) appear superior to warfarin for net clinical benefit, regardless of risk of bleeding. If compared with 'no treatment', the NNT to prevent one ischaemic stroke per 100 person-years depended on the CHA_2DS_2-VASc score and dabigatran dose, and varied between 1,761 (CHA_2DS_2-VASc = 1, dabigatran 110 mg twice daily) and 78 (CHA_2DS_2-VASc = 2–9, dabigatran 150 mg twice daily).

In the first report of the RE-LY study [20], dabigatran appears to be associated with a greater risk of MI than warfarin (RR 1.38; 95 % CI 1.00–1.91; $p = 0.048$). Although not being statistically significant for dabigatran 150 mg versus warfarin in the revised RE-LY data analysis (RR 1.27; 95 % CI 0.94–1.71; $p = 0.12$) [41], the topic stirred up controversy. It was discussed whether the increased risk is unique to dabigatran, a class effect shared by other oral direct thrombin inhibitors, or the result of a protective effect of warfarin against MI [50]. Artang et al. [50] found that oral direct thrombin inhibitors are associated with increased risk of MI, even without considering RE-LY data. These findings were confirmed in other meta-analysis where dabigatran was significantly associated with a higher risk (RR 1.27; 95 % CI 1.00–1.61; $p = 0.05$) even when using revised RE-LY trial results [51]. The authors conclude that regardless of the comparator, dabigatran is associated with an increased risk of acute coronary events in a broad spectrum of patients, but at the same time they also provide evidence that dabigatran reduces all-cause mortality. However, elsewhere it was argued that in the absence of a plausible biochemical mechanism to explain the increased MI rates with dabigatran compared with warfarin and with few supporting clinical data, the likelihood is that dabigatran does not actually cause coronary events [52]. This is also reflected in other meta-analyses that compared dabigatran with warfarin: the composite endpoint in one of these studies was MI, total stroke, and vascular death, and numerically fewer events in patients with dabigatran 150 mg (RR 0.87; 95 % CI 0.77–1.00) were found, but similar event rates for dabigatran 110 mg (RR 0.99; 95 % CI 0.87–1.13). Dabigatran had similar MI rates when compared with enoxaparin or placebo. The association of dabigatran use with MI will probably remain a matter of debate for a while, since also, in another meta-analysis, data from 14 comparative trials ($n = 42,484$) in different indications (NVAF, treatment and prophylaxis of deep vein thrombosis) the occurrence of MI was higher with dabigatran as with warfarin (RR 1.30, 95 % CI 0.96–1.76 for dabigatran 110 mg; and RR 1.42, 95 % CI 1.07–1.88 for dabigatran 150 mg). Since dabigatran had similar MI rates when compared with enoxaparin or placebo, the authors conclude that MI is not an adverse drug reaction associated with the use of dabigatran, but warfarin exerts a protective effect against MI [53].

5.3 Benefit–Risk Assessment in Post-Approval Cohorts

Up until now, only a limited number of data on bleeding and thromboembolic event complications in dabigatran patients have been available, which are not based on the RE-LY cohort. The known obstacle with studies for approval purposes is their external validity, and, for example, exclusion of vulnerable subjects and tighter surveillance during a study likely contributes to findings that were not necessarily reflected in the real-world of NVAF treatment. For example, elderly patients who are more likely to need stroke prevention therapy represent a difficult population to treat owing to their higher likelihood of receiving co-medication, higher susceptibility to comorbidities, and increased risk of renal impairment [54], compared with younger patients.

The safety of dabigatran in its post-approval phase was first assessed in a study by Sorensen et al. [34]. For the period between 22 August 2011 and 31 December 2011, and using registry data from the nationwide Danish cohort of patients under either dabigatran or warfarin, this group investigated the influence of several patient factors (comorbidities, previously VKA-treated or naïve) on stroke and bleeding risk in a cohort of about 2,726 patients receiving dabigatran, and compared them with about 49,640 patients receiving warfarin. Patients treated with dabigatran 150 mg twice daily were younger (68 years vs. 80 years), with less comorbidity than those treated with dabigatran 110 mg twice daily and VKA, as were VKA-naïve patients ($n = 1,595$) compared with previous VKA users ($n = 1,131$). Label advice regarding dosing or contraindications for dabigatran were met in 90.3 % of patients treated with 110 mg but only in 55.5 % of patients treated with dabigatran 150 mg. Patients treated with dabigatran 150 mg who did not match the label advice were aged >80 years, patients with liver or kidney disease, or patients with previous bleeding. Compared with VKA, the thromboembolic risk associated with dabigatran 110 and 150 mg was RR 3.52 (95 % CI 1.40–8.84) and 5.79 (95 % CI 1.81–18.56), respectively, in previous VKA users, and RR 0.95 (95 % CI 0.47–1.91) and 1.14 (95 % CI 0.60–2.16), respectively, in VKA-naïve patients. Bleeding risk was increased in previous VKA users receiving dabigatran 110 mg twice daily, but not in patients receiving 150 mg twice daily, nor in the VKA-naïve users.

An anticoagulant-naïve AF population was investigated using registry data from the same Danish cohort of patients [34] under either dabigatran or warfarin [55]. For the period between 1 August 2011 and 31 December 2012, about 5,100 patients receiving dabigatran were identified and propensity-matched with about 9,000 patients under warfarin. The median follow-up period after incident AF was 10.5 months (interquartile range 7.9–13.4 months). They found that stroke and systemic embolism were not significantly different between warfarin- and dabigatran-treated patients. Adjusted mortality was significantly lower with both dabigatran doses (110 mg twice daily [RR 0.79; 95 % CI 0.65–0.95]/150 mg twice daily [RR 0.57; 95 % CI 0.40–0.80]) when compared with warfarin. Pulmonary embolism was lower compared with warfarin for both doses of dabigatran. Less intracranial bleeding was seen with both dabigatran doses (110 mg twice daily [RR 0.24; 95 % CI 0.08–0.56]/150 mg twice daily [RR 0.08; 95 % CI 0.01–0.40]). Interestingly, the incidence of MI was lower with both dabigatran doses (110 mg twice daily [RR 0.30; 95 % CI 0.18–0.49]/150 mg twice daily [RR 0.40; 95 % CI 0.21–0.70)]. Gastrointestinal bleeding was lower with dabigatran 110 mg twice daily (hazard ratio [HR] 0.60; 95 % CI 0.37–0.93) compared with warfarin, but not dabigatran 150 mg twice daily. The main findings were broadly consistent in the subgroup of dabigatran users with >12 months follow-up ($n = 1,865$).

The exploitation of this database was continued by yet another report from the same authors [39], focussing on bleeding events. For the period 1 August 2011 (dabigatran market entry) to 30 May 2013, a total of 11,315 first-time dabigatran users with AF were identified and matched to warfarin controls in a 2:1 ratio according to their VKA-experience status. Average follow-up time was 13 months. Across the six combinations of treatment (dabigatran 110 mg, dabigatran 150 mg, and warfarin) and VKA-experience status (naïve or experienced), VKA-naïve warfarin initiators had the highest rate of any bleeding event. Cox regressions adjusted for baseline characteristics showed reductions relative to this group ranging from 19 % for VKA-experienced dabigatran 110 mg users (HR 0.81; 95 % CI 0.66–1.00) to 41 % for VKA-experienced dabigatran 150 mg users (HR 0.59; 95 % CI 0.46–0.75). Among switchers to dabigatran from warfarin, and when compared against warfarin-persisting users, the rate of any bleeding was non-significantly decreased for switchers to dabigatran 150 mg (HR 0.80; 95 % CI 0.62–1.03) but not for switchers to dabigatran 110 mg (HR 1.12; 95 % CI 0.90–1.41). Results for major bleeding were similar.

The most recent analysis from the Danish cohort, provided by Larsen et al [35], covers the potential excess of MI under dabigatran, a topic already issued by previous analysis, for example, of RE-LY data [51]. Cohorts of VKA-naïve 'new starters' on dabigatran or warfarin, and cohorts of prior VKA-experienced 'switchers' to dabigatran or 'continuers' on warfarin were followed for an average of 16.0 months. Relative to warfarin, there was a non-significant trend to lower MI rates with dabigatran among VKA-naïve users (110 mg—HR 0.71, 95 % CI 0.47–1.07; 150 mg—HR 0.94, 95 % CI 0.62–1.41); however, there was a non-significant trend to increased MI rates among prior VKA-experienced users (110 mg—HR 1.45. 95 % CI 0.98–2.15; 150 mg—HR 1.30, 95 % CI 0.84–2.01). An increased MI rate relative to warfarin among prior VKA-experienced users was clearly significant during the early follow-up period of <60 days (110 mg—HR 3.01, 95 % CI 1.48–6.10; 150 mg—HR 2.97, 95 % CI 1.31–6.73). These findings agree with the previous analysis [34] where rates of MI were lower in new users of oral anticoagulation with both doses of dabigatran compared with warfarin. This study now adds that VKA-experienced patients who switch to dabigatran may have an increased rate of myocardial ischaemic events (particularly in the early treatment period) compared with patients continuing VKA treatment. These data also support the hypothesis that VKA confer some protection if patients are prone to acute coronary events. Perhaps this represents the

flip-side of the coin that warfarin users have a larger risk of ICH than users of DOACs due to VKA-induced inhibition of tissue factor-mediated haemostasis.

Some figures on the pattern of dabigatran use have been reported from US data by ORBIT-AF [37]. Among 9,974 AF patients included between June 2010 and August 2011 and followed for 12 months, 1,217 (12 %) were treated with dabigatran during the study. Patients receiving dabigatran were younger, at a lower risk of stroke and bleeding, and had more new-onset AF than those under VKA. However, more than half of the patients with severe kidney disease ($n = 14/25$) were not prescribed reduced dosing, whereas 10 % ($n = 91/920$) with preserved renal function received lower dosing.

5.4 Pharmacovigilance Data from Spontaneous Data

Since the beginning of the post-approval phase, concerns have been raised about an excess of bleeding events among dabigatran-treated patients. Because the RE-LY trial had clearly shown that bleeding is a serious side effect of dabigatran, it was expected that bleeding events would be reported after the product was approved, and at end of 2012 the number of reports was sufficiently high to prompt the FDA to initiate a review of the spontaneous reports. As already indicated by some of the above-mentioned registry analyses [34, 37], the postmarketing use of dabigatran might be different from its use in the RE-LY trial, especially given that adjustments for renal function and/or age have not been made correctly. Indeed, a compilation of single case reports on bleeding under dabigatran [56–60] also indicate that elderly patients, most often with impaired renal function, experienced bleeding episodes. Therefore, bleeding rates for dabigatran and warfarin were compared using insurance-claim data and administrative data from the FDA Mini-Sentinel database, a pilot program of the Sentinel Initiative [61]. It was found that bleeding rates associated with dabigatran use during the period of interest (19 October 2010, the date of dabigatran approval, to 31 December 2011) did not appear to be higher than those associated with warfarin. The incidence (number of events/100,000 days at risk) for gastrointestinal haemorrhage in NVAF patients was 1.6 for dabigatran and 3.5 for warfarin, whereas the incidence for intracerebral bleeding was 0.8 for dabigatran and 2.4 for warfarin. A renewed sentinel analysis is planned for Spring 2014 [62].

6 Alternative Therapies: No Treatment or Other Drugs

As mentioned above, recent guidelines on NVAF do no longer recommend aspirin use [63], and DOACs are the preferred option before VKA. Generally, DOACs have delivered similar results for stroke prevention in patients with NVAF when compared with VKAs. Rivaroxaban, apixaban, edoxaban and dabigatran significantly reduced the risk of haemorrhagic stroke, and apixaban and dabigatran 110 mg significantly reduced the risk of major bleeding (Table 3). Rates of intracranial haemorrhage were significantly lower with rivaroxaban, apixaban, and dabigatran compared with warfarin [18–20]. No head-to-head studies are available for these new drugs, and cross-trial indirect comparisons in the field of NVAF are not easily done; in the studies described, both dabigatran and apixaban showed superiority to warfarin in patient populations that had a lower overall risk for stroke than the population used in the rivaroxaban study. Some indirect comparisons and network meta-analyses for venous thromboembolism prevention and stroke prevention in patients with NVAF have been published but do not report definite conclusions regarding the superiority of one drug over another [64–66]. All-cause mortality in the NVAF setting did not differ between the agents or regimens studied in phase III trials [65], and in another meta-analysis, the occurrence of thromboembolic events and bleeding in a total of 44,733 patients from four studies with the DOACs was analysed. The composite of stroke or systemic emboli were significantly reduced with dabigatran compared with warfarin (RR 0.75; 95 % CI 0.57–1.00; $p < 0.001$), whereas major bleeding was not increased compared with warfarin. Also, all-cause mortality (RR 0.87; 95 % CI 0.80–0.97; $p = 0.001$) and haemorrhagic stroke (RR 0.46; 95 % CI 0.27–0.77; $p = 0.0001$) were significantly lower with dabigatran versus warfarin. When compared with rivaroxaban, dabigatran was associated with a significantly lower risk of the composite of stroke or systemic emboli (RR 0.76; 95 % CI 0.58–0.99) and ischaemic stroke (RR 0.68; 95 % CI 0.49–0.93), whereas no difference in mortality was seen. No significant difference in either major bleeding or gastrointestinal bleeding was seen between the agents, but dabigatran significantly reduced the risk of haemorrhagic stroke (RR 0.45; 95 % CI 0.21–0.98). Dabigatran, when compared with apixaban, did not show different efficacy outcomes, including the composite endpoint of stroke or systemic emboli, the occurrence of ischaemic stroke and mortality rate. However, apixaban had a lower risk of major (RR 0.75; 95 % CI 0.62–0.92) and gastrointestinal bleeding (RR 0.60; 95 % CI 0.43–0.84) [67].

7 Measures to Prevent or Treat Bleeding Complications

7.1 Renal Function

Renal impairment is, in general, one of the risk factors for bleeding and thrombosis during anticoagulant therapy [68],

Table 3 Incidence of efficacy and safety outcomes from phase III studies of oral anticoagulants for stroke prevention in patients with NVAF

	Novel oral anticoagulant		Warfarin	*p* value
Dabigatran				
RE-LY [20]	110 mg ($n = 6,015$)[b]	150 mg ($n = 6,076$)[b]	($n = 6,022$)[b]	
Stroke and SE (%/year)	1.53	1.11	1.69	<0.001 (110 mg, non-inferiority)
				<0.001 (150 mg, superiority)
Major bleeding (%/year)	2.71	3.11	3.36	0.003 (110 mg, superiority)
				0.31 (150 mg, superiority)
Rivaroxaban				
ROCKET AF [18]				
Stroke and SE (%/year)	2.10 ($n = 7,081$)[b]		2.40 ($n = 7,090$)[b]	<0.001 (non-inferiority)
Bleeding (%/year)[a]	14.90 ($n = 7,111$)[c]		14.50 ($n = 7,125$)[c]	0.44
Apixaban				
ARISTOTLE [19]				
Stroke and SE (%/year)	1.27 ($n = 9,102$)[b]		1.60 ($n = 9,081$)[b]	0.01 (superiority)
Major bleeding (%/year)	2.13 ($n = 9,088$)[c]		3.09 ($n = 9,052$)[c]	<0.001 (superiority)
Edoxaban				
ENGAGE AF TIMI [21]	60 mg ($n = 7,035$)	30 mg ($n = 7,034$)	($n = 7,036$)	
Stroke and SE (%/year)	1.57	2.04	1.80	0.08 (60 mg)
				0.10 (30 mg) (superiority)
Major bleeding (%/year)	1.61	2.75	3.43	<0.001

ARISTOTLE Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation, *ENGAGE AF TIMI* Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction, *NVAF* non-valvular atrial fibrillation, *RE-LY* Randomized Evaluation of Long-Term Anticoagulation Therapy, *SE* systemic embolism, *ROCKET AF* Rivaroxaban Once-daily oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation

[a] Composite endpoint of major bleeding and non-major clinically relevant bleeding

[b] Intention-to-treat population

[c] Safety population

and adversely affects outcomes in patients with NVAF [69, 70]. Renal excretion is the dominant elimination pathway for dabigatran, and impaired renal function prompts enhanced exposure and subsequent enhanced bleeding risks [71]. However, although no pre-specified dose adjustment of dabigatran was used in the RE-LY study, subgroup analyses did not indicate imbalance of benefit–risk in patients with moderate renal impairment [20, 70]. In NVAF patients, dabigatran has strict labelling advice regarding renal function and age [31], stating that (1) renal function should be assessed by calculating the estimated glomerular filtration rate (eGFR) prior to initiation of treatment using the Cockroft–Gault-formula; (2) dabigatran is contraindicated if eGFR is below <30 mL/min; and (3) no dose adjustment is necessary in patients with mild renal impairment (eGFR 50–80 mL/min). For patients with moderate renal impairment (eGFR 30–50 mL/min), the recommended dose of dabigatran is also 150 mg twice daily. However, for patients with high risk of bleeding, a dose reduction of dabigatran to 110 mg twice daily (US 75 mg) should be considered. Close clinical surveillance is recommended in patients with renal impairment. Renal function should also be assessed when a decline in renal function is suspected during treatment (e.g. hypovolemia, dehydration, and in case of concomitant use of certain co-medications). In patients with mild to moderate renal impairment and in patients aged over 75 years, renal function should be assessed during treatment at least once a year or more frequently as needed in certain clinical situations when it is suspected that the renal function could decline or deteriorate (e.g. hypovolemia, dehydration). From pharmacovigilance and other observational data it becomes obvious that these requirements are frequently not met, and missing the labelling advice seems associated with bleeding events. Controlling for renal function in appropriate intervals, and when clinical conditions change, is therefore essential.

7.2 Bleeding

The relatively short half-life and the reversible inhibition of thrombin by dabigatran (bypassing the need for new

synthesis of coagulation factors) shorten the duration of increased bleeding risk to about 24–48 h, depending on renal function. Calibrated assays are available to determine dabigatran plasma concentrations, although availability is so far limited to academic centres [30]. Although dabigatran can be dialyzed, it should be noted that there is only limited clinical experience in using dialysis in this setting. However, an appropriate treatment strategy after overdose and/or bleeding needs to be established. Recently published guidance on emergency treatment of bleeding with the novel DOACs suggests routine supportive care and activated charcoal if DOAC ingestion was within 2–3 h prior to the bleeding event [72–74]. The use of blood products or platelets, and then prothrombin complex concentrate, activated prothrombin complex concentrate, or recombinant factor VIIa if blood products or platelets are not effective, are potentially useful [75]. Detailed advice for dabigatran has recently been delivered by the German regulatory [76], but the authors are not aware of similar publications elsewhere. Recently, the first clinical data for an antidote to dabigatran, which is an antibody fragment delivered as an intravenous infusion, have been presented. A study in healthy volunteers showed the antidote to be well tolerated and producing immediate, complete and sustained reversal of dabigatran-induced anticoagulation [77]. However, it is unlikely that this agent will be available before 2015.

7.3 Overall Assessment and Conclusion

The approval of dabigatran in NVAF was based mainly on the results of one large randomized controlled trial, including its follow-up, for more than 4 years. The RE-LY study comprised about 18,000 patients with NVAF who received dabigatran 110 mg twice daily or 150 mg twice daily, or dose-adjusted warfarin. Compared with warfarin, dabigatran 110 mg twice daily was associated with similar rates of stroke and systemic embolism (i.e. non-inferior) and lower rates of haemorrhage. Dabigatran 150 mg twice daily was associated with lower rates of stroke and systemic embolism (i.e. superior) but similar rates of haemorrhage. The rate of ICH was significantly lower in both dabigatran arms. So far, observational data from registries are grossly consistent with the findings of the RE-LY data, although the superiority of dabigatran 150 mg twice daily over warfarin is not entirely reflected in the real-world setting. Similar stroke/systemic embolism and major bleeding rates were seen with dabigatran (both doses) compared with warfarin. Mortality, intracranial bleeding and pulmonary embolism were lower with dabigatran compared with warfarin. However, VKA-experienced patients who switch to dabigatran may have an increased rate of myocardial ischaemic events (particularly in the early treatment period). Currently available pharmacovigilance data from postmarketing spontaneous reporting do not indicate an excess of bleeding events or MI among dabigatran-treated patients. The current appraisal of dabigatran benefit–risk relationship is therefore that it does confer an advantage over warfarin regarding stoke prevention without the burden of the VKA setting, especially in patients with high stroke risk. However, especially in elderly patients with impaired renal function or with considerable bleeding risk, labelling advice regarding dosing needs strict observation. A possible loss of coronary protection by VKA after switching to dabigatran might need consideration.

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