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Unanswered questions and research priorities to optimise stroke prevention in atrial fibrillation with the new oral anticoagulants

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Summary

This review article discusses the following, as yet unanswered, questions and research priorities to optimise patient management and stroke prevention in atrial fibrillation with the new direct oral anticoagulants (NOACs): 1. In patients prescribed a NOAC, can the anticoagulant effects or plasma concentrations of the NOACs be measured rapidly and reliably and, if so, can “cut-off points” between which anticoagulation is therapeutic (i.e. the “therapeutic range”) be defined? 2. In patients who are taking a NOAC and bleeding (e.g. intracerebral haemorrhage), can the anticoagulant effects of the direct NOACs be reversed rapidly and, if so, can NOAC-associated bleeding and complications be minimised and patient outcome improved? 3. In patients taking a NOAC who experience an acute ischaemic stroke, what is the optimal time to start (or re-start) anticoagulation with a NOAC (or warfarin)? 4. In anticoagulated patients who experience an intracranial haemorrhage, can anticoagulation with a NOAC be re-started safely and effectively, and if so when? 5. Are the NOACs effective and safe in multimorbid geriatric people (who commonly have atrial fibrillation and are at high risk of stroke but also bleeding)? 6. Can dose-adjusted NOAC therapy augment the established safety and efficacy of fixed-dose unmonitored NOAC therapy? 7. Is there a dose or dosing regimen for each NOAC that is as effective and safe as adjusted-dose warfarin for patients with atrial fibrillation who have mechanical prosthetic heart valves? 8. What is the long-term safety of the NOACs?

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The new direct oral anticoagulant (NOAC) agents, dabigatran, rivaroxaban and apixaban, are as effective and safe as the vitamin K antagonist (VKA) warfarin, and endorsed by professional groups and regulatory authorities for the prevention of stroke in patients with atrial fibrillation (AF) (1-6). However, several questions and research priorities to optimise stroke prevention in AF with the NOACs remain (see Table 1 for an overview).

1. In patients who are prescribed a NOAC, can the anticoagulant effects or plasma concentrations of the NOACs be measured rapidly and reliably and, if so, can “cut-off points” in anticoagulation effects or plasma concentrations between which anticoagulation is therapeutic (i.e. the “therapeutic range”) be defined?

Routine measurement of the anticoagulant effect of the NOACS is not necessary because the pharmacokinetic and pharmacodynamic characteristics of the NOACs are predictable (7), the therapeutic window is sufficiently large to allow fixed dose administration without the need for routine monitoring of response (8), and large randomised, controlled trials (RCTs) have shown that the NOACs are as effective and safe as dose-adjusted warfarin when administered to selected patients without routine monitoring (1-3).

However, the blood concentrations of the NOACs may vary (7). In the RE-LY trial, trough plasma concentrations of dabigatran varied more than five-fold among participants allocated dabigatran (8). The anticoagulant effects of dabigatran vary according to patients’ age, sex, body weight, renal function, and polymorphisms in genes that encode P-glycoprotein and esterases involved in dabigatran metabolism, and according to concurrent intake of drugs that interact with P-glycoprotein (7-10). The anticoagulant effects of rivaroxaban and apixaban vary according to patients’ renal and hepatic function, and concurrent intake of drugs that interact with P-glycoprotein and CYP3A4 (7, 11, 12).

Furthermore, there are situations in which a measurement of the plasma concentrations or anticoagulant effect of the NOACs could be useful (13). These include emergencies (e.g. overdose, bleeding, surgery), planning invasive procedures, inter-current renal or hepatic impairment or intake of interacting drugs, assessment of ad-
In patients who are prescribed a NOAC, can the anticoagulant effects or plasma concentrations of the NOACs be measured? Are the NOACs effective and safe in multimorbid geriatric people (who commonly have atrial fibrillation and are at high risk of haemorrhagic events)? Is there a dose or dosing regimen for each NOAC that is as effective and safe as adjusted-dose warfarin for patients with atrial fibrillation? In patients taking a NOAC who experience an acute ischaemic stroke, to what degree of anticoagulation or plasma concentration of the NOAC is therapeutic (i.e. the “therapeutic range”) be defined? What is the long-term safety of the NOACs? In anticoagulated patients who experience an intracranial haemorrhage, can anticoagulation with a NOAC be re-started safely and effectively? In patients who are taking a NOAC and bleeding (e.g. intracerebral haemorrhage), can the anticoagulant effects of the direct factor Xa inhibitors be reversed rapidly and, if so, can NOAC-associated bleeding and bleeding-associated complications be minimised and patient outcome improved? In the event of anticoagulant-associated major bleeding, specific antidotes or general haemostatic agents are usually required to supplement general measures that include withholding the anticoagulant, compressing or ligating the source (if possible), replacing

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lost fluids, transfusing blood products, minimising further drug absorption (charcoal administration), and waiting for the anticoagulant to be metabolised and excreted.

Specific antidotes to the NOACs are not available. However, clinical trials are evaluating the effectiveness and safety of an antidote to dabigatran (aDabi-Fab), which is a humanized antibody fragment that binds dabigatran stronger than its affinity for thrombin, and rapidly reverses its anticoagulant effects in vitro and in vivo (29). Also in development is r-Antidote (PRT064445), a recombinant protein which binds factor Xa inhibitors and reverses the anticoagulant effects of apixaban and rivaroxaban (30, 31).

The general haemostatic agents, epsilon-aminocaproic acid and recombinant activated factor VII (rFVIIa), given within 4 hours (h) of spontaneous ICH to 1,398 adults in five phase II RCTs and one phase III RCT, did not reduce case fatality (risk ratio [RR] 0.85, 95% confidence interval [CI] 0.58 to 1.25), and rFVIIa did not reduce death or dependence (RR 0.91, 0.72 to 1.15) or increase thromboembolic events (RR 1.37, 0.74 to 2.55) at 90 days after ICH (32).

There is no published experience of haemostatic agents in acute ICH in patients taking NOACs, but animal studies suggest that prothrombin complex concentrates (PCC) can prevent expansion of dabigatran-associated ICH (33) and PCC, fresh frozen plasma, and Factor VIIa can prevent expansion of rivaroxaban-associated ICH (34).

PCC (50 IU/kg) reversed prolongation of the PT in healthy male volunteers pre-treated with rivaroxaban but did not reverse prolongation of the aPTT, ECT, and TT in those treated with dabigatran in one small study (35). However, in another study, the addition of PCC did not normalise the PT and thrombin generation test (TGT) lag time/T-Lag of blood spiked with Rivaroxaban (up to 800 µg/l), but total thrombin potential could be normalised (36). PCC and Factor VIII inhibitor bypassing activity (FEIBA; Baxter, Deerfield, IL, USA), an activated PCC, reversed the anticoagulant effect of a single 150 mg dose of dabigatran, as well as a single 20 mg dose of rivaroxaban, in an ex vivo study involving healthy male volunteers (37). In the same study, recombinant factor VIIa corrected the altered lag time after a single 150 mg dose of dabigatran, and reversed the lag time and time to peak after a single 20 mg dose of rivaroxaban (37).

Currently, there is a lack of consensus, at least among 221 US board-certified vascular neurologists, regarding the treatment of a patient with dabigatran-associated ICH; 73% reported that they would attempt reversal of dabigatan, and with the following agents: PCC (61%), fresh frozen plasma (53%), factor VIIa (24%), haemodialysis (24%), and platelet transfusion (7%) (38).

Prospective studies are needed to clarify which assay condition and parameter optimally describe in vivo haemostasis in patients taking the respective NOACs who are treated with PCC and other haemostatic agents.

Randomised controlled trials are required to compare, in humans who are bleeding (e.g. ICH), the effect of non-activated PCC and FEIBA on bleeding rate and volume (e.g. ICH volume on CT brain scan, transfusion requirements), bleeding complications (e.g. hydrocephalus requiring surgery), thrombotic complications (e.g. myocardial infarction, ischaemic stroke), survival and functional ability, in addition to coagulation parameters. It would be optimal scientifically, and perhaps acceptable ethically, if the control group were administered placebo because it has not been proven that rapid reversal of anticoagulation in bleeding patients (e.g. ICH) improves survival-free of complications and disability. Indeed, the lack of an antidote or systematic approach to the use of haemostatic agents in patients who experienced major bleeding complications of NOACS (e.g. ICH) did not result in excess fatal bleeding in the comparative trials with warfarin (for which there was an antidote) (1-3, 39).

3. In patients taking a NOAC who experience an acute ischaemic stroke (AIS), to what degree of anticoagulation or plasma concentration of NOAC, if any, can thrombolysis be administered safely and effectively?

Clinical trials of the direct OACs suggest that, each year, 1.0–2.0% of individuals with AF (1-3) and 0.1–0.2% of those with venous thromboembolism (40) who are receiving one of these agents can be expected to experience an AIS.

Patients who experience an AIS should be considered for urgent thrombolytic therapy with alteplase, a recombinant tissue plasminogen activator (rt-PA), to restore perfusion and function of the ischaemic brain (41, 42). However, effective anticoagulation at the time of reperfusion is considered a contraindication for thrombolysis because of the greater risk of symptomatic haemorrhagic transformation of the fresh brain infarct (HTI).

A systematic review of 65,264 patients with AIS who were treated with rt-PA found that pre-stroke use of warfarin was associated with a trend toward an increased the risk of subsequent ICH (odds ratio [OR] 2.46, 95% CI: 0.92 to 6.59) (43). If the INR was subtherapeutic (<1.7), the risk of symptomatic ICH after thrombolytic therapy was still increased among 3,631 patients enrolled in seven studies (OR 2.6; 95% CI 1.1 to 5.9; p=0.02) (44). However, two subsequent larger observational studies reported that, compared to AIS patients who were thrombolysed and had not been pre-treated with warfarin, a subtherapeutic INR (i.e. ≤1.7) was not associated with an increased adjusted rate of symptomatic ICH or poor functional outcome in the warfarin-treated patients (45, 46). However, an increasing degree of anticoagulation between INR 1.0 to 1.7 was associated with a trend, albeit not statistically significant, toward an increased risk of symptomatic ICH (adjusted OR, 1.10 per 0.1-unit increase in INR [95% CI, 1.00-1.20]; p = 0.06) (45).

Current guidelines therefore recommend against using iv rt-PA in patients with AIS who have an INR >1.7, or whose PT is elevated (41).

Although a point-of-care INR test result ≤1.7 indicates a sufficiently low level of anticoagulation for thrombolysis of AIS patients receiving warfarin, it does not reliably exclude effective anticoagulation in AIS patients who are taking a NOAC, and neither does a normal PT; there is no comparable rapid, standardised, widely available point-of-care test for the anticoagulant effect or plasma concentration of the NOACs (see above).
Human studies are limited to isolated case reports (n=9) of patients taking dabigatran who experienced an AIS and were treated with thrombolyis (47-55); there are no reports of thrombolyis in stroke patients taking rivaroxaban or apixaban.

Animal studies of experimental AIS treated with thrombolyis suggest that plasma concentrations of dabigatran similar to those used in humans do not increase HTI whereas supra-therapeutic plasma concentrations of dabigatran and warfarin do (56, 57). These findings are similar to animal studies of experimental AIS without thrombolyis (58, 59), and consistent with the lower rate of ICH in patients taking NOACs, compared with warfarin, in trials of stroke prevention in AF (1-3, 36), but they await confirmation in human studies.

Currently, there is a lack of consensus among 221 vascular neurologists regarding the treatment of a typical ischaemic stroke patient who is eligible for iv rt-PA but has been taking dabigatran (time of last dose unknown); 49% would not treat with tPA regardless of PTT, 28% would treat if PTT was normal, 9% would treat if PTT was < 40 seconds, and 4% would treat regardless of PTT (38). Even more variability in responses was seen when presented with a normal PTT but variable times from last dabigatran dose. Between 8-14% of respondents were not sure what they would do (38).

A simple solution may be to treat anticoagulated AIS patients by means of endovascular devices (e.g. stent retrievers), as attempted in isolated cases (60, 61), but this strategy remains unproven as a safe and effective alternative or addition to thrombolysis (62-64).

Large, observational studies, or RCTs, are required in AIS patients who are taking a NOAC to determine if rapidly obtained measures of the anticoagulant effect or plasma concentration of the NOAC can independently and significantly predict symptomatic HTI and functional outcome among patients treated and not treated with thrombolyis, after adjusting for other determinants of the measures (e.g. renal function, interacting drugs, time since last intake of NOAC) and other clinical and imaging predictors of HTI and functional outcome, with and without thrombolysis (42).

4. In patients with recent cardioembolic ischaemic stroke, what is the optimal time to start (or re-start) anticoagulation with a NOAC (or warfarin)?

The optimal time to start (or re-start) anticoagulation therapy after acute cardioembolic ischaemic stroke is uncertain.

Anticoagulation (with heparins) started within 48 h of cardioembolic ischaemic stroke significantly increased symptomatic ICH over 7-14 days compared with no anticoagulation in 4,624 patients in seven RCTs (2.5% vs 0.7%, OR 2.89, 95% CI 1.19–7.01), without significantly reducing recurrent ischaemic stroke, mortality or disability (65).

There are no clinical trial data evaluating the safety and efficacy of the NOACs in the first 7-14 days after ischaemic stroke (1-3, 66, 67).

The optimal time after ischaemic stroke when the declining risk of HTI has fallen sufficiently below the increasing risk of recurrent cardiogenic ischaemic stroke is likely to vary between 3-21 days after stroke, depending on individual patient risk factors for these events (68-74). In patients with a high risk of early recurrent ischaemic stroke (e.g. high CHA2DS2-VASc score and echocardiographic evidence of left ventricular systolic dysfunction and left atrial spontaneous echo contrast) (72-74) and a low risk of HTI (e.g. small area of brain infarction, blood pressure <140 mmHg systolic, and normal blood glucose and platelet counts) (68-71), early anticoagulation might be safe and effective. Experimental studies in animals suggest that the risk of HTI may be lower with a NOAC than warfarin (56-59).

RCTs should compare the effectiveness and safety of early (e.g. first week) vs delayed (e.g. 7-10 days later) anticoagulation with a NOAC in patients with recent cardioembolic ischaemic stroke, and identify which patients, if any, are most and least likely to benefit.

5. In anticoagulated patients who experience an ICH, can anticoagulation with a NOAC be re-started (or started) safely and effectively, and if so when?

The decision to re-start anticoagulation after an anticoagulant-associated ICH depends on the indication for anticoagulation (e.g. AF), the treatment history with anticoagulation, the cause of the ICH, the co-morbidities of the patient, and ultimately the estimated absolute risk of recurrent ischaemic stroke without and with anticoagulation, and the risk of haematoma growth, recurrent ICH and other major bleeding, without and with anticoagulation.

For patients whose indication for anticoagulation is AF, the risk of recurrent stroke is likely to be ≥2% per year without anticoagulation, and ≥1% per year with anticoagulation, depending on their CHADS2 or CHA2DS2-VASc score and echocardiographic features (72-75). The risk of cardioembolic ischaemic stroke is linear and cumulative, increasing steadily over time (1-3).

The risk of recurrent ICH is about 2-3% (1 to 4%) per year, similar to the rate of ischaemic stroke after ICH (76-80). The risk of recurrent ICH is influenced by the location of the ICH, as this tends to indicate the arterial pathology (e.g. lobar ICH is commonly caused by amyloid angiopathy in the elderly and tends to recur [81-84] whereas deep ICH is commonly caused by hypertensive small vessel disease and has a lower rate of recurrence if blood pressure is well controlled [85-87]). The risk of recurrent ICH is also determined by the age of the patient (39, 78, 88), a history of previous ischaemic stroke (39, 89), diabetes mellitus (89), chronic kidney disease (90, 91), brain imaging evidence of widespread cerebral leukoaraiosis and multiple microbleeds (92), high intensity (e.g. poorly controlled) anticoagulation (39), concurrent use of antiplatelet therapy (39, 89, 93), and the early period of anticoagulation use (88). Hence, the HAS-BLED score, which contains many of these factors, correlates with risk of ICH (94). The risk of recurrent ICH is highest early after the index bleeding and decreases over time (76-81, 95).

A retrospective analysis of 177 survivors of warfarin-associated ICH who were followed for a median of 69 weeks (interquartile range [IQR]: 19–144) found that, compared with 118 patients with
ICH who did not resume warfarin, the 59 patients who resumed warfarin a median of 5.6 weeks (IQR: 2.6–17.0) after the ICH had an increased risk of recurrent ICH (hazard ratio (HR): 5.6; 95% CI: 1.8–17.2) but a reduced risk of ischaemic stroke (HR: 0.11; 95% CI: 0.014–0.89) (95). The incidence of recurrent ICH was highest in the first 35 days after recommencing warfarin (0.75% per day; HR: 4.13), after which it began to plateau at a much lower rate. Among the 118 patients who did not re-start warfarin, the rate of recurrent ICH was 0.18% per day in the first 35 days and the rate of ischaemic stroke was 0.068% per day in the first 77 days. The combined risk of recurrent ICH or ischaemic stroke reached its lowest point if warfarin was resumed approximately 10 to 30 weeks after the initial ICH, suggesting that this timeframe may be optimal for resuming warfarin (95). However, other publications advocate re-starting anticoagulation as early as at 1–4 weeks after ICH (96).

Based on the available data, it is uncertain if and when to start or restart anticoagulation (or antiplatelet therapy) in patients who survive ICH during treatment with oral anticoagulation.

In the REstart of Strop Antithrombotics Randomised Trial (RESTART), patients with spontaneous ICH who had taken anti-thrombotic drugs before ICH onset are randomised > 24 h after ICH onset to start vs avoid antiplatelet drug(s) (97). The primary outcome is recurrent symptomatic ICH, which is expected to occur at an annual rate of 1.8-7.4% among participants who avoid antiplatelet drugs (97). The trial aims to randomise 720 patients to realise 90% power of detecting a doubling of an annual ICH rate of 4.5% by starting antiplatelet therapy, and 93% power of detecting a quadrupling of an annual rate of 1%, over two years. Secondary outcomes include extracranial haemorrhage, ischaemic events, death, disability, and adherence to antiplatelet drug(s).

A similar randomized trial to RESTART, which assesses the relative risks and benefits of starting vs avoiding a NOAC, but perhaps ≥ 2 weeks after a NOAC-related ICH, in patients at high risk of thromboembolism and low risk of ICH, is warranted. It has been estimated that such a trial should involve at least 300 patient-years of follow-up (98).

6. Are the NOACs effective and safe in multimorbid geriatric people (who commonly have AF and are at high risk of stroke but also bleeding)?

Nearly half of people with AF are older than 75 years. Older individuals with AF are at high risk of ischaemic stroke. Although VKAs substantially reduce the risk of stroke, the risk of major bleeding is increased because of co-existent morbidity and suboptimal anticoagulant management (88, 99-101).

The NOACs offer some potential advantages to VKAs in the elderly. They do not interact with food or many drugs, do not require routine monitoring, and have a shorter half-life and offset of action. They were also at least as effective and safe as warfarin in the subgroup of AF patients aged ≥75 years in the large phase III trials of NOACs vs warfarin compared with AF patients <75 years (1-3). The only exception was among older patients allocated dabigatran in whom the benefit of dabigatran (vs warfarin) in reducing extracranial major bleeding complications attenuated with increasing age (102).

The NOACs also have some potential disadvantages to VKAs in the elderly, such as a twice-daily dosage regimen, the lack of an anticoagulation monitoring option, the relatively short duration of action and the lack of an antidote. However, the main disadvantage of the NOACs, compared to VKAs, in the elderly is that the NOACs are mainly excreted by the kidney (particularly dabigatran), and renal function gradually declines with advancing age (103). Hence, in contrast to VKA treatment, it is essential to consider renal function before deciding on the appropriate dose of the NOACs, and to monitor renal function.

Despite the random allocation of 19,100 AF patients aged ≥75 years to a NOAC or warfarin in the three phase III trials (i.e. 38% of the total 50,578 patients) and the generally consistent relative benefits of the NOACs vs warfarin in the phase III trials, irrespective of age and renal function (patients with severe renal impairment [creatinine clearance of <30 ml min⁻¹] excluded) (1-3), the NOACs do not appear to have been studied sufficiently in multimorbid geriatric patients with AF to reassure geriatricians of their safety and efficacy (67, 104). Hence, further observational evidence at least, or preferably controlled trials, of the NOACs vs warfarin, and of the NOACs vs no anticoagulation, in multimorbid older patients with AF appears necessary (104).

7. Can dose-adjusted NOAC therapy augment the established safety and efficacy of fixed-dose unmonitored NOAC therapy?

If the “therapeutic range” of the NOACs can be established (question 1 above), and doses of NOACs adjusted to maintain the therapeutic range, the safety and efficacy of dose-adjusted NOAC therapy could be compared with the established safety and efficacy of fixed-dose unmonitored NOAC therapy in a RCT. However, because the rate and number of clinically relevant primary efficacy and safety outcomes are likely to be low in both treatment groups, perhaps unrealistically large number of patients would be required to reliably identify or exclude a modest, yet clinically significant, benefit of dose-adjusted NOAC therapy.

8. Is there a dose, or dosing regimen, for each NOAC that is as effective and safe as adjusted-dose warfarin for patients with AF who have mechanical prosthetic heart valves?

Many AF patients with valvular heart disease as the underlying cause of the AF have undergone mechanical prosthetic heart valve replacement, and therefore require anticoagulation life-long.

The Randomized, Phase II Study to Evaluate the Safety and Pharmacokinetics of Oral Dabigatran Etexilate in Patients after Heart Valve Replacement (RE-ALIGN) trial was terminated prematurely because of an excess of thromboembolic and bleeding events among patients assigned a specific dosing algorithm of dabigatran (initial dose 150, 220, or 300 mg twice daily based on kidney function, and adjusted to obtain a trough plasma level of at
least 50 ng/ml) compared with warfarin (dose adjusted to obtain an INR of 2.3 or 2.5-3.5 on the basis of thromboembolic risk) (105).

The lack of efficacy of dabigatran in the RE-ALIGN may reflect different mechanisms of thrombosis (i.e. in the left atrial appendage vs on prosthetic valves) but it may also reflect suboptimal plasma concentrations of dabigatran (e.g. administration of the same total daily dose of dabigatran three times a day may have realised lower peak and higher trough concentrations).

Pre-clinical studies suggest that high dose rivaroxaban (300 ng/ml, as achieved with oral administration of 20 mg), but not low dose rivaroxaban (30 ng/ml) is as effective as enoxaparin and unfractionated heparin in preventing thrombus formation on mechanical heart valves (106).

Further evaluation of the likely optimal dosing regimen for each NOAC, that will prevent thrombosis on mechanical prosthetic heart valves, without excessive bleeding, is indicated.

9. What is the long-term safety of the NOACs?

For AF patients oral anticoagulation is usually life-long.

There is a large body of observational clinical experience with the use of long-term warfarin. However, it is noteworthy that experience with long-term warfarin in clinical trials is limited. The mean duration of follow-up of the 2,900 patients with AF who were exposed to warfarin in the six RCTs that validated the efficacy of warfarin for this indication was only 1.6 years per participant (107). In the 12 RCTs that compared warfarin with antiplatelet agents, the mean follow-up of 11,748 participants was only 1.5 years per participant (107). The longest duration of follow-up was a mean 2.7 years (standard deviation [SD] 1.2) (108).

The NOACs are at least as effective and safe as warfarin in the short-term (1-3 years), but data regarding long-term drug exposure and patient outcome in clinical trials and observational clinical experience are lacking.

The Long-term Multicenter Extension of Dabigatran Treatment in Patients with Atrial Fibrillation (RELY-ABLE) study followed up a select group of 5,851 (48%) patients who were randomly assigned dabigatran in RE-LY, had maintained study drug at their final RE-LY visit, and continued their originally assigned study medication (i.e. the double-blind dabigatran dose) for an additional 2.3 years (median) to a total mean follow-up of 4.3 years (109). The rates of major bleeding and ICH, as observed in RE-LY, were maintained, and the rates of stroke or systemic embolism remained acceptable (1.5% per year). However, there was no warfarin control group for comparison.

Following the approval and marketing of dabigatran for stroke prevention in AF, a review of reports of major bleeding among insurance-claim data and administrative data from the US FDA Mini-Sentinel database found that dabigatran was safer than warfarin for gastrointestinal haemorrhage (1.6 vs 3.5 events per 100,000 days at risk) and ICH (0.8 vs 2.4 events per 100,000 days at risk) in >54,000 patients with AF (110). A nationwide register in Denmark found similar rates of major bleeding and stroke/systemic embolism with dabigatran (both doses) compared with warfarin, including the subgroup with > 1 year follow-up, among 14,000 anticoagulant-naive patients (111). However, another Danish study reported frequent deviations from recommended use of dabigatran among 1,114 patients with treated with 150 mg bid (i.e. age > 80 years, liver or kidney disease, previous bleeding), and an increased risk of bleeding and thromboembolism with dabigatran compared to vitamin K antagonists among previous users of vitamin K antagonists (112). It remains uncertain whether dabigatran is as safe and effective as warfarin in the longer term.

Long-term phase 4 post-marketing surveillance studies, such as the GLORIA (NCT01468701) and GARFIELD (NCT01090362) registries (113), aim to optimise ascertainment of cases and major outcome events and establish the long-term safety of the NOACs.

Conflicts of interest

GJH has received honoraria for serving on the Executive Committees of the AMADEUS trial (Sanofi-Aventis), ROCKET-AF trial (Johnson & Johnson), and the BOREALIS trial (Sanofi Aventis); for serving on the Stroke outcome adjudication committee of the RE-LY trial and AVERROES trial, and for speaking at scientific symposia and consulting on advisory boards sponsored by Bayer Pharmaceuticals, Boehringer Ingelheim, and Pfizer Australia.

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