The safety of NOACs in atrial fibrillation patient subgroups

A narrative review

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Title: The safety of NOACs in atrial fibrillation patient subgroups: A narrative review

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Abstract

Aim: Four non-vitamin K oral anticoagulants (NOACs) have been evaluated in clinical trials for the prevention of stroke in patients with atrial fibrillation (AF). Although each of the NOACs have been shown to be at least non-inferior to warfarin for efficacy and safety outcomes, controversy remains over the relative safety of each NOAC in patient subgroups. This narrative review provides an overview of phase III data on NOAC trials for the prevention of stroke in AF, with a focus on reporting the safety of each agent in key patient subgroups based on age, gender, accumulated risk factors, and primary or secondary prevention of stroke.

Methods: A comprehensive literature search was completed and, where data permit, analyses of phase III trials of the NOACs are presented for each patient subgroup.

Results: Analyses of key safety outcomes from NOAC trials were completed using primary trial data, including major bleeding and all-cause mortality. The safety of NOACs was generally consistent and favourable compared to warfarin according to patient age, gender, previous history of stroke, and the presence of risk factors for stroke.

Conclusions: The safety of the NOACs compared to warfarin was generally favourable across different patient subgroups, including those perceived to be at ‘high risk’ for adverse outcomes. However, certain NOACs may be preferable to warfarin in some subgroups, based on indirect analyses.

Review criteria:

- A comprehensive literature search was completed using online databases.
- Primary study data were extracted and analysed.

Take home message:

- NOACs generally have a favourable safety profile to warfarin in all patient subgroups.
- Some NOACs may have better safety profiles than others based on indirect analyses.

Introduction

Atrial fibrillation (AF) is associated with an increased risk of morbidity and mortality, in part due to an increased risk of stroke in this population (1,2). AF increases the risk of stroke five-fold compared to the general population (1). Accordingly, lifelong anticoagulation therapy is recommended for patients with AF (3).Typically, this has involved the use of vitamin K antagonists, primarily warfarin (4). Well-controlled warfarin therapy has been shown to be highly effective in the prevention of stroke in patients with AF and is associated with a relative risk reduction of 64% compared with control/placebo, as well as a 26% reduction in all cause mortality (5).

However, achieving well-controlled warfarin therapy in practice is a demanding process (6,7). Warfarin has a narrow therapeutic range, defined as an international normalised ratio (INR) of 2.0–3.0 and this time in therapeutic range (TTR) should be achieved for >70% of the treatment period to ensure optimal outcomes (7). When the INR is too low, the risk of stroke increases, while an elevated INR increases the risk of bleeding (8,9). Maintaining the INR within this range is complicated by the multiple drug and food interactions observed with warfarin therapy, as well as significant intra- and inter-individual variability in the pharmacological profile of the drug and the healthcare system in which a service operates (6,7). Multiple commonly occurring risk factors have been defined and prospectively validated, predicting a failure to achieve TTR (10). The risk of bleeding on warfarin therapy is

one of the most significant concerns of patients and physicians, due to the morbidity and mortality associated with major bleeding events (7,11). Therefore, anticoagulation therapy with the non-vitamin K oral anticoagulants (NOACs), which do not require routine anticoagulant monitoring and have a more predictable pharmacological profile, may be practically advantageous and more acceptable to patients compared to warfarin therapy.

Four NOACs are licenced for use in patients with non-valvular AF in the United States and Europe: apixaban, dabigatran, edoxaban, and rivaroxaban. Evidence from phase III trials suggests that the NOACs have a favourable efficacy and safety profile compared with warfarin (12). Whilst there have not be direct comparisons with antiplatelet drugs or placebo (apart from apixaban (13)), indirect comparisons clearly show superior efficacy and the safety of NOACs versus antiplatelet drugs or placebo (14).

However, it is recognised that the efficacy and safety profiles of anticoagulant therapy are not homogeneous in the AF population. Different patient risk factors may contribute towards an increased risk of stroke or bleeding (15). It is important that these risk factors are identified and factored into clinical decision-making, as the risk of bleeding complications remains a significant reason for avoiding anticoagulation therapy in eligible patients (16,17).

Bleeding risk factors have been identified by multiple bleeding risk scoring schemes, including the HAS-BLED score (18) which allows for identification of modifiable risk factors prior to initiation of anticoagulation therapy and to 'flag up' those at high bleeding risk for early review and follow up (eg. 4 weeks rather than 4-6 months) (19). Clarifying the relative safety profiles of the NOACs compared with warfarin and other the other agents from the NOAC class in individual patient populations will be vital in promoting the appropriate use of anticoagulant therapy in the future.

Despite the available data supporting the use of NOACs as an alternative to warfarin in patients with AF, there are significant gaps in the knowledge base. Of particular concern, is the lack of data that allow physicians to differentiate between specific NOACs based on individual patient characteristics (20). Certain patient subgroups may be associated with different relative risks of stroke and/or bleeding with anticoagulation (21). Both the American

College of Chest Physicians (ACCP) (22) and the National Institute for Health and Care Excellence (NICE) (23) in the UK suggest the need for tailored NOAC recommendations to reflect the differences of efficacy and safety of each NOAC in different patient risk profiles, and consideration of patient choice.

Determining the most appropriate NOAC for these subgroups requires a careful assessment of the net clinical benefit of each agent in the context of patient-specific factors (24). However, head-to-head trials of the NOACs are non-existent, disempowering physicians aiming to tailor therapy to the needs of the patient. The recent 2018 ACCP guidelines also makes suggestions for particular OAC drugs to fit the patient clinical profile, based on subgroup data from trials and real world postmarketing observational evidence (25)

The use of NOACs in the management of valvular AF is controversial, and warfarin use persists in this diverse population. However, evaluation of clinical trial data (26) suggests that NOACs may be an alternative to warfarin in patients with AF and native aortic valve disease, tricuspid valve disease, or mitral regurgitation, and a CHA_2DS_2-VASc score of 2 or greater, leading to incorporation of these indications in recent guidelines for valvular heart disease (27). A recent consensus guideline notes that the term 'valvular AF' is obsolete, and should be replaced by the term 'AF with valvular heart disease', further categorised into Evaluated Heartvalves, Rheumatic or Artificial (EHRA) Type I and Type II, depending on the possible use (or not) of NOACs (28). EHRA Type I refers to patients with valvular heart disease needing VKA therapy (mitral stenosis and mechanical prostheses), while EHRA Type II refers to patients with valvular heart disease needing therapy with VKA or NOAC, taking into consideration CHA_2DS_2VASc score risk factor components.

Thus, there may be an emerging role for NOACs in this patient group, consistent with the general principle of minimising the elevated bleeding risk seen with the use of any anticoagulant in these patients.

The aim of this narrative review is to provide an overview of existing clinical trial data on NOACs for patients with AF, focusing on the safety of NOACs in specific patient subgroups.

Analyses of available data are presented to provide objective, indirect comparisons between NOACs, thereby highlighting the roles of each NOAC in specific patient subgroups.

Methodology

This review examined data pertaining to four NOACs (apixaban, dabigatran, edoxaban and rivaroxaban) evaluated in phase III trials, assessing the favourability of agents in specific patient subgroups for the treatment of AF, using pooled analyses where appropriate. Study-specific event rates among patient subgroups were pooled using a fixed effects meta-analysis model. Statistical heterogeneity across the trials was found to be minimal, as assessed using the I^2 statistic. In the absence of reported effect estimates, risk ratios were calculated from raw data in every available trial.

The phase III NOAC trials, and beyond

Four main NOAC trials have been conducted in the context of the management of AF. Overall, the NOAC trials demonstrate that each agent is at least non-inferior to warfarin for the prevention of stroke/systemic embolic events (SEE) and with respect to bleeding safety endpoints, compared with warfarin therapy (13,29–31). Results of the NOAC trials are summarised in table 1. Although these trials are similar in many respects, there are important differences in trial design, study participants and outcome measures that should be considered, and have been the subject of numerous reviews (32–34).

There have not been any head-to-head clinical trials of the NOACs, and apart from the AVERROES trial comparing apixaban to aspirin in patients ineligible for (or refusing) VKA (13) there have been no direct comparisons of dabigatran, rivaroxaban or edoxaban against aspirin or placebo. The AVERROES trial was stopped early due to a clear superiority of apixaban over aspirin for reducing stroke/SEE, with no significant difference in major bleeding or ICH (13).

Indirect comparisons of the NOACs have shown that the efficacy of apixaban, dabigatran (both doses) and rivaroxaban is comparable, but dabigatran 150 mg BID was superior to rivaroxaban for some efficacy endpoints, while major bleeding was lower with dabigatran 110 mg BID or apixaban (35). Rasmussen and colleagues (36) found that apixaban, dabigatran and rivaroxaban had similar efficacy for the main endpoints when used for secondary stroke prevention. However, haemorrhagic stroke, vascular death, major bleeding and intracranial bleeding were less common with dabigatran 110 mg BID than with rivaroxaban. For primary prevention of stroke, apixaban was associated with less major bleeding than dabigatran 150 mg BID and rivaroxaban less and gastrointestinal bleeding than dabigatran 150 mg BID (36).

An indirect analysis (37) including edoxaban has also been published, demonstrating that both high- and low-dose regimens of edoxaban have comparable efficacy and safety to apixaban, dabigatran and rivaroxaban, although some differential effects were evident (e.g. lower rates of stroke/SEE but a higher rate of major bleeding with apixaban versus low dose regimen edoxaban). Blann et al. (38) have shown that both 30 mg and 60 mg doses of edoxaban have a favourable net clinical benefit (NCB) compared with no treatment, which is superior to the NCB of warfarin versus no treatment.

With regard to indirect comparisons of NOACs against aspirin or placebo a network meta-analysis of nine phase III trials found that primary efficacy endpoints were consistently inferior with aspirin compared with the NOACs (39). Similarly, a recent network meta-analysis found that all NOACs were superior to aspirin or placebo for stroke prevention, while aspirin, apixaban, dabigatran 110 mg and edoxaban were associated with less major bleeding than warfarin (40). Dabigatran has also been shown to have benefits for the prevention of stroke/SEE and mortality over antiplatelets and placebo, based on indirect evidence, without an indication of increased risk of ICH (41). Similarly, indirect evidence supports the use of edoxaban over placebo, aspirin alone or aspirin plus clopidogrel based on a reduction in stroke/SEE and mortality, as well as a reduction in ICH compared with aspirin plus clopidogrel (14).

The randomised trials and network meta-analyses are now augmented by numerous real world data analyses that have examined the effectiveness and safety of NOACs compared to warfarin, as well as comparative effectiveness of the NOACs against each other. The numbers of papers have largely reflected the sequence these drugs have been approved and licensed for clinical use.

For the comparisons of NOACs versus warfarin, various studies have reported the effectiveness and safety of dabigatran compared to warfarin (42–44) that have been summarised in a systematic review and meta-analysis (45). The latter shows that dabigatran was associated with a lower risk of ischaemic stroke than VKA therapy as well as a lower risk of major bleeding (HR, 0.79; 95%CI, 0.69–0.89), intracranial bleeding (HR, 0.45; 95%CI, 0.38–0.52) and mortality (HR, 0.73; 95%CI, 0.61–0.87). The risk of gastrointestinal bleeding was higher with dabigatran and the risk of myocardial infarction was comparable between groups.

For rivaroxaban, real world data such as the XANTUS study (46) shows that the rates of stroke and major bleeding are low in patients taking rivaroxaban (0.7 and 2.1 events per 100 patient-years, respectively). An analysis of the Dutch subset of the XANTUS registry (47) also shows a low major bleeding rate in patients taking rivaroxaban in routine clinical practice (2.4 events per 100 patient-years).

For apixaban a real-world propensity-matched analysis of 76,940 patients with AF showed that apixaban initiators had a lower risk of stroke/SEE (HR, 0.67; 95%CI, 0.59–0.76) and major bleeding (HR, 0.60; 95CI, 0.54–0.65) than warfarin initiators (48). These findings were consistent across all analysed patient subgroups and subtypes of stroke/SEE and major bleeding. A recent analysis of the safety and effectiveness of apixaban versus VKA therapy in routine German practice evaluated the composite endpoint of ischaemic stroke, TIA, myocardial infarction or intracranial haemorrhage in one year after initiation of therapy (49). The findings suggested that apixaban and VKA therapy had a similar impact on this endpoint.

Two recent real-world evaluations of edoxaban versus warfarin therapy have been published, and show that edoxaban is likely to be associated with a reduced risk of ischaemic stroke, major haemorrhage and all-cause death compared with warfarin, even in high risk subgroups (50) and for both doses of edoxaban, although low-dose edoxaban (30/15 mg) had lower effectiveness for the prevention of stroke compared with warfarin where creatinine clearance was above 95 mL/min, suggesting that the higher dose regimen (60/30 mg) should be used in this group to maintain efficacy, while preserving safety (51).

Comparative effectiveness and safety studies have been published between the NOACs and warfarin. The REVISIT-US study (52) evaluated real-world effectiveness and safety of apixaban or rivaroxaban versus warfarin and found that both drugs were associated with a reduction in the combined endpoint of stroke or intracranial haemorrhage compared with warfarin. However, ischaemic stroke was non-significantly increased with apixaban versus warfarin (HR, 1.13; 95% CI, 0.49–2.63), but small numbers and the short followup preclude over-interpretation of these data. A real-world analysis of claims databases in the United States found no difference in the risk of stroke/SEE between apixaban, dabigatran and rivaroxaban (53). Apixaban was associated with a lower risk of major bleeding than dabigatran or rivaroxaban, while rivaroxaban was associated with an increased risk of major bleeding and intracranial bleeding compared with dabigatran.

Yao and colleagues (54) found that apixaban was associated with lower risks of stroke/SEE and major bleeding compared with warfarin, while stroke/SEE risk was similar between warfarin, dabigatran and rivaroxaban and major bleeding was lower with dabigatran. It has also been shown that among newly anticoagulated patients, apixaban and dabigatran were associated with a lower risk of major bleeding compared to warfarin initiation, while rivaroxaban was associated with a higher risk of major bleeding compared with apixaban (55). An analysis of 118,891 patients also found that rivaroxaban treatment was associated with an increased risk of intracranial haemorrhage and major extracranial bleeding, including major gastrointestinal bleeding, compared with dabigatran treatment (56).

High risk patient subgroups from the RCTs

The remainder of this paper will focus on four key patient subgroups that are of particular importance when considering anticoagulation therapy in patients with AF. These subgroups are: elderly patients, female patients, patients with a high number of stroke risk factors, and patients with previous stroke. For each subgroup, a detailed examination of the available literature is provided, accompanied by a novel analysis of raw trial data, aimed at supplementing available knowledge on the safety of NOACs for each subgroup.

Age

Patient age is considered one of the major risk factors for stroke and bleeding in the context of anticoagulation therapy for AF (57). The majority of patients with AF are aged over 60 years, with approximately one-third ≥75 years old (58). It is estimated that at least 10% of patients over the age of 75 years have AF (59). The risk of major bleeding increases with age in patients with AF, particularly when receiving anticoagulation therapy (60,61). An increased risk of stroke has been related to underuse of anticoagulation in the elderly population, with one study demonstrating 75% of AF patients aged <75 years receiving anticoagulation following a stroke compared with 33% of patients aged >85 years, based on hospital admission records (62). Furthermore, one study has found that rates of warfarin prescription declined with increasing age on hospital discharge and that age was the single greatest reason cited for non-prescription of warfarin in the elderly (63). This is despite the finding that the clinical benefit of anticoagulation is greatest in the most elderly patients (> 85 years old) (64). This is a worrying phenomenon, suggesting under-treatment of patients with AF, particularly as the relative benefits of anticoagulation tend to outweigh the potential negative effects, regardless of age (12).

Analyses of phase III trials have suggested that the efficacy and safety of the NOACs remain favourable compared to warfarin, even in patients aged ≥75 years old (Table 2). In the subgroup analysis of the ROCKET-AF, efficacy and safety data for patients aged ≥75 years was consistent with the overall results of the study (65). A subgroup analysis of older patients (65-74 years and ≥75 years) in the ARISTOTLE trial found that stroke/systemic embolic events (SEE) and major bleeding outcomes were consistent with those seen in younger patients and the general study population (66). In both ROCKET-AF and

ARISTOTLE, doses of NOACs were not adjusted based on patient age. However, for RE-LY and ENGAGE AF-TIMI 48, a number of patients aged ≥75 years old underwent pre-specified dose reductions (150mg to 110mg for dabigatran and 60mg to 30mg for the high-dose edoxaban regimen). In the RE-LY subgroup analysis, both doses of dabigatran (150mg and 110mg) were associated with a reduction in stroke/SEE comparable to warfarin therapy, regardless of patient age, while the risk of intracranial haemorrhage was reduced with both doses of dabigatran compared with warfarin therapy (110mg: 0.37% per year; 150mg: 0.41% per year; versus 1.00% per year on warfarin therapy). However, there was an increased risk of extracranial bleeding with both doses of dabigatran in older patients compared with warfarin therapy (67).

For edoxaban, the overall findings of the ENGAGE AF-TIMI 48 trial showed that edoxaban was non-inferior to warfarin for the prevention of stroke/SEE and was associated with a lower rate of major bleeding compared to warfarin, regardless of patient age (30). A more detailed analysis has been conducted of patients stratified according to age: <65, 65 to 74, and ≥75 years (68). This analysis found that, in patients aged ≥75 years, edoxaban and warfarin therapy were associated with similar rates of stroke/SEE (Hazard ratio [HR], 0.83; 95% CI 0.66–1.04) but the risk of major bleeding was significantly lower with edoxaban (HR, 0.83; 95% CI, 0.70–0.99). The absolute difference in intracranial bleeding rates also favoured edoxaban in this analysis (68).

Therefore, subgroup analyses of phase III trials highlight some differences in the relative safety of NOACs compared to warfarin. To explore this issue further, data from the RE-LY, ARISTOTLE and ROCKET-AF trials were extracted with reference to the rates of major bleeding in patients aged <75 years or ≥75 years old (raw data from the ENGAGE AF-TIMI 48 trial were not available). The findings of the analysis (Figure 1) suggest that, overall NOACs are favourable to warfarin in preventing major bleeding, in patients <75 years old. However, this effect appears to be less pronounced in patients ≥75 years old, particularly for dabigatran and rivaroxaban, while apixaban appears to have a favourable bleeding risk compared to warfarin therapy. The general trend for the three NOACs in this analysis suggests consistent favourability over warfarin even in older patients, although this effect is largely attributable to the favourable effects of apixaban.

Further randomised trial data would provide insights into the true effect of age on NOAC safety, when taking into account age-associated risk factors, such as hypertension, renal impairment and polypharmacy. Untangling comorbidities in the elderly is challenging however, as declining renal function in elderly patients may confound the observed benefit seen with age alone, while the frailty phenotype will likely become a more important subgroup in the next ten years.

The selection of NOACs based on patient age is a complex process and care must be taken to ensure that the comorbidities associated with increased age are considered during this decision-making process. Hypertension, congestive heart failure, type 2 diabetes and previous stroke are all risk factors for future stroke and bleeding risk and are more common in the elderly population than in younger patients (69). Similarly, renal function declines with age (70) and polypharmacy increases with age (71); both may influence the effectiveness and safety of NOAC therapy (72). Therefore, basing the selection of NOACs on age alone may be inappropriate, unless these other factors are also considered. Dose-reduced regimens of NOACs may also be justified based on patient age, in combination with other factors (i.e. body weight, concomitant medication, and renal function) (73).

Current European recommendations (73) advise dose reductions of NOACs in patients aged over 75 years only where other risk factors are present, such as low body weight or renal impairment, with the exception of dabigatran where dose reduction from 150mg to 110mg is advised in patients aged >80 years, due to the increased risk of bleeding in older patients on the higher dose.

Gender

Compared with men, women develop AF at an older age (74–76) and have a higher risk of stroke (77). Being female affords an increased risk of stroke, which is reflected in the CHA_2DS_2-VASc score and female gender is also a risk factor for maintaining time in the therapeutic range of warfarin therapy, reflected in the SAMe-TT_2R_2 score (10). Even when women spend a significant amount of time within the therapeutic range (>66%) their risk of stroke is higher than for men (78). Whilst women have an increased stroke risk compared to men, there is no significant difference in composite cardiovascular death and stroke/SEE (79). The reasons underlying the increased risk of stroke in women with AF are unclear,

although an increased rate of hypertension (80) and structural differences in the left atrium compared with men (81), have been proposed to account for some of this increased risk. Regardless of the underlying reasons, the efficacy and safety of NOACs in women with AF remains uncertain at present.

A meta-analysis of NOACs versus warfarin showed that women with AF have a greater risk of cerebrovascular events and systemic embolism compared with men, but that these differences are not seen when both sexes are treated with NOACs (apixaban, dabigatran or rivaroxaban) (82). This meta-analysis also found that women had a lower risk of major bleeding then men on NOAC therapy (OR 0.849, CI 0.745-0.955, p=0.007). An indirect comparison of NOAC therapy in women suggested that there were no differences in the safety and efficacy of NOACs in this population (83).

Our analysis of data extracted from phase III NOAC trials in patients with AF was used to explore the effect of gender on a single key safety outcome: major bleeding (Figure 2). Data were only available for absolute patient numbers from the RE-LY, ARISTOTLE and ROCKET-AF trials, while data on all-cause mortality were not available for all studies according to patient gender. The results of this analysis suggest that there is little difference in the rates of major bleeding with individual NOACs when comparing male and female patients. In both male and female patients the NOACs collectively showed statistically favourable results compared to warfarin therapy. Apixaban may be associated with a more pronounced reduction in major bleeding versus warfarin therapy in women compared with men.

Therefore, the available evidence suggests that safety outcomes for men and women are similar, with a reduction in major bleeding compared warfarin therapy, regardless of the individual NOAC used. Therefore, no specific agent may be preferred based on patient gender alone. Data on edoxaban suggests that outcomes in men and women are very similar (84), but pending a more robust analysis of data on edoxaban, and head-to-head trials comparing the safety of NOACs, NOAC selection in both men and women should be based on patient preference and clinical characteristics (e.g. renal function, bleeding risk factors).

Accumulated risk factors for stroke

As noted above, there are multiple risk factors for stroke that are of particular relevance in patients with AF. The CHA_2DS_2-VASc stroke risk stratification score identifies congestive heart failure, hypertension, previous stroke/TIA/thromboembolic event, vascular disease, type 2 diabetes, female gender and advanced age (≥75 years) as risk factors for stroke in patients with AF (85). This score is beneficial in refining the identification of low- and intermediate-risk patients in a patient population with $CHADS_2$ 0–1 (86).

Most guidelines currently recommend the use of the CHA_2DS_2-VASc score to determine the indication for antithrombotic therapy in patients with AF (87–89). Current European guidelines suggest that a threshold CHA_2DS_2-VASc score of ≥2 for men and ≥3 for women should be used to (strongly) recommend oral anticoagulant therapy whilst for 1 stroke risk factor (ie CHA_2DS_2-VASc score of 1 for men and 2 for women, OAC 'should be considered' (89). The latter reflects the lack of RCTs specifically studying patients with 1 stroke risk factor. However, stroke rates vary depending on the risk factor that is present (64). One analysis from a National Primary Care Database found that the stroke rate was highest when advanced age or previous stroke was present, compared to other risk factors (92). Therefore, it remains challenging to accurately stratify patients according to stroke risk based on the use of standardised risk scoring; the impact of individual risk factors appears to be important in AF patients on the borderline of the treatment threshold (93).

The 2018 ACCP guidelines recommend a stepwise approach, to initially identify low risk patients (CHA_2DS_2VASc 0 in males or 1 in females), for whom no antithrombotic therapy is recommended; the next step is to offer stroke prevention (i.e. oral anticoagulants) to those with ≥1 stroke risk factors (25). This reflects that the default strategy should be to offer stroke prevention unless the patient is low risk.

The phase III NOAC trials utilised $CHADS_2$ scores to calculate patient risk of stroke and to stratify patient subgroups, hence the $CHADS_2$ score is used in analyses of data from these trials. It should be noted that the ENGAGE AF-TIMI 48 trial used a $CHADS_2$ score ≥2 as an inclusion criterion for patients in both the edoxaban and warfarin treatment groups. As a

result, it is not possible to compare the safety of edoxaban in patients with $CHADS_2$ <2 with those achieving higher scores, based on phase III trial data.

Data extracted from phase III trials indicated that all NOACs were associated with a reduction in major bleeding compared to warfarin, regardless of the $CHADS_2$ score (Figure 3). This effect was statistically significant only in patients with $CHADS_2$ scores of 2 or more (P <0.001), indicating that NOACs may be more favourable than warfarin in preventing major bleeding in patients at a greater risk of stroke. This effect was less pronounced for all-cause mortality (Figure 4), although the NOACs remained favourable compared with warfarin therapy, although this was not statistically significant. Further data on apixaban suggested that patients with $CHADS_2$ >3 showed the greatest reduction in stroke, with better efficacy and safety than in patients with lower $CHADS_2$ scores (94). In the RE-LY study, the greatest absolute risk reduction in stroke is seen in patients with the highest risk of stroke or bleeding treated with dabigatran versus warfarin (95).

Analyses of the NCB of NOACs have suggested that these agents are generally favourable compared to warfarin for both efficacy and safety outcomes (96). When the risk of bleeding and stroke are both elevated, the NOACs generally demonstrate a greater NCB compared with warfarin, suggesting the broad application of NOACs in patients with a number of bleeding risk factors and stroke risk factors (96). However, these analyses are based on indirect data comparisons excluding edoxaban and head-to-head trials would be needed to clarify the relative safety of individual NOACs. An analysis of the NCB of edoxaban suggested that the efficacy and safety of the high-dose regimen (60/30mg) was favourable compared to warfarin, even in patients at higher risk of bleeding or stroke (38).

In summary, there are insufficient data to suggest that one NOAC may be preferable over another based on stroke risk stratification using the $CHADS_2$ or CHA_2DS_2-VASc, where ≥2 risk factors are present.

Primary versus secondary stroke prevention

The phase III NOAC trials generally found that patients with previous stroke/transient ischaemic attack (TIA) had a higher rate of stroke than patients without a history of stroke/TIA. Enrolment rates of patients with previous stroke/TIA did vary between phase III trials however, with ROCKET-AF showing the highest rate of patients with previous stroke/TIA (55%) (31). Subgroup analyses of trials exploring the use of dabigatran, rivaroxaban and apixaban found similar efficacy and safety with these NOACs, regardless of stroke/TIA history (97–99). A meta-analysis of dabigatran, rivaroxaban and apixaban found that NOACs were comparable to warfarin for the prevention of stroke/SEE in patients with a history of stroke/TIA, with indirect comparisons of NOACs demonstrating no significant difference in stroke, disabling stroke, or all-cause mortality (100). However, the rate of intracranial bleeding was lower with NOACs compared with warfarin in patients with previous stroke/TIA (71).

For edoxaban, pre-specified analyses have shown a consistent level of efficacy and safety compared with warfarin in patients with or without a previous history of stroke/TIA (30). A recent formal subgroup analysis found that the high-dose edoxaban regimen (60mg reduced to 30mg, based on patient characteristics) had comparable efficacy for stroke prevention and improved safety compared with warfarin in patients with or without a history of stroke/TIA (101).

Phase III trial data was analysed in order to explore the relative safety of NOACs based on the use of NOACs for primary versus secondary stroke prevention in the AF population (Figures 5 and 6). The findings showed that the NOACs were favourable compared to warfarin in both primary and secondary stroke prevention contexts, when the outcome of major bleeding was considered ($P<0.001$ for both primary and secondary populations; Figure 5). The strongest benefits were apparent with apixaban and edoxaban, while the rate of major bleeding with rivaroxaban, in particular, was less favourable compared with warfarin in the primary prevention context. When all-cause mortality was considered as a key safety outcome, the NOACs performed similarly and were favourable compared to warfarin for both primary and secondary stroke prevention populations, although these effects did not reach statistical significance (Figure 6).

In summary, the NOACs appear to be associated with a lower rate of major bleeding than warfarin in patients receiving anticoagulation for primary or secondary stroke prevention, with the exception of rivaroxaban. Edoxaban and apixaban had particularly favourable safety outcomes in both patient populations.

Additional safety considerations

The heterogeneity of patients with AF adds to the complexity of managing patients effectively, particularly when balancing bleeding risk and anticoagulant effect. Patients with impaired renal and liver function are at risk of increased exposure to NOACs and dose adjustment is advised according to available guidelines (102) in order to maintain comparable efficacy and safety to warfarin use. In patients with chronic liver disease data are limited for NOACs versus warfarin, but a recent retrospective cohort study suggests similar bleeding rates for both anticoagulant approaches (103). More data are needed to clarify the relative risks and benefits of NOACs compared to warfarin in liver disease.

Asian patients with AF have different characteristics than non-Asian patients with AF, including an increased tendency towards bleeding and a reduced chance of achieving therapeutic INR levels with warfarin therapy (104,105). Warfarin use in Asian patients with AF is associated with higher rates of stroke than that seen in non-Asians (104). The use of NOACs in the Asian population has been shown to reduce the risk of stroke and does not lead to increased bleeding events compared with warfarin therapy, based on Phase III trial data (106). Similarly, real-world data suggest that the risk of ischaemic stroke is similar with NOACs and warfarin use in Asian patients, while the risk of ICH is lower with NOACs (107).

One of the perceived advantages of warfarin therapy is the ability to monitor the anticoagulation effect through INR levels, which provides reassurance to clinicians that effective anticoagulation is achieved and maintained. Uncertainty over the 'true' anticoagulant effects of NOACs, based on specific plasma markers, may lead to doubt over the achievement of effective anticoagulation among clinicians (108). However, as NOACs achieve a more predictable anticoagulant effect than warfarin, plasma level monitoring of NOACs is not recommended on a routine basis. Indeed, plasma levels may not be indicative

of anticoagulant effect and limited data support this strategy (102). Therefore, there is no clear place for monitoring plasma levels of NOACs to maximise benefits or minimise risks in routine practice at present.

Despite the many advantages of NOACs compared to VKA therapy, careful decision-making is required to ensure the safety of selecting on option over another. As more data emerge from clinical trials and real-world analyses, the use of NOACs is becoming more diverse, replacing VKA therapy in many contexts as a safe, reliable and effective treatment approach (109). VKA therapy still has a role to play in many contexts, including situations where NOACs are contraindicated (e.g. renal failure). However, uncertainty over the relative efficacy of different NOACs and clinical inertia often accounts for the preference for VKA therapy in clinical practice (110) and this must be addressed through careful examination of NOAC safety and clarity in clinical guidelines to ensure patient safety and the effectiveness of anticoagulation.

Limitations

All of the analyses presented in this manuscript are based on indirect comparisons of NOAC patient subgroups, which have inherent limitations compared to analyses based on head-to-head trials (111). However, no head-to-head trials exist for the NOACs and therefore indirect comparisons of data may provide an insight into the comparative effects of the drugs, provided key limitations are borne in mind (35,112). For instance, the design of the phase III NOAC trials varied, with different criteria for patient selection, variable levels of anticoagulation control with warfarin, and different approaches to drug comparison (e.g. the RE-LY trial was a three-arm open clinical trial comparing two doses of dabigatran and warfarin, while the remaining trials were double-blind and dose adjustments were made depending on patient characteristics).

Conclusion

This review highlights the importance of considering patient subgroups and specific stroke risk factors when initiating antithrombotic therapy in patients with AF. The safety of the NOACs compared to warfarin was generally favourable across different patient subgroups. However, certain NOACs may be preferable to warfarin in some subgroups, based on indirect analyses. It will be important to confirm these findings in head-to-head trials in order to effect changes in clinical practice consistent with optimisation of patient safety.

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Table 1. Summary of data from phase III clinical trials of non-vitamin K antagonists (NOACs) for the prevention of stroke and systemic embolic events in patients with atrial fibrillation. TTR, time in therapeutic range.

Trial	N	Drug and dose	Mean TTR in warfarin arm of study (%)	Relative risk (95% confidence interval) vs. warfarin			
				Stroke or systemic embolism	Major haemorrhage	Intracranial haemorrhage	All-cause mortality
RE-LY (29)	18,113	Dabigatran 150 mg twice daily Dabigatran 110 mg twice daily	64	0.66 (0.53–0.82) 0.91 (0.74–1.11)	0.93 (0.81–1.07) 0.80 (0.69–0.93)	0.40 (0.27–0.60) 0.31 (0.20–0.47)	0.88 (0.77–1.00) 0.91 (0.80–1.03)
ROCKET-AF (31)	14,264	Rivaroxaban 20 mg once daily	55	0.88 (0.75–1.03)	1.04 (0.90–1.20)	0.67 (0.47–0.93)	0.85 (0.70–1.02)
ARISTOTLE (13)	18,201	Apixaban 5 mg twice daily	62	0.79 (0.66–0.95)	0.69 (0.60–0.80)	0.42 (0.30–0.58)	0.89 (0.80–0.99)
ENGAGE AF-TIMI 48 (30)	21,105	Edoxaban 60 mg once daily Edoxaban 30 mg once daily	68	0.87 (0.73–1.04) 1.13 (0.96–1.34)	0.80 (0.71–0.91) 0.47 (0.41–0.55)	0.47 (0.34–0.63) 0.30 (0.21–0.43)	0.92 (0.83–1.01) 0.87 (0.79–0.96)

Table 2. Summary of phase III clinical trial data for the NOACs compared to warfarin in patients aged 75 years or older.
NB: Relative risk data according to age subgroups are not available for edoxaban- hazard ratios are presented.

Trial	N (aged 75 years or over)	Drug and dose	Relative risk (95% confidence interval) vs. warfarin*			
			Stroke or systemic embolism	Major bleeding	Intracranial bleeding	Gastrointestinal bleeding
RE-LY	7,258	Dabigatran 150 mg twice daily Dabigatran 110 mg twice daily	0.67 (0.49–0.90) 0.88 (0.66–1.17)	1.18 (0.98–1.42) 1.01 (0.83–1.23)	0.42 (0.25–0.70) 0.37 (0.21–0.64)	1.79 (1.35–2.37) 1.39 (1.03–1.98)
ROCKET-AF	6,229	Rivaroxaban 20 mg once daily	0.80 (0.63–1.02)	1.11 (0.92–1.34)	0.80 (0.50–1.28)	N/A
ARISTOTLE	5,678	Apixaban 5 mg twice daily	0.71 (0.53–0.95)	0.64 (0.52–0.79)	0.34 (0.20–0.57)	N/A
ENGAGE AF-TIMI 48	8,474	Edoxaban 60 mg once daily Edoxaban 30 mg once daily	0.83 (0.66–1.04) 1.12 (0.91–1.37)	0.83 (0.70–0.99) 0.47 (0.38–0.58)	0.40 (0.26–0.62) 0.30 (0.19–0.49)	1.32 (1.01–1.72) 0.72 (0.63–0.98)

Figure 1. Major bleeding among individuals receiving anticoagulation aged <75 and ≥75 years.

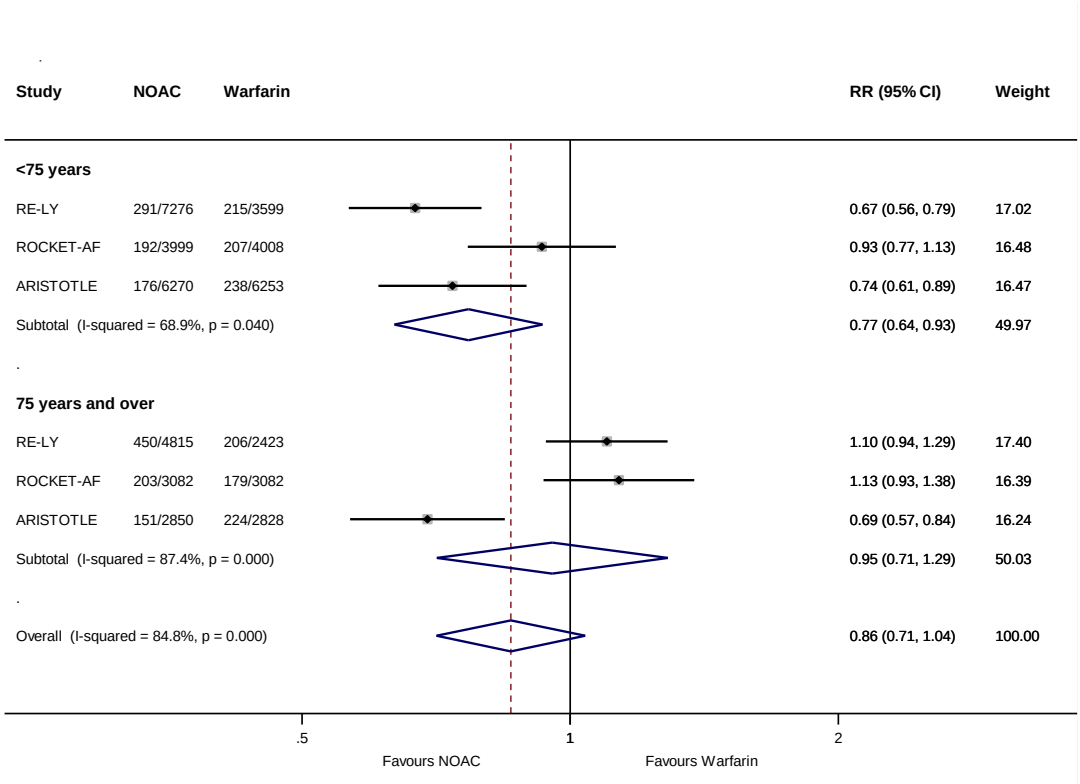

Figure 2. Major bleeding among female and male individuals receiving anticoagulation.

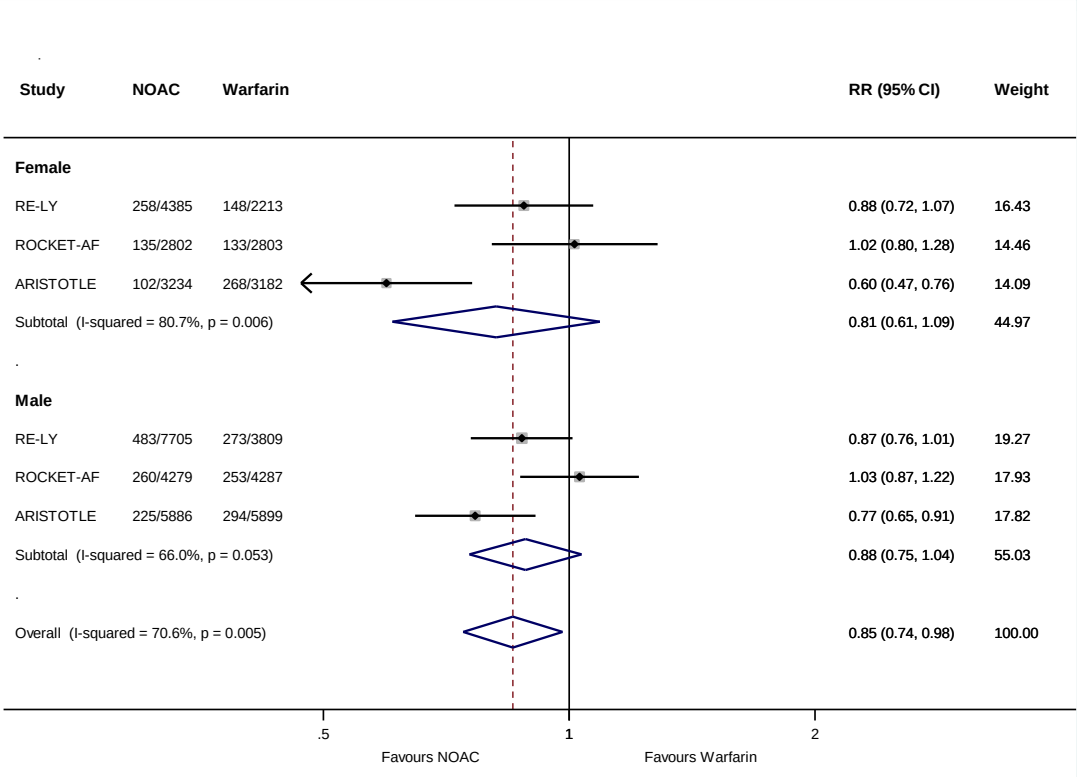

Figure 3. Major bleeding among individuals receiving anticoagulation for CHADS 0-1 vs CHADS 2-6.

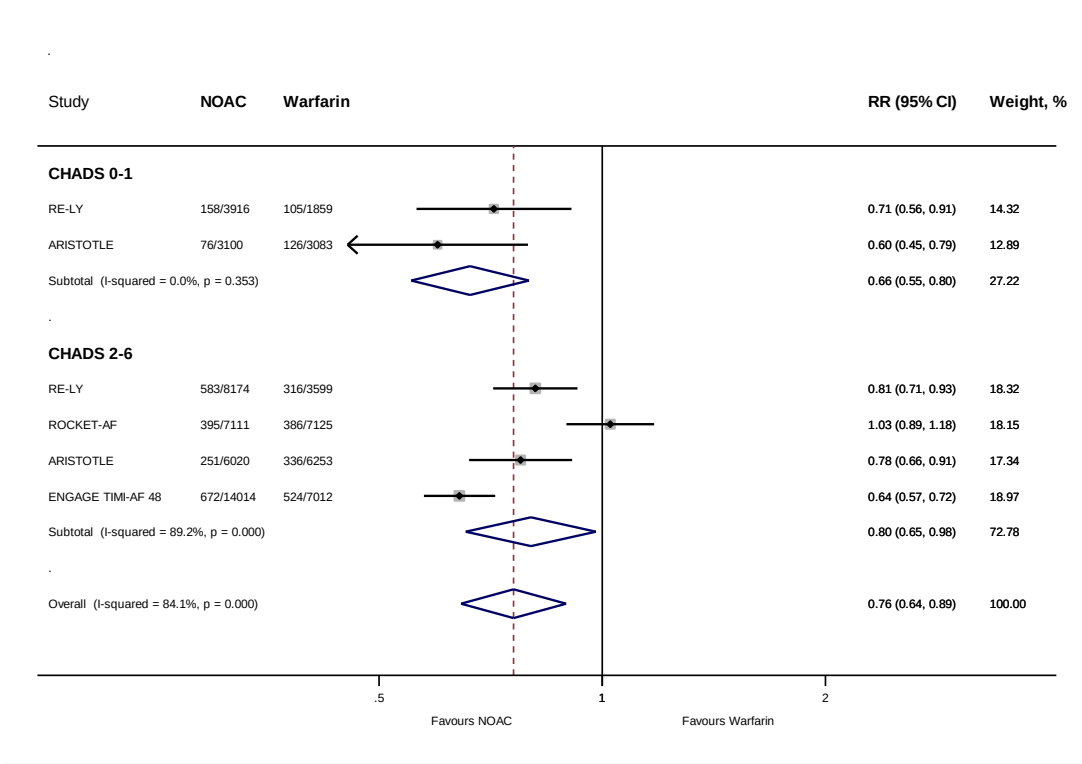

Figure 4. All-cause mortality among individuals receiving anticoagulation for CHADS 0-1 vs CHADS 2-6.

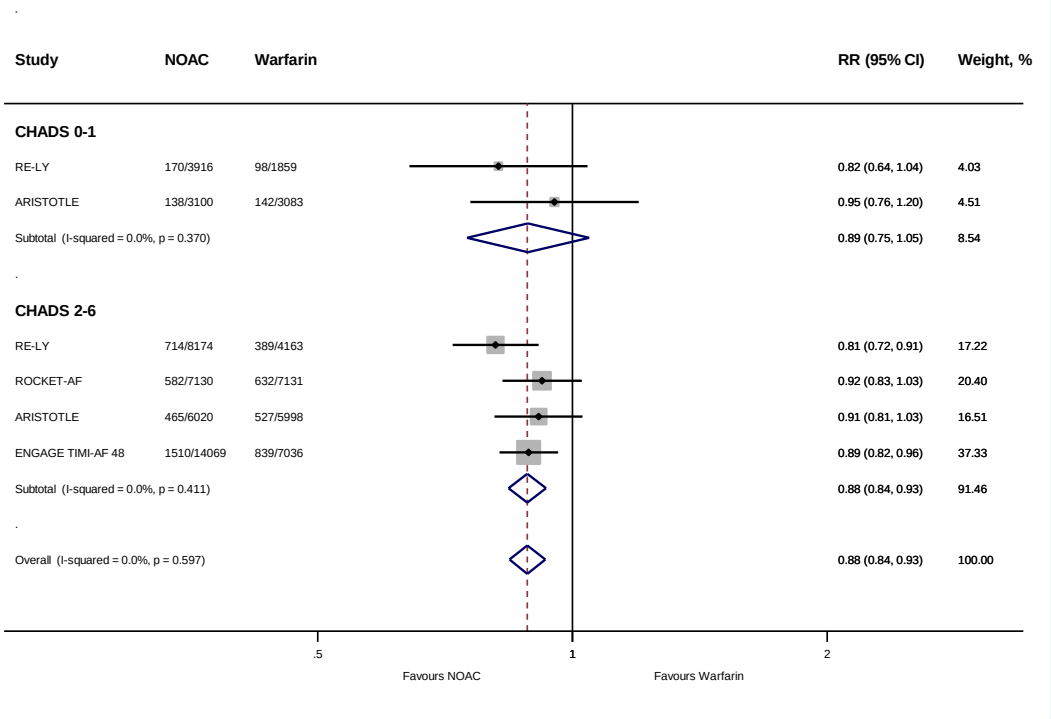

Figure 5. Major bleeding among individuals receiving anticoagulation for primary versus secondary prevention.

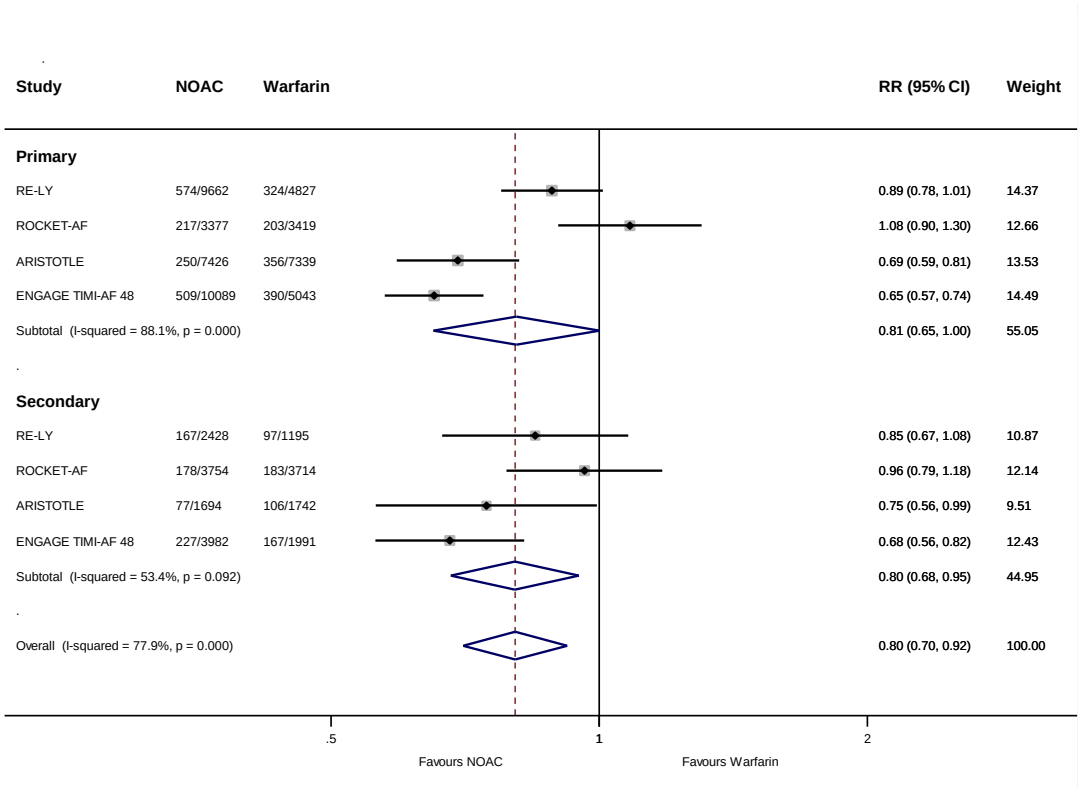

Figure 6. All-cause mortality among individuals receiving anticoagulation for primary versus secondary prevention.