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CARDIOVASCULAR DISEASE AND STROKE (D LEIFER AND JE SAFDIEH, SECTION EDITORS)

Novel Oral Anticoagulants for Atrial Fibrillation

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Abstract Three novel oral anticoagulants (NOACS)—dabigatran etexilate, rivaroxaban, and apixaban—have been approved in many countries for stroke prevention in atrial fibrillation, because they are associated with the same or lower rates of stroke, bleeding (particularly intracranially) and death compared with warfarin; and unlike warfarin, they can be given in fixed doses without routine coagulation monitoring. The effects of NOACs compared with warfarin are consistent in almost all populations and patient subgroups studied. Pharmacoeconomic analyses indicate that the NOACs are also cost-effective in Europe and North America. The lack of an antidote to the NOACs in patients who experience major bleeding has not been associated with a worse outcome among patients treated with NOACs compared with warfarin in secondary analyses. Multiple guidelines for the management of AF now recommend the NOACs for stroke prevention among atrial fibrillation (AF) patients at risk for stroke.

Keywords Atrial fibrillation · Novel oral anticoagulants · Stroke prevention

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Introduction

The past 4 years have seen the publication of the results of four large phase III clinical trials that showed that three novel oral anticoagulants (NOACS)—the direct thrombin inhibitor dabigatran etexilate [1, 2], and the factor Xa inhibitors rivaroxaban [3] and apixaban [4]—were at least as efficacious and safe as warfarin, and that apixaban [5] was superior to, and as safe as, aspirin for preventing stroke among patients with atrial fibrillation (AF). These results have realized widespread regulatory approval for the NOACS, and thus new therapeutic options for stroke prevention in AF. However, they have also generated many questions, and several meta-analyses and subanalyses of the trials data. In this paper, we review the relevant literature published over the past year and discuss the interesting and important new findings.

Effects of NOACs Versus Warfarin Overall

A meta-analysis of data from 12 phase II and phase III randomized, controlled trials comparing NOACs with vitamin K antagonists in patients with atrial fibrillation (three administering dabigatran, four administering rivaroxaban, two administering apixaban, and three administering edoxaban) in a total of 54,875 patients indicates that, compared with vitamin K antagonists, the NOACs significantly reduced stroke/systemic embolism (2.40 % versus 3.13 %; risk ratio [RR]: 0.77, 95 % confidence interval [95 % CI]: 0.70–0.86, $p<0.00001$; $I^2=0$ %; p value for heterogeneity/interaction = 0.56) (Fig. 1); major bleeding (RR: 0.86; 95 % CI: 0.80–0.93, $p<0.0001$; $I^2=57$ %; heterogeneity $p=0.02$) (Fig. 2); intracranial hemorrhage (RR: 0.46; 95 % CI: 0.39–0.56, $p<0.00001$; $I^2=34$ %; heterogeneity $p=0.17$) (Fig. 2); total mortality (5.61 % versus 6.02 %; RR: 0.89, 95 % CI: 0.83–0.96, $p=0.001$; $I^2=0$ %; heterogeneity $p=0.93$); and

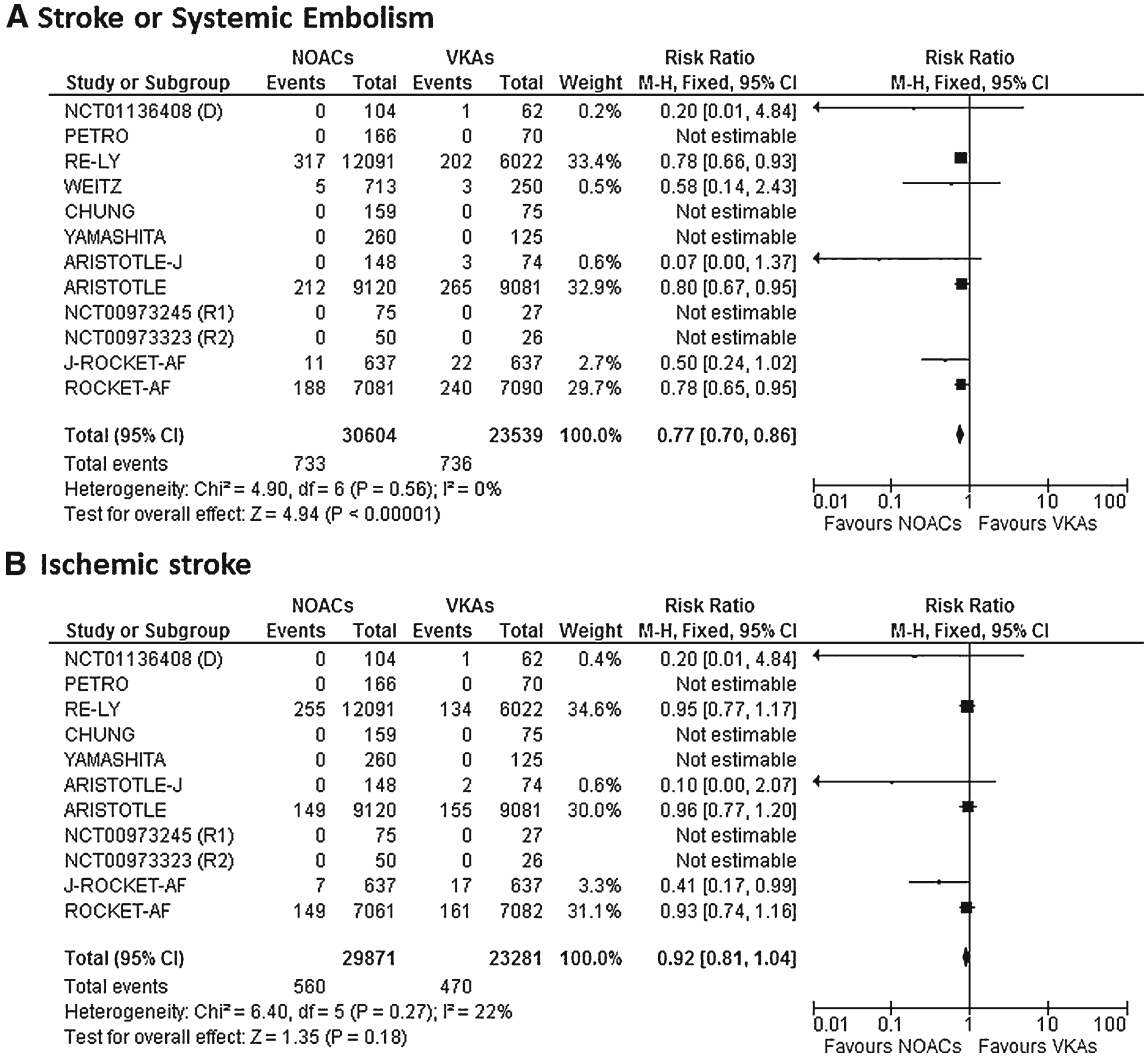

Fig. 1 Stroke or systemic embolism (*A*) and ischemic stroke (*B*) during oral anticoagulant treatment. *NOAC*—novel oral anticoagulant; *VKA*—vitamin K antagonists; *M-H*—Mantel-Haenszel; *CI*—confidence interval; *RE-LY*—Randomized Evaluation of Long-Term Anticoagulant Therapy; *ARISTOTLE*—Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation; *J-ARISTOTLE*—Japanese Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation; *ROCKET-AF*—An Efficacy and Safety Study of Rivaroxaban With Warfarin for the Prevention of Stroke and Non-Central Nervous System Systemic Embolism in Patients With Non-Valvular Atrial Fibrillation; *J-ROCKET-AF*—An Efficacy and Safety Study of Rivaroxaban With Warfarin for the Prevention of Stroke and Non-Central Nervous System Systemic Embolism in Patients With Non-Valvular Atrial Fibrillation in Japan (Adapted from [6••] with permission from the publisher)

cardiovascular mortality (3.45 % versus 3.65 %; RR: 0.89, 95 % CI: 0.82–0.98, p=0.01; I^2=0 %; heterogeneity p=0.80) [6••]. There was no difference in myocardial infarction (RR: 0.99, 95 % CI: 0.85–1.15, p=0.89; I^2=55 %; heterogeneity p=0.06) [6••]. Similar results have been reported with meta-analyses of the large phase III trials only [7–16].

In the absence of any direct comparison of the NOACs by means of head-to-head trials, indirect comparisons of how each of the NOACs performed, compared with warfarin, suggest that the relative effects of each of the NOACs, compared with warfarin, were consistent for four major outcomes: stroke and systemic embolism (I^2=0 %), intracranial hemorrhage (I^2=34 %), mortality (I^2=0 %), and cardiovascular mortality (I^2=0 %) [6••, 7–16].

However, the results were not consistent for two other major outcomes: major bleeding (I^2=57 %)—particularly gastrointestinal (GI) bleeding (RR 1.25, 95 % CI: 0.91–1.72; I^2=82 %; heterogeneity p=0.003) and myocardial infarction [MI] (I^2=55 %) [6••, 7–16]. Compared to warfarin, dabigatran 150 mg bid and rivaroxaban were associated with more GI bleeding, whereas dabigatran 110 mg bid and apixaban were not. Compared to warfarin, dabigatran was associated with an increase in MI whereas rivaroxaban and apixaban were not.

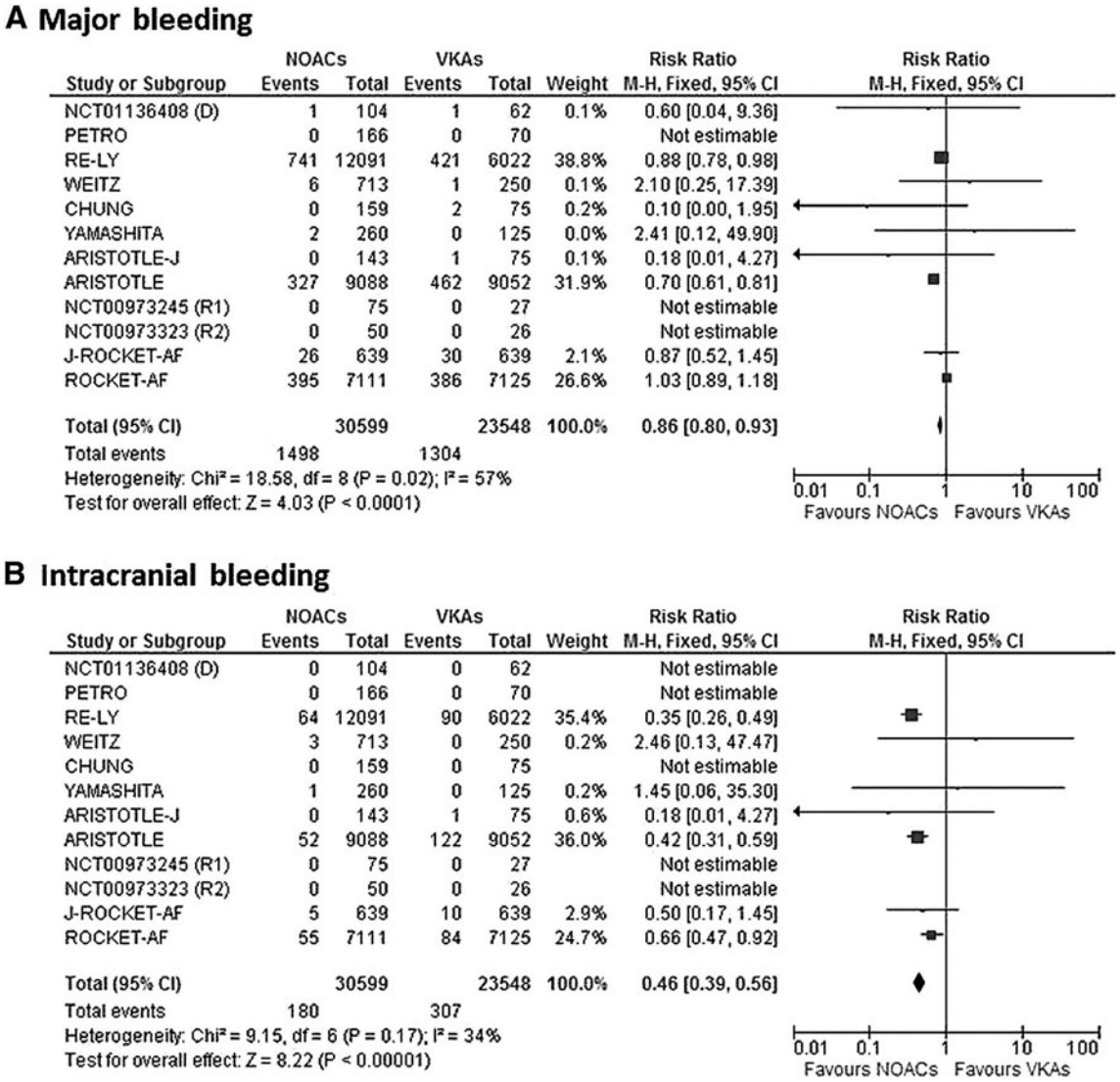

Fig. 2 Major (*A*) and intracranial (*B*) bleeding during oral anticoagulant treatment. *NOAC*—novel oral anticoagulant; *VKA*—vitamin K antagonists; *M-H*—Mantel-Haenszel; *CI*—confidence interval; *RE-LY*—Randomized Evaluation of Long-Term Anticoagulant Therapy; *ARISTOTLE*—Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation; *J-ARISTOTLE*—Japanese Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation; *ROCKET-AF*—An Efficacy and Safety Study of Rivaroxaban With Warfarin for the Prevention of Stroke and Non-Central Nervous System Systemic Embolism in Patients With Non-Valvular Atrial Fibrillation; *J-ROCKET-AF*—An Efficacy and Safety Study of Rivaroxaban With Warfarin for the Prevention of Stroke and Non-Central Nervous System Systemic Embolism in Patients With Non-Valvular Atrial Fibrillation in Japan (Adapted from [6••] with permission from the publisher)

Gastrointestinal Bleeding

The excess GI bleeding associated with dabigatran 150 mg bid vs. warfarin appeared to be only for lower GI bleeding, not upper GI bleeding, and may therefore reflect local effects of dabigatran on any lower GI mucosa that is afflicted by hemorrhagic disorders, such as diverticulosis and angiodysplasia [17]. Dabigatran has a low bioavailability after oral ingestion, and it is possible that metabolism of dabigatran etexilate by esterases leads to progressively higher concentrations of the active drug during transit of the gastrointestinal tract. Unlike dabigatran, warfarin has over 99 % bioavailability, and any unabsorbed warfarin is inactive and cannot cause local GI bleeding because warfarin requires metabolism by hepatic enzymes before it can exert an anticoagulant effect [18].

The higher rate of GI bleeding with rivaroxaban relative to warfarin in ROCKET AF (3.15 % rivaroxaban vs.2.16 % warfarin, $p<0.001$) [3] could also be due to exacerbation of surface bleeding by the presence of active anticoagulant in the gut [18].

Myocardial Infarction

Compared to warfarin, dabigatran was associated with a trend towards more MI, whereas rivaroxaban and apixaban were not [19, 20]. In the RE-LY study (Randomized

Evaluation of Long-Term Anticoagulation Therapy), MI occurred at annual rates of 0.82 % and 0.81 % with dabigatran 110 or 150 mg BID, compared with 0.64 % with warfarin (hazard ratio [HR] 1.29, 95 % CI: 0.96–1.75, P=0.09 for dabigatran 110 mg; HR 1.27, 95 % CI 0.94–1.71, P=0.12 for dabigatran 150 mg), indicating a nonsignificant increase in MI with dabigatran compared with warfarin [19]. Other myocardial ischemic events such as unstable angina were not increased. A similar pattern of increase in myocardial infarction was demonstrated in the REMEDY trial comparing dabigatran with warfarin for prevention of recurrent venous thromboembolism [21]. In a small substudy of RE-LY, which aimed to examine why dabigatran may be associated with more MI than warfarin but less ICH than warfarin, there was less suppression of thrombin generation in plasma from 36 dabigatran-treated patients compared to 18 warfarin-treated patients [22]. These results suggest that dabigatran suppresses thrombin generation less efficiently than warfarin. Less suppression of pathological thrombosis at sites of atherosclerotic plaque disruption could explain higher rates of myocardial infarction with dabigatran than warfarin, and less suppression of normal hemostasis in patients with brain microbleeds could explain lower rates of symptomatic intracranial bleeding with dabigatran compared with warfarin.

Note of Caution

The above indirect comparisons of the new anticoagulants should be interpreted cautiously, despite their apparent consistency in the trials where participants and investigators were blinded and not blinded (outcome assessors were blinded in all trials) [23], and in the more homogeneous sub-population of participants with prior stroke [24]. High quality evidence about the relative benefits of two treatments requires head-to-head randomized comparisons.

Net Clinical Benefit

When modeling analyses are used to subtract the absolute hazards of the NOACS vs. warfarin in causing any excess GI bleeding or myocardial infarction from absolute benefits of the NOACS vs. warfarin in reducing the risk of ischemic stroke and systemic embolism, intracranial hemorrhage, and mortality as observed in the phase III clinical trials, and applied to “real world” populations of individuals with non-valvular AF, it appears that all of the new oral anticoagulant agents have a greater net clinical benefit than warfarin in patients with AF, particularly those who are at highest risk of stroke and thromboembolism (CHA_2DS_2-VASc score of 2 or more) [25, 26].

Effects of NOACs Versus Warfarin in Patient Subgroups

Different Populations

The large phase III clinical trials were conducted in a wide range of patients from different ethnic and racial groups throughout the world, and the relative effects of the NOACs vs. warfarin were broadly consistent across ethnic and racial groups [27]. In the ROCKET-AF trial, the geographic region where patients were managed was a dominant determinant of time-in-therapeutic-range at the individual patient level (i-TTR), a measure of the quality of warfarin therapy for participants assigned warfarin [28]. Regions with the lowest i-TTRs had INR distributions that shifted toward lower INR values and had longer inter-INR test intervals.

In Japan, 326 patients were randomized in the global RE-LY trial and the efficacy and safety profiles of dabigatran were essentially the same as for the study population overall [27]. However, Japanese patients with AF were not enrolled in the global ROCKET-AF trial for two reasons. First, Japanese clinicians and guidelines prefer a lower level of anticoagulation (INR target 1.6–2.6 for warfarin) in AF patients aged ≥70 years. Second, the dose of rivaroxaban required to obtain similar pharmacokinetic modeling data to 20 mg once daily in Caucasians was lower among Japanese (15 mg once daily). Accordingly, a separate trial, J-ROCKET AF, was undertaken in Japan comparing the safety of a lower dose of rivaroxaban (15 mg once daily, 10 mg once daily if Cr CL 30–49 ml/min)) with warfarin, administered according to Japanese guidelines, in 1280 Japanese patients (INR 2.0–3.0 aged <70 years, INR 1.6–2.6 aged ≥70 years) with AF [29].

For the principal safety outcome of major and non-major clinically relevant bleeding, the non-inferiority margin was chosen as an upper boundary of the 95 % CI for the HR of rivaroxaban to warfarin of 2.0. The rate of major and non-major clinically relevant bleeding in the on-treatment safety population was 18.04 % per year in rivaroxaban-treated patients and 16.42 % per year in warfarin-treated patients (HR 1.11; 95 % CI: 0.87–1.42; P<0.001 [non-inferiority]). Intracranial hemorrhage rates were 0.8 % with rivaroxaban and 1.6 % with warfarin. The rate of stroke or non-central nervous system (CNS) systemic embolism in the intention to treat population was 2.38 % per year in rivaroxaban-treated patients and 2.91 % per year in warfarin-treated patients (HR 0.82; 95 % CI: 0.46–1.45), and in the per-protocol population while on treatment 1.26 % per year rivaroxaban vs. 2.61 % per year warfarin (HR 0.49, 0.24–1.00) [29]. A similarly designed, but much smaller (222 patients) phase II study (the ARISTOTLE-J study), reported the safety of apixaban in Japanese patients with non-valvular AF [30].

Comorbid Conditions

Among participants with and without prior stroke or transient ischemic attack (TIA), the relative effectiveness of all three NOACS compared with warfarin was consistent [31–33]; among participants with and without prior MI, the relative effectiveness of dabigatran compared with warfarin was consistent [19]; and among participants with and without moderate kidney disease, the relative effectiveness of apixaban compared with aspirin was consistent [34].

Predicted Risks of Stroke and Bleeding

Irrespective of the predicted risk of stroke as assessed by the CHADS2, and CHA2DS2VASc scores [35•], and the predicted risk of bleeding as assessed by the HAS-BLED score [35•, 36], the relative effectiveness of apixaban compared to warfarin [35•] and to aspirin [36] were consistent. However, the absolute rate of stroke and bleeding (in both treatment groups) increased with higher CHADS2 scores [36]. Among patients at higher and lower risk of myocardial ischemic events, the relative effectiveness of dabigatran compared to warfarin was also consistent [19].

In ROCKET AF, impaired renal function, defined as reduced creatinine clearance <60 mL/min, was an independent, significant predictor of stroke and systemic embolism among patients with non-valvular AF at moderate to high risk of stroke, in addition to factors included in the CHADS2 and CHA2DS2VASc scores, and second only to prior stroke or TIA in its potency as a predictor of risk [37]. A new risk score was developed (R2CHADS2) in ROCKET AF and validated in ATRIA (AnTicoagulation and Risk factors In Atrial fibrillation), an independent AF patient cohort [37].

Concomitant Antiplatelet Therapy

Among the 6,952 of 18,113 patients (38.4 %) enrolled in the RE-LY trial who received concomitant antiplatelet therapy (ASA or clopidogrel) at some time during the study, the relative effects of both doses of dabigatran (110 mg bid and 150 mg bid) vs. warfarin were consistent with the relative effects of both doses of dabigatran vs. warfarin in patients who were not taking antiplatelet therapy for both stroke or systemic embolism and major bleeding [38]. However, concomitant use of antiplatelet therapy with the allocated anticoagulant therapy increased the absolute risk of major bleeding in all treatment groups. The absolute increase in risk of major bleeding was greater for concomitant use of dual antiplatelet therapy with anticoagulation (HR 2.31; 95 % CI: 1.79–2.98) than single antiplatelet therapy with anticoagulation (HR 1.60; 1.42–1.82) [38].

Effects of NOACs Versus Warfarin on Bleeding Complications

Features of Bleeding

In the Apixaban versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin k Antagonist Treatment (AVERROES) trial, where the rate of a bleeding event (first occurrence of either major bleeding or clinically relevant nonmajor bleeding) was 3.8 %/year with aspirin and 4.5- %/year with apixaban (hazard ratio with apixaban, 1.18; 95 % CI, 0.92–1.51; P=0.19), the anatomic sites and predictors of bleeding (use of nonstudy aspirin >50 % of the time and a history of daily/occasional nosebleeds) did not differ between therapies [36].

Intracranial Hemorrhage

In the RE-LY trial, where the rates of intracranial hemorrhage (ICH) and fatal ICH were lower among participants assigned dabigatran 150 mg and 110 mg vs. warfarin, the clinical spectrum and case fatality of intracranial hemorrhage was similar for patients given warfarin and dabigatran [39]. Independent predictors of ICH were assignment to warfarin (relative risk, 2.9; P<0.001), concomitant aspirin use (relative risk, 1.6; P=0.01), age (relative risk, 1.1 per year; P< 0.001), and previous stroke/transient ischemic attack (relative risk, 1.8; P=0.001) [39].

The significantly lower risk of intracranial bleeding with all of the NOACs compared with warfarin [1–5, 6••, 7–17], irrespective of age, may reflect the possibility that warfarin predisposes to, or exacerbates intracerebral hemorrhage. In the event of injury to a vessel wall in the brain, tissue factor, which is found in high concentrations in the brain, interacts with activated factor VII (VIIa) to initiate coagulation and provide hemostatic protection [40, 41]. Rivaroxaban and apixaban selectively inhibit factor X and dabigatran inhibits thrombin. All new oral anticoagulants therefore do not compromise the formation of TF-VIIa complexes, which are primary cellular initiators of coagulation. In contrast, warfarin blocks vitamin K–dependent γ-carboxylation of coagulation factors II, VII, IX, and X; suppresses the production of factor VIIa; compromises the formation of tissue factor (TF)-VIIa complexes; and thereby compromises this hemostatic mechanism in the brain. Other mechanisms such as reduced suppression of thrombin at the site of cerebral injury by the new oral anticoagulants compared with warfarin [22] and the fact that rivaroxaban does not substantially penetrate the blood brain barrier, may also be important [42].

Periprocedural Bleeding

When surgery or other invasive procedures are required, there is concern that the NOACs might increase bleeding compared with warfarin, because of the lack of an antidote for the NOACs. In RE-LY, a total of 4,591 patients underwent at least one invasive procedure: 24.7 % of patients received dabigatran 110 mg, 25.4 % received dabigatran 150 mg, and 25.9 % received warfarin; $P=0.34$ [43]. Procedures included: pacemaker/defibrillator insertion (10.3 %), dental procedures (10.0 %), diagnostic procedures (10.0 %), cataract removal (9.3 %), colonoscopy (8.6 %), and joint replacement (6.2 %). Dabigatran facilitated a shorter interruption of oral anticoagulation; among patients assigned to either dabigatran dose, the last dose of study drug was given 49 (35–85) hours before the procedure in comparison with 114 (87–144) hours in patients receiving warfarin; $P<0.001$. Periprocedural bleeding rates were evaluated from 7 days before until 30 days after the first invasive procedure for each patient. Dabigatran and warfarin were associated with similar rates of periprocedural bleeding (dabigatran 110 mg: 3.8 %, dabigatran 150 mg: 5.1 %, and warfarin: 4.6 %), including patients having urgent surgery (dabigatran 110 mg: 17.8 %, dabigatran 150 mg: 17.7 %, and warfarin: 21.6 %) [43].

Effects of Interruption of Anticoagulant Therapy

A post-hoc analysis of data from the ROCKET AF trial revealed that among AF patients who temporarily discontinued anticoagulation for ≥3 days, the risk of stroke or non-CNS embolism within the next 30 days was similar with rivaroxaban vs. warfarin (6.20 vs. 5.05 per 100 patient-years, HR: 1.28, 95 % CI: 0.49 to 3.31, $p=0.62$), as it was for AF patients who permanently discontinued anticoagulation (25.60 vs. 23.28 per 100 patient-years, HR: 1.10, 95 % CI: 0.71 to 1.72, $p=0.66$) [44]. However, patients transitioning to open-label therapy at the end of the study took longer to reach a therapeutic INR with rivaroxaban vs. warfarin and had more strokes with rivaroxaban vs. warfarin (6.42 vs. 1.73 per 100 patient years, HR: 3.72, 95 % CI: 1.51 to 9.16, $p=0.0044$) [44]. These findings emphasize the importance of therapeutic anticoagulation coverage during such a transition.

Cost Effectiveness of the NOACs Versus Warfarin

Medical Costs

The medical costs (excluding drug costs) associated with the use of individual NOACs instead of warfarin in a patient year, from the US payer perspective, have been estimated to be −$179 (95 % CI: −$424 to +$71) for dabigatran, −$89 (−$301 to +$135) for rivaroxaban, and −$485 (−$741 to −$252) for apixaban, with a negative number indicating a cost reduction of the NOAC vs. warfarin [45].

Dabigatran Versus Warfarin

Several economic analyses suggest that the use of dabigatran etexilate as a first-line treatment for the prevention of stroke and systemic embolism is likely to be cost-effective in eligible patients with AF in the US [46], UK [47], Denmark [48] and several other countries [49].

In the US, where the threshold of willingness to pay is about US$50,000 per quality-adjusted life year (QALY), dabigatran 150 mg bid is a cost-effective alternative to adjusted-dose warfarin for the lifetime prevention of ischemic stroke in patients 65 years of age or older with non-valvular AF and CHADS2 ≥1 ($12,286 per QALY) [46]. The cost effectiveness of dabigatran improves if it can be obtained for ≤US$13/day or is used in populations with high risk of stroke or intracranial hemorrhage [46].

In the UK, for patients starting treatment at ages <80 years, the incremental cost-effectiveness ratio (ICER) for dabigatran versus warfarin is estimated to be £4831/QALY and the probability of cost-effectiveness at a threshold of £20,000/QALY gained is 98 %. For patients starting treatment at ages ≥80- years, the ICER for dabigatran versus warfarin is estimated to be £7090/QALY and the probability of cost-effectiveness at a threshold of £20,000/QALY gained is 63 % [47]. For patients starting treatment at ages <80 years, the ICER of dabigatran vs. aspirin was £3457/QALY gained and dabigatran was dominant (i.e., was less costly and more effective) compared with no therapy [47].

In Denmark, it has been estimated that the mean cost per patient for remaining life time is EUR 16,886 if treated with warfarin and EUR 18,752 if treated with dabigatran [48]. This was associated with mean QALYs per patient of 8.32 with warfarin and 8.59 with dabigatran. The resulting ICER for dabigatran compared with warfarin of EUR 7,000 per QALY gained is regarded as cost-effective by Danish standards.

A modeled cost-utility analyses from several countries over a lifetime (or 20-year) time horizon demonstrated that twice-daily dabigatran 150 mg (or age-adjusted, sequential dosing) was cost effective with regard to the incremental cost per QALY gained relative to adjusted-dose warfarin in the prevention of stroke and systemic embolism in AF patients. In contrast, the incremental cost per QALY gained for dabigatran 110 mg twice daily versus warfarin exceeded cost-effectiveness thresholds in all studies except one. Sensitivity analyses suggested that the cost utility of dabigatran versus warfarin was generally robust to variations in the majority of parameters, except that the incremental cost per

QALY gained for dabigatran versus warfarin improved when levels of INR control in warfarin recipients decreased and when the baseline level of risk of stroke increased [49].

Dabigatran Versus Genotype-Guided Management of Warfarin

Genotype-guided warfarin dosing and management could improve patient-time in target range (TTR) >77 % and thereby improve efficacy and safety. In a hypothetical cohort of AF patients aged 65 years old with CHADS(2) score 2, and in which genotype-guided anticoagulation care (genotype-guided AC) was assumed to achieve TTR=78.9 % in a Markov model, dabigatran 150 mg gained higher QALYs than genotype-guided AC (10.065QALYs vs. 9.554 QALYs) but at higher cost (USD 92,684 versus USD 85,627), yet with an ICER=USD ($) 13,810 [50]. Dabigatran 110 mg and usual AC gained less QALYs, but cost more than dabigatran 150 mg and genotype-guided AC, respectively. The ICER of dabigatran 150 mg versus genotype-guided AC would be >$50,000 (and genotype-guided AC would be most cost-effective) when TTR in genotype-guided AC was >77 % and utility value of warfarin was the same or higher than that of dabigatran [50].

Rivaroxaban Versus Warfarin

In the US, a Markov model found that 65-year-old patients with AF and a CHADS2 score of 3, if treated with rivaroxaban, lived an average of 10.03 QALYs at a lifetime treatment cost of $94,456, and if treated with warfarin lived an average of 9.81 QALYs and incurred costs of $88,544 [51]. The ICER for rivaroxaban was $27,498 per QALY. Rivaroxaban was cost-effective in 80 % and 91 % of iterations at willingness-to-pay thresholds of $50,000 and $100,000 per QALY, respectively [51].

Apixaban Versus Warfarin

In the US, a Markov model found that 65-year-old patients with AF and a CHADS2 score of 2.1, if treated with apixaban, lived an average of 11.16 QALYs at a lifetime treatment cost of $86,007, and if treated with warfarin lived an average of 10.69 QALYs and incurred costs of $94,941, demonstrating apixaban to be a dominant economic strategy [52]. Apixaban was cost-effective in 98 % of simulations at a willingness-to-pay threshold of $50,000 per QALY [52].

Dabigatran Versus Rivaroxaban

A Markov model that indirectly compared the effects of dabigatran vs. rivaroxaban relative to warfarin from a Canadian perspective found that, over a lifetime, dabigatran-treated patients experienced fewer ICHs (0.33 dabigatran vs. 0.71 rivaroxaban) and ischemic strokes (3.40 vs. 3.96) per 100 patient-years, and accrued more QALYs (6.17 vs. 6.01) [53]. Dabigatran-treated patients had lower acute care and long-term follow-up costs per patient ($52,314 vs. $53,638) which more than offset differences in drug costs ($7,299 vs. $6,128) [53]. In probabilistic analysis, dabigatran had a high probability of being the most cost-effective therapy, compared with rivaroxaban, at common thresholds of willingness-to-pay (93 % at a $20,000/QALY threshold).

Patients with AF and Prior Stroke or Transient Ischemic Attack

The cost and quality-adjusted life expectancy associated with dabigatran 150 mg bid and apixaban 5 mg bid compared with warfarin (target INR 2.0–3.0) in patients with AF and prior stroke or transient ischemic attack (TIA) have been compared in two studies [54, 55]. Using data from the large phase III trials [1, 4], other trials of warfarin therapy for AF, and the published costs of dabigatran, a Markov decision model was constructed.

In the base case of patients aged 70 years with non-valvular AF, prior stroke or TIA, and no contraindication to anticoagulation, warfarin resulted in an expectancy of 3.91 quality-adjusted life years (QALYs) at a cost of $378,500. In comparison, dabigatran was associated with 4.27 QALYs (i.e. 0.36 additional QALYs) at a cost of $387,500 (i.e. $9,000 extra), yielding an ICER of $25,000 per QALY [54]. Treatment with apixaban led to an expected 4.19 QALYs (i.e. a gain of 0.28 QALYs) at a cost of $381,700 (i.e. an additional cost of $3,200), resulting in an ICER of $11,400 per QALY [55]. In sensitivity analyses, the cost-effectiveness of dabigatran was inversely related to the quality of INR control achieved with warfarin therapy. In Monte Carlo analysis, dabigatran and apixaban were cost-effective in 57 % and 62 %, respectively, of simulations using a threshold of $50,000 per QALY, and 78 % and 81 %, respectively, of simulations using a threshold of $100,000 per QALY [54, 55]. These data suggest that dabigatran and apixaban appear to be cost-effective relative to warfarin for stroke prevention in patients with atrial fibrillation and prior stroke or transient ischemic attack. The analyses are limited, however, by their reliance on data from a subgroup of patients enrolled in single randomized trials who had uncommonly good INR control using warfarin, and an assumption that apixaban is introduced at a price similar to that of dabigatran.

Summary of Cost Effectiveness Data

The evidence to date suggests that each of the NOACs is likely to be more cost-effective than warfarin. The cost

effectiveness of the NOACS improves with the higher dose of dabigatran (150 mg bid) compared to the lower dose of dabigatran (110 mg bid), in populations with increasing baseline risk of stroke or intracranial hemorrhage, and among warfarin recipients with suboptimal INR control and TTR<77 %.

Effects of NOACs Versus Warfarin in Untested Populations

The large phase III clinical trials did not include patients with severe valvular heart disease, severe renal impairment, active liver disease or acute stroke, and so their results are not generalizable to these patients. The randomized, phase II study to evaluate the safety and pharmacokinetics of oral dabigatran etexilate in patients after heart valve replacement (RE-ALIGN) has been terminated early [56].

Long-Term Safety of the NOACs

RELY-ABLE was a long-term follow-up study involving patients randomized to receive dabigatran in the RE-LY trial [57]. Patients were eligible for participation in RELY-ABLE if they were still taking blinded dabigatran at the completion of RE-LY. During up to 28 months of follow-up of 5,851 patients, the effects of dabigatran 150 mg bid compared with 110 mg bid were similar to those seen in the RE-LY trial, and no unexpected adverse events were observed.

Higher than expected reporting of adverse outcomes soon after the approval of dabigatran prompted the US Food and Drug Administration (FDA) to explore bleeding events in the community using insurance-claim data and administrative data from the FDA mini-sentinel database [58]. Between 19 October 2010 (the date of dabigatran approval) and 31 December 2011, the incidence of gastrointestinal bleeding events among 10,599 patients with a diagnosis of AF started on

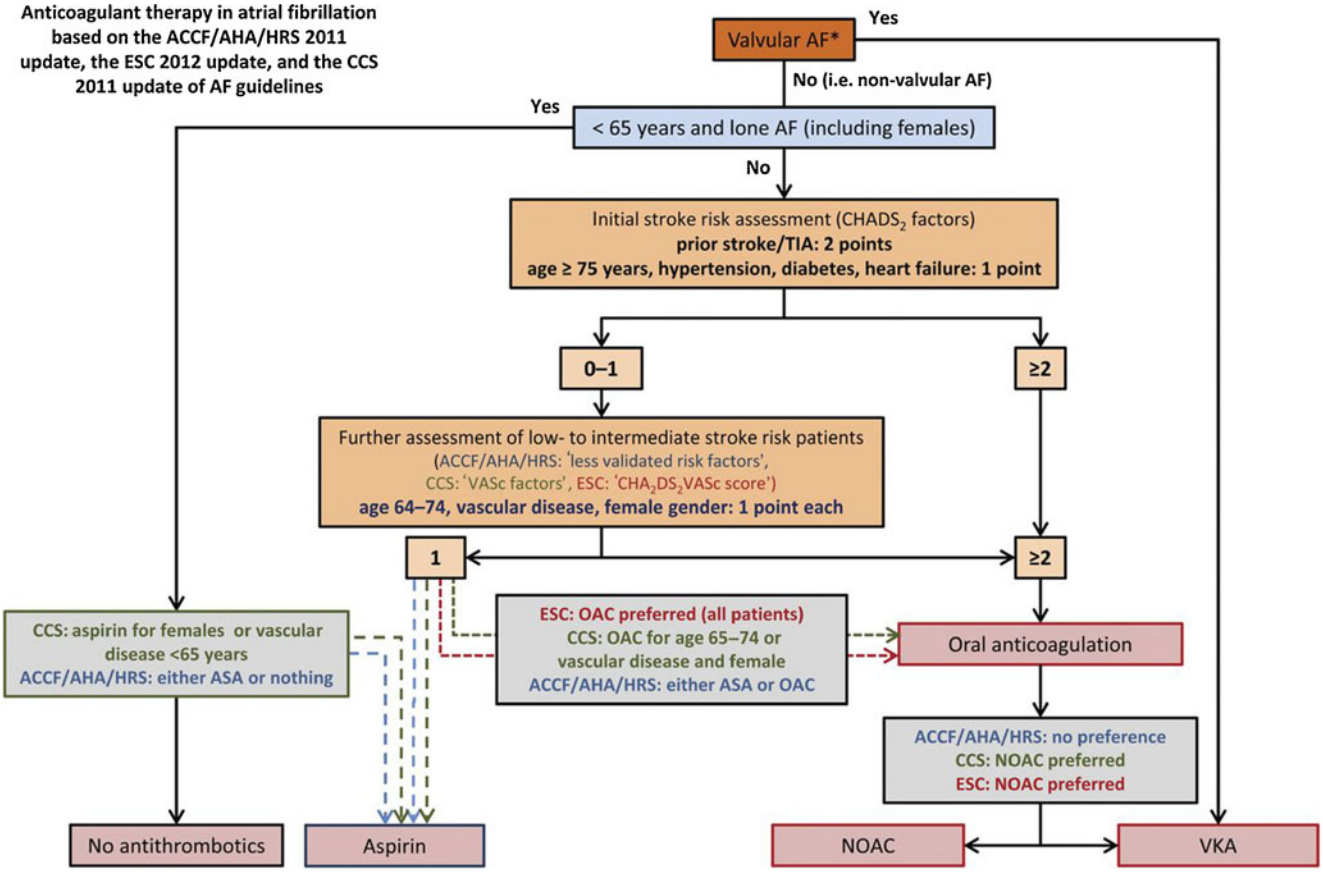

Fig. 3 Decision tree for antithrombotic therapy in patients with non-valvular atrial fibrillation. The figure combines the recommendations described in the 2010 ESC/EHRA/EACTS guidelines and in the updated ACCF/AHA/HRS guidelines: *Blue boxes* indicate parts of the tree that are common to the ESC and ACCF/AHA/ESC recommendations. *Pink boxes* indicate parts in which the two sets of recommendations differ. These are also areas where clear evidence is lacking. *Valvular AF, rheumatic valvular disease, prosthetic valves; hypertrophic cardiomyopathy. *AF*—atrial fibrillation; *OAC*—oral anticoagulant; *TIA*—transient ischaemic attack; *NOAC*—Novel oral anticoagulants; *VKA*—vitamin K antagonist; *ACCF/AHA/HRS*—American College of Cardiology Foundation, American Heart Association, Heart Rhythm Society; *CCS*—Canadian Cardiovascular Society; *ESC*— European Society of Cardiology. *The suggestion to use oral anticoagulants rather than aspirin is substantiated by the safety data from BAFTA and AVERROES (Adapted from [63] with permission from the publisher)

dabigatran was 1.6/100,000 days at risk compared with 3.5/100,000 among 43,541 patients with a diagnosis of AF started on warfarin. The incidence of intracranial haemorrhage was 0.8/100,000 for dabigatran and 2.4/100,000 for warfarin. Although unadjusted for potential confounding, these real world post-marketing data provide no evidence that dabigatran produced a higher rate of bleeding than warfarin.

Guideline Recommendations

Recently published American, Canadian, and European guidelines for the management of AF emphasize the importance of identifying 'truly low-risk' patients who do not need prophylactic antithrombotic therapy, and offering effective stroke prevention by means of oral anticoagulation therapy to patients with AF and more than one stroke risk factor. Oral anticoagulation therapy with one of the novel oral anticoagulants is recommended as the preferred best option, and well controlled adjusted-dose warfarin as an alternative option (Fig. 3). The guidelines provide additional guidance on advances in the assessment of stroke risk (by CHADS2 and CHA2DS2VASC scores) and bleeding risk (by HAS-BLED score), and recommendations on the use (indications, contraindications, precautions) of the NOACs and the left atrial appendage occlusion devices [59–63].

Conclusion

Secondary analyses of the three large completed randomized controlled trials comparing a NOAC, dabigatran, rivaroxaban or apixaban, with warfarin for stroke prevention in atrial fibrillation are providing physicians with answers to questions about the efficacy and safety of these agents compared with warfarin and one another and in key patient subgroups. The NOACs, compared with warfarin, are associated with similar or superior efficacy and safety and, as expected, the estimates of the treatment effect are consistent in almost all patient subgroups studied. The NOACs are however associated with bleeding, and in different sites to warfarin (i.e. less intracranial hemorrhage, and with two of the agents, more gastrointestinal hemorrhage), probably reflecting the different targets and mechanisms by which the NOACs inhibit coagulation. Concerns that lack of an antidote may lead to worse outcomes in patients treated with NOACs compared with warfarin who require interruption for surgery or experience major bleeding are not supported by secondary analyses from the RE-LY trial. Pharmacoeconomic analyses have meanwhile concluded that the NOACSs are cost-effective in European and North American markets. Collectively, these data are expected to lead to a progressive increase in the uptake of new oral anticoagulants and their preferred use over warfarin in patients with atrial fibrillation at risk for stroke.

Conflict of Interest Graeme J. Hankey has been a consultant to Pradaxa Advisory Board, Boehringer Ingelheim, Apixaban Advisory Board, and Bristol Myers Squibb and has received honoraria from Bayer.

John W. Eikelboom has been a consultant to and received honoraria from Boehringer Ingelheim, Bristol Myers Squibb, Bayer, Daiichi, Eli Lilly, Astra Zeneca, GlaxoSmithKline, Pfizer, and Sanofi Aventis.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009;361:1139–51.
2. Connolly SJ, Ezekowitz MD, Yusuf S, Reilly PA, Wallentin L, for the Randomized Evaluation of Long-Term Anticoagulation Therapy Investigators. Newly identified events in the RE-LY trial (letter to the editor). N Engl J Med. 2010;363:1875–6.
3. Patel MR, Mahaffey KW, Garg J, Pan G, Singer D, Hacke W, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011;365:883–91.
4. Granger CB, Alexander JH, McMurray JJV, Lopes RD, Hylek EH, Hanna M, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011;365:981–92.
5. Connolly SJ, Eikelboom J, Joyner C, Diener HC, Hart R, Golitsyn S, et al. Apixaban in patients with atrial fibrillation. N Engl J Med. 2011;364:806–17.
6. •• Dentali F, Riva N, Crowther M, Turpie AG, Lip GY, Ageno W. Efficacy and safety of the novel oral anticoagulants in atrial fibrillation: a systematic review and meta-analysis of the literature. Circulation. 2012;126(20):2381–91. *Meta-analysis of all phase II and phase III randomized, controlled trials comparing NOACs with vitamin K antagonists in patients with atrial fibrillation in a total of 54,875 patients showing that, compared with vitamin K antagonists, the NOACs significantly reduced stroke/systemic embolism, major bleeding; intracranial hemorrhage, total mortality, and cardiovascular mortality.*
7. Miller CS, Grandi SM, Shimony A, Filion KB, Eisenberg MJ. Meta-analysis of efficacy and safety of new oral anticoagulants (dabigatran, rivaroxaban, apixaban) versus warfarin in patients with atrial fibrillation. Am J Cardiol. 2012;110:453–60.
8. Lip GY, Larsen TB, Skjoth F, Rasmussen LH. Indirect comparisons of new oral anticoagulant drugs for efficacy and safety when used for stroke prevention in atrial fibrillation. J Am Coll Cardiol. 2012;60:738–46.

9. Schneeweiss S, Gagne JJ, Patrick AR, Choudhry NK, Avorn J. Comparative efficacy and safety of new oral anticoagulants in patients with atrial fibrillation. Circ Cardiovasc Qual Outcomes. 2012;5:480–6.
10. Harenberg J, Marx S, Diener HC, et al. Comparison of efficacy and safety of dabigatran, rivaroxaban and apixaban in patients with atrial fibrillation using network meta-analysis. Int Angiol. 2012;31:330–9.
11. Mantha S, Ansell J. An indirect comparison of dabigatran, rivaroxaban and apixaban for atrial fibrillation. Thromb Haemost. 2012;108:476–84.
12. Testa L, Agnifili M, Latini RA, et al. Adjusted indirect comparison of new oral anticoagulants for stroke prevention in atrial fibrillation. QJM. 2012;105:949–57.
13. Baker WL, Phung OJ. Systematic review and adjusted indirect comparison meta-analysis of oral anticoagulants in atrial fibrillation. Circ Cardiovasc Qual Outcomes. 2012;5:711–9.
14. O'Dell KM, Igawa D, Hsin J. New oral anticoagulants for atrial fibrillation: a review of clinical trials. Clin Ther. 2012;34(4):894–901.
15. Capodanno D, Capranzano P, Giacchi G, Calvi V, Tamburino C. Novel oral anticoagulants versus warfarin in non-valvular atrial fibrillation: a meta-analysis of 50,578 patients. Int J Cardiol. 2012 Apr 9. [Epub ahead of print].
16. Adam SS, McDuffie JR, Ortel TL, Williams Jr JW. Comparative effectiveness of warfarin and new oral anticoagulants for the management of atrial fibrillation and venous thromboembolism: a systematic review. Ann Intern Med. 2012;157(11):796–807.
17. Eikelboom JW, Wallentin L, Connolly SJ, Ezekowitz M, Healey JS, Oldgren J, et al. Risk of bleeding with 2 doses of dabigatran compared with warfarin in older and younger patients with atrial fibrillation: an analysis of the randomized evaluation of long-term anticoagulant therapy (RE-LY) trial. Circulation. 2011;123(21):2363–72.
18. Weitz JI. New oral anticoagulants: a view from the laboratory. Am J Hematol. 2012;87:S133–6.
19. Hohnloser SH, Oldgren J, Yang S, Wallentin L, Ezekowitz M, Reilly P, et al. Myocardial ischemic events in patients with atrial fibrillation treated with dabigatran or warfarin in the RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) trial. Circulation. 2012;125(5):669–76.
20. Uchino K, Hernandez AV. Dabigatran association with higher risk of acute coronary events: meta-analysis of noninferiority randomized controlled trials. Arch Intern Med. 2012;172(5):397–402.
21. Schulman S, Kearon C, Kakkar AK, Schellong S, Eriksson H, Baanstra D, et al. Extended use of dabigatran, warfarin, or placebo in venous thromboembolism. N Engl J Med. 2013;368(8):709–18.
22. Dale B, Eikelboom JW, Weitz JI, Young E, Paikin JS, Coppens M, 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(2):295–301. doi:10.1007/s11239-012-0857-9.
23. O'Neil WM, Welner SA, Lip GY. Do open label blinded outcome studies of novel anticoagulants versus warfarin have equivalent validity to those carried out under double-blind conditions? Thromb Haemost. 2013;109(3). [Epub ahead of print].
24. Rasmussen LH, Larsen TB, Graungaard T, Skjøth F, Lip GY. Primary and secondary prevention with new oral anticoagulant drugs for stroke prevention in atrial fibrillation: indirect comparison analysis. BMJ. 2012;345:e7097. doi:10.1136/bmj.e7097.
25. Banerjee A, Lane DA, Torp-Pedersen C, Lip GY. 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.
26. Pisters R, Nieuwlaat R, Lane DA, Crijns HJ, Lip GY. 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. 2012;109(2). [Epub ahead of print.
27. Hori M, Connolly SJ, Ezekowitz MD, Reilly PA, Yusuf S, Wallentin L, et al. Efficacy and safety of dabigatran vs. warfarin in patients with atrial fibrillation–sub-analysis in Japanese population in RE-LY trial. Circ J. 2011;75(4):800–5.
28. Singer DE, Hellkamp AS, Piccini JP, Mahaffey KW, Lokhnygina Y, Pan G, et al. Impact of global geographic region on time in therapeutic range on warfarin anticoagulant therapy: data from the ROCKET AF clinical trial. J Am Heart Assoc. 2013;2:e000067. doi:10.1161/JAHA.112.000067.
29. Hori M, Matsumoto M, Tanahashi N, Momomura S, Uchiyama S, Goto S, et al. Rivaroxaban vs. warfarin in Japanese patients with atrial fibrillation – the J-ROCKET AF study –. Circ J. 2012;76(9):2104–11.
30. Ogawa S, Shinohara Y, Kanmuri K. Safety and efficacy of the oral direct factor xa inhibitor apixaban in Japanese patients with non-valvular atrial fibrillation. -The ARISTOTLE-J study-. Circ J. 2011;75(8):1852–9.
31. Diener HC, Eikelboom J, Connolly SJ, Joyner CD, Hart RG, Lip GY, et al. Apixaban versus aspirin in patients with atrial fibrillation and previous stroke or transient ischaemic attack: a predefined subgroup analysis from AVERROES, a randomised trial. Lancet Neurol. 2012;11(3):225–31.
32. Hankey GJ, Patel MR, Stevens SR, Becker RC, Breithardt G, Carolei A, et al. Rivaroxaban compared with warfarin in patients with atrial fibrillation and previous stroke or transient ischaemic attack: a subgroup analysis of ROCKET AF. Lancet Neurol. 2012;11(4):315–22.
33. Easton JD, Lopes RD, Bahit MC, for the ARISTOTLE Committees and Investigators, et al. Apixaban compared with warfarin in patients with atrial fibrillation and previous stroke or transient ischaemic attack: a subgroup analysis of the ARISTOTLE trial. Lancet Neurol. 2012;11:503–11.
34. Eikelboom JW, Connolly SJ, Gao P, Paolasso E, De Caterina R, Husted S, et al. Stroke risk and efficacy of apixaban in atrial fibrillation patients with moderate chronic kidney disease. J Stroke Cerebrovasc Dis. 2012;21(6):429–35.
35. • Lopes RD, Al-Khatib SM, Wallentin L, Yang H, Ansell J, Bahit MC, et al. Efficacy and safety of apixaban compared with warfarin according to patient risk of stroke and of bleeding in atrial fibrillation: a secondary analysis of a randomised controlled trial. Lancet. 2012;380(9855):1749–58. *Secondary analysis of the ARISTOTLE trial across patient risk, categorized according to two thromboembolic risk scores (CHADS2 and CHA2DS2VASc) and one bleeding score (HAS-BLED). The authors report no statistical heterogeneity of the relative effect of apixaban compared with warfarin across the different risk categories, and conclude that the benefit of apixaban is seen across all categories of thromboembolic and bleeding risk.*
36. Flaker GC, Eikelboom JW, Shestakovska O, Connolly SJ, Kaatz S, Budaj A, et al. Bleeding during treatment with aspirin versus apixaban in patients with atrial fibrillation unsuitable for warfarin: the apixaban versus acetylsalicylic acid to prevent stroke in atrial fibrillation patients who have failed or are unsuitable for vitamin K antagonist treatment (AVERROES) trial. Stroke. 2012;43:3291–7.
37. Piccini JP, Stevens SR, Chang Y, Singer DE, Lokhnygina Y, Go AS, et al. Renal dysfunction as a predictor of stroke and systemic embolism in patients with nonvalvular atrial fibrillation: validation of the R2CHADS2 Index in the ROCKET AF and ATRIA study cohorts. Circulation. 2013;127:224–32.
38. Dans AL, Connolly SJ, Wallentin L, Yang S, Nakamya J, Brueckmann M, et al. Concomitant use of antiplatelet therapy with dabigatran or warfarin in the randomized evaluation of long-term anticoagulation therapy (RE-LY(R)) Trial. Circulation. 2012 Dec 27. [Epub ahead of print].

39. Hart RG, Diener HC, Yang S, Connolly SJ, Wallentin L, Reilly PA, et al. Intracranial hemorrhage in atrial fibrillation patients during anticoagulation with warfarin or dabigatran: the RE-LY trial. Stroke. 2012;43(6):1511–7.
40. Fleck RA, Rao LV, Rapaport SI, Varki N. Localization of human tissue factor antigen by immunostaining with monospecific, polyclonal anti-human tissue factor antibody. Thromb Res. 1990;59:421–37.
41. Mackman N. The role of tissue factor and factor VIIa in hemostasis. Anesth Analg. 2009;108:1447–52.
42. Haas S. Rivaroxaban—an oral, direct Factor Xa inhibitor: lessons from a broad clinical study programme. Eur J Haematol. 2009;82(5):339–49.
43. Healey JS, Eikelboom J, Douketis J, Wallentin L, Oldgren J, Yang S, et al. 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.
44. Patel MR, Hellkamp AS, Lokhnygina Y, Piccini JP, Zhang Z, et al. Outcomes of discontinuing rivaroxaban compared with warfarin in patients with nonvalvular atrial fibrillation: analysis from the ROCKET AF Trial (Rivaroxaban once-daily, oral, direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation). J Am Coll Cardiol. 2013;61(6):651–8.
45. Deitelzweig S, Amin A, Jing Y, Makenbaeva D, Wiederkehr D, Lin J, et al. Medical cost reductions associated with the usage of novel oral anticoagulants vs.warfarin among atrial fibrillation patients, based on the RE-LY, ROCKET-AF, and ARISTOTLE trials. J Med Econ. 2012;15(4):776–85.
46. Adcock AK, Lee-Iannotti JK, Aguilar MI, Hoffman-Snyder CR, Wingerchuk DM, et al. Is dabigatran cost effective compared with warfarin for stroke prevention in atrial fibrillation? A critically appraised topic. Neurologist. 2012;18(2):102–7.
47. Kansal AR, Sorensen SV, Gani R, Robinson P, Pan F, Plumb JM, et al. Cost-effectiveness of dabigatran etexilate for the prevention of stroke and systemic embolism in UK patients with atrial fibrillation. Heart. 2012;98(7):573–8. doi:10.1136/heartjnl-2011-300646.
48. Langkilde LK, Bergholdt Asmussen M, Overgaard M. Cost-effectiveness of dabigatran etexilate for stroke prevention in nonvalvular atrial fibrillation. Applying RE-LY to clinical practice in Denmark. J Med Econ. 2012;15(4):695–703.
49. McKeage K. Dabigatran etexilate: a pharmacoeconomic review of its use in the prevention of stroke and systemic embolism in patients with atrial fibrillation. PharmacoEconomics. 2012;30(9):841–55.
50. You JH, Tsui KK, Wong RS, Cheng G. Cost-effectiveness of dabigatran versus genotype-guided management of warfarin therapy for stroke prevention in patients with atrial fibrillation. PLoS One. 2012;7(6):e39640.
51. Lee S, Anglade MW, Pham D, Pisacane R, Kluger J, Coleman CI. Cost-effectiveness of rivaroxaban compared to warfarin for stroke prevention in atrial fibrillation. Am J Cardiol. 2012;110(6):845–51.
52. Lee S, Mullin R, Blazawski J, Coleman CI. Cost-effectiveness of apixaban compared with warfarin for stroke prevention in atrial fibrillation. PLoS One. 2012;7(10):e47473. doi:10.1371/journal.pone.0047473. Epub 2012 Oct 9.
53. Kansal AR, Sharma M, Bradley-Kennedy C, Clemens A, Monz BU, Peng S, et al. Dabigatran versus rivaroxaban for the prevention of stroke and systemic embolism in atrial fibrillation in Canada. Comparative efficacy and cost-effectiveness. Thromb Haemost. 2012;108(4):672–82.
54. Kamel H, Johnston SC, Easton JD, Kim AS. Cost-effectiveness of dabigatran compared with warfarin for stroke prevention in patients with atrial fibrillation and prior stroke or transient ischemic attack. Stroke. 2012;43(3):881–3.
55. Kamel H, Easton JD, Johnston SC, Kim AS. Cost-effectiveness of apixaban vs.warfarin for secondary stroke prevention in atrial fibrillation. Neurology. 2012;79(14):1428–34.
56. Van de Werf F, Brueckmann M, Connolly SJ, Friedman J, Granger CB, Härtter S, et al. A comparison of dabigatran etexilate with warfarin in patients with mechanical heart valves: the randomized, phase II study to evaluate the safety and pharmacokinetics of oral dabigatran etexilate in patients after heart valve replacement (RE-ALIGN). Am Heart J. 2012;163(6):931–7.
57. Connolly SJ, Wallentin L, Ezekowitz M, Eikelboom J, Oldgren J, Pogue J, et al. Randomized comparison of the effects of two doses of dabigatran etexilate on clinical outcomes over 4.3 years: results of the RELY-ABLE Double-blind Randomized Trial. Presented on 7 November 2012 at the American Heart Association Scientific Sessions 2012.
58. Southworth MR, Reichman ME, Unger EF. Dabigatran and post-marketing reports of bleeding. N Engl J Med 2013 (Epub ahead of print)
59. Skanes AC, Healey JS, Cairns JA, Dorian P, Gillis AM, McMurtry MS, et al. Focused 2012 update of the Canadian Cardiovascular Society atrial fibrillation guidelines: recommendations for stroke prevention and rate/rhythm control. Can J Cardiol. 2012;28(2):125–36.
60. Camm AJ, Lip GY, De Caterina R, Savelieva I, Atar D, Hohnloser SH, 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. Developed with the special contribution of the European Heart Rhythm Association. Eur Heart J. 2012;33(21):2719–47.
61. Furie KL, Goldstein LB, Albers GW, Khatri P, Neyens R, Turakhia MP, et al. Oral antithrombotic agents for the prevention of stroke in nonvalvular atrial fibrillation: a science advisory for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2012;43(12):3442–53. doi:10.1161/STR.0b013e318266722a. Epub 2012 Aug 2. No abstract available. Erratum in: Stroke. 2012;43(12):e181.
62. Anderson JL, Halperin JL, Albert NM, Bozkurt B, Brindis RG, Curtis LH, et al. Management of patients with atrial fibrillation (Compilation of 2006 ACCF/AHA/ESC and 2011 ACCF/AHA/HRS Recommendations): a Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2013 Apr 1. [Epub ahead of print] PMID: 23545139
63. Kirchhof P, Curtis AB, Skanes AC, Gillis AM, Samuel Wann L, John Camm A. Atrial fibrillation guidelines across the Atlantic: a comparison of the current recommendations of the European Society of Cardiology/European Heart Rhythm Association/European Association of Cardiothoracic Surgeons, the American College of Cardiology Foundation/American Heart Association/Heart Rhythm Society, and the Canadian Cardiovascular Society. Eur Heart J. 2013 Jan 25. [Epub ahead of print] PMID: 23355653