

REVIEW

Stroke Prevention with Oral Anticoagulants: Summary of the Evidence and Efficacy Measures as an Aid to Treatment Choices

José Francisco Kerr Saraiva

Received: December 1, 2017 / Published online: February 27, 2018
© The Author(s) 2018. This article is an open access publication

ABSTRACT

Atrial fibrillation (AF) is an established risk factor for a first or recurrent stroke. Despite proven efficacy in preventing stroke in patients with AF, warfarin is underused, partly due to safety concerns. Recent randomized trials have shown that non-vitamin K antagonist oral anticoagulants (NOACs) such as dabigatran (a direct thrombin inhibitor) and apixaban, edoxaban, and rivaroxaban (factor Xa inhibitors) are not only non-inferior or superior to warfarin but also demonstrate a decreased risk of cerebrovascular bleeding among patients with AF and moderate to high risk of stroke. Additionally, NOACs have an advantage of requiring no monitoring of the international normalized ratio compared with warfarin. This review summarizes the published literature on NOACs for the primary and secondary prevention of ischemic strokes, with an emphasis on the expected absolute benefits from the

introduction of such agents. As compared with warfarin, NOACs significantly reduce the risk of hemorrhagic stroke, and only dabigatran (150 mg twice daily) was found to significantly reduce the risk of ischemic stroke. However, measures of relative benefits from medical interventions do not immediately provide the estimated benefit to be derived from an individual patient, something best done by considering the expected absolute benefit. The number needed to treat (NNT) is presented for various outcomes in the phase 3 trials of NOACs. Despite the important progress achieved with the introduction of NOACs, the availability of at least four agents with different efficacy and safety performances in comparison with warfarin prompts the question of whether any of these agents is preferable to another. It is hoped that future studies on the efficacy, safety, and economic performance of NOACs will further allow for rational choices within this important therapeutic class. Meanwhile, the NNT may be a valid metric to be considered by clinicians faced with the need to make such choices.

Enhanced content To view enhanced content for this article go to <https://doi.org/10.6084/m9.figshare.5798961>.

J. F. K. Saraiva (✉)
Cardiology Discipline, Pontifical Catholic
University of Campinas School of Medicine,
Campinas, Brazil
e-mail: jfsaraiva@uol.com.br

Keywords: Atrial fibrillation; Hemorrhagic stroke; Ischemic stroke; Non-vitamin K antagonist oral anticoagulants; Stroke prevention

INTRODUCTION

Atrial fibrillation (AF), the most common sustained cardiac arrhythmia, was estimated to affect 33.5 million people worldwide in 2010, with a notable increase in incidence and prevalence in comparison with previous decades [1]. In the next 50 years, the prevalence of AF, which increases with age, is expected to double [2, 3], which may be of concern in rapidly developing countries such as Brazil, China, India, and Indonesia [1, 4].

AF is an established risk factor for a first or recurrent stroke [5]. The risk of stroke among patients with AF has been estimated between 1 and 20% per year [6, 7]. Despite the efficacy of warfarin in preventing a first or recurrent stroke among patients with AF [8], and notwithstanding the recommendation for stroke prophylaxis in selected individuals with AF [6, 9], there is evidence of underuse of anticoagulants in such patients [10, 11]. Additionally, underuse of warfarin among patients with AF at moderate or high risk for stroke has been reported in various countries [12, 13]. It is conceivable that underuse of warfarin when indicated is, in part, due to the concerns about its safety profile and need for close monitoring of the international normalized ratio (INR).

Large randomized trials have shown that direct thrombin and factor Xa inhibitors are either non-inferior or superior to warfarin in terms of efficacy, with a decreased risk of severe bleeding, among patients with AF and moderate to high risk of stroke. The use of agents from these classes—also known as non-vitamin K antagonist oral anticoagulants (NOACs)—allows for fixed dosing and does not require laboratory monitoring. The rapid onset and relatively short half-life of anticoagulant action offers advantages for NOACs over warfarin in some clinical settings. It is expected that the use of such agents will progressively replace warfarin in the future. This review summarizes the published literature with an emphasis on the expected absolute benefits from the introduction of such agents. This article is based on previously conducted studies, and does not involve any new studies of human or animal subjects performed by any of the authors.

SUMMARY OF RESULTS WITH NEW ORAL ANTICOAGULANTS

Direct Comparisons Between Warfarin and New Oral Anticoagulants

NOACs include direct thrombin inhibitors (e.g., dabigatran) and factor Xa inhibitors (e.g., rivaroxaban, apixaban, and edoxaban). To date, a direct comparison of commercially available NOACs in a prospective head-to-head trial has not been performed. In a systematic review of 12 randomized trials, each comparing one of these NOACs against warfarin, the pooled relative risk (RR) of death from any cause was 0.89 [95% confidence interval (CI) 0.83–0.96], thus indicating a significant reduction of all-cause mortality of 11% in favor of NOACs. Likewise, significant benefits were demonstrated for NOACs in terms of stroke or systemic embolism (RR 0.77, 95% CI 0.70–0.86), as well as major bleeding (RR 0.86, 95% CI 0.80–0.93). Conversely, no statistically significant benefit was found for the pooled risk of ischemic stroke, for which separate data were available from 11 trials (RR 0.92, 95% CI 0.081–1.04) [14]. These pooled relative results include data from eight randomized phase 2 trials and four phase 3 trials, although none of these trials studied edoxaban. In the following paragraphs, the individual results of phase 3 trials of dabigatran, rivaroxaban, apixaban, and edoxaban are briefly discussed in chronological publication order.

In the RE-LY® (Randomized Evaluation of Long-term anticoagulation therapy) trial, a pivotal, open-label, phase 3 trial, two doses of dabigatran (150 and 110 mg, both twice daily) were compared with warfarin (adjusted to achieve a target INR of 2.0–3.0) in 18,113 patients with AF plus at least one additional risk factor for stroke [15, 16]. All comparisons were made according to the intention-to-treat principle, and the participants were randomly assigned to receive one of the two doses of dabigatran with no prior selection. The dose of dabigatran currently approved by the US Food and Drug Administration (FDA; 150 mg twice daily) was found to be superior to warfarin in reducing stroke or systemic embolism (RR 0.65,

95% CI 0.52–0.81, $p < 0.001$), which was the primary trial end point. At a lower dose (110 mg twice daily) dabigatran was non-inferior to warfarin, thus also achieving the protocol-specified primary objective (RR 0.90, 95% CI 0.74–1.10, $p = 0.30$). Dabigatran at 150 mg twice daily was superior to warfarin for both ischemic (RR 0.76, 95% CI 0.59–0.98, $p = 0.0351$) and hemorrhagic (RR 0.26, 95% CI 0.14–0.49, $p < 0.001$) strokes, whereas at 110 mg twice daily it was non-inferior to warfarin for ischemic stroke and superior for hemorrhagic stroke (RR 0.31, 95% CI 0.17–0.56, $p < 0.001$). There was no significant reduction in mortality from the use of dabigatran ($p = 0.051$ for 150 mg twice daily and $p = 0.13$ for 110 mg twice daily), but the rate of the composite of major vascular events, major bleeding, or death (i.e., net clinical benefit) was significantly reduced by the 150 mg twice-daily dose ($p = 0.02$). The rate of major bleeding was lower with dabigatran 110 mg twice daily (RR 0.80, 95% CI 0.70–0.93, $p = 0.003$), but similar for dabigatran 150 mg twice daily ($p = 0.31$), in comparison with warfarin. The rates of intracranial hemorrhage and fatal bleeding with both doses of dabigatran were also lower. The rates of major gastrointestinal bleeding were significantly higher with the dabigatran 150 mg twice-daily dose when compared with warfarin (RR 1.50, 95% CI 1.19–1.89, $p < 0.001$). Selected results of this study and others are summarized in Table 1. In subgroup analyses of patients with previous stroke or transient ischemic attack, RR reductions were consistent with those observed in the overall study population—albeit with no statistical significance, possibly as a result of insufficient power in subgroups [17]. Dyspepsia was the only adverse event that was significantly more common with dabigatran than with warfarin [15].

Rivaroxaban was compared with warfarin in two phase 3 trials. The larger ROCKET AF (Rivaroxaban Versus Warfarin in Nonvalvular AF) trial was a double-blind, non-inferiority study in 14,264 patients with AF at moderate to high risk of stroke [18]. The primary end point was the composite of stroke or systemic embolism. Although rivaroxaban (20 mg per day) was found to be non-inferior to warfarin (target INR

2.0–3.0) in the per-protocol analysis of the primary end point [hazard ratio (HR) 0.79, 95% CI 0.66–0.96, $p < 0.001$ for non-inferiority], the intention-to-treat analysis could not confirm the superiority of rivaroxaban (HR 0.88, 95% CI 0.74–1.03, $p < 0.001$ for non-inferiority and $p = 0.12$ for superiority). There was no significant difference between the arms in the rate of major and non-major clinically relevant bleeding, a major composite safety end point (RR 1.03, 95% CI 0.96–1.11, $p = 0.44$), but there were lower rates of intracranial hemorrhage ($p = 0.02$) and fatal bleeding ($p = 0.003$) with rivaroxaban. Gastrointestinal bleeding was more common with rivaroxaban versus warfarin (3.2 vs. 2.2%, $p < 0.001$). Selected results of this trial and others are presented in Table 1. There was a trend toward an interaction between the primary end point and a history of prior stroke, transient ischemic attack, or systemic embolism ($p = 0.072$), and a significant interaction between the primary end point and safety ($p = 0.039$). Among subjects without a history of stroke, transient ischemic attack, or systemic embolism, rivaroxaban was significantly superior to warfarin in achieving the primary efficacy (HR 0.71, 95% CI 0.54–0.94) and safety (HR 0.59, 95% CI 0.42–0.83) end points. Conversely, there was no difference between the primary efficacy (HR 0.98, 95% CI 0.8–1.2) or safety (HR 0.91, 95% CI 0.72–1.14) of rivaroxaban and warfarin in the subgroup with a history of prior stroke, transient ischemic attack, or systemic embolism.

Apixaban was compared with warfarin (target INR 2.0–3.0) in the double-blind ARISTOTLE (Apixaban for Reduction In STroke and Other Thromboembolic Events in AF) trial, which enrolled 18,201 patients with AF plus at least one additional risk factor for stroke [19]. The apixaban dose was 5 mg twice daily, unless patients met two or more of the criteria for a 2.5 mg twice-daily dose (age ≥ 80 years, body weight ≤ 60 kg, or serum creatinine ≥ 1.5 mg/dl). Apixaban was superior to warfarin for the primary end point (stroke or systemic embolism; HR 0.79, 95% CI 0.66–0.95). The relative risk reduction was greater for hemorrhagic (49%) than for ischemic or uncertain types of stroke (8%, not statistically significant; HR 0.92,

Table 1 Selected patient features and results from pivotal phase 3 trials of four new anticoagulants [15, 18–20]

Features and results	Dabigatran 110 mg ^a	Dabigatran 150 mg ^a	Rivaroxaban 20 mg	Apixaban 5 mg ^a	Edoxaban 30 mg	Edoxaban 60 mg
Patients, <i>N</i>	6015	6076	7131	9120	7034	7035
Age, years	71.4 ^b	71.5 ^b	73 ^c	70 ^c	72 ^c	72 ^c
CHADS ₂ score, mean	2.1	2.2	3.5	2.1	2.8	2.8
Median follow-up, years	2 ^d	2 ^d	1.9	1.8	2.8 ^d	2.8 ^d
TTR (%), mean	64	64	55	62	65	65
Primary end point	NI	Superior	NI	Superior	NI	NI
Ischemic stroke	NI	Superior	NI	NI	Inferior	NI
Hemorrhagic stroke	Superior	Superior	Superior	Superior	Superior	Superior
Intracranial bleeding	Superior	Superior	Superior	Superior	Superior	Superior
Any bleeding	Superior	Superior	NI	Superior	Superior	Superior

Results refer to doses compared head-to-head with warfarin in each trial. All trials had stroke or systemic embolism as a primary end point

CHADS₂ Congestive heart failure, Hypertension, Age (> 65 = 1 point, > 75 = 2 points), Diabetes, and Stroke/TIA (2 points), NI noninferior, TTR time in therapeutic range (for warfarin arms of corresponding trial)

^a Twice-daily doses; for apixaban, the criteria for a 2.5 mg twice-daily dose is discussed earlier in the results section

^b Mean

^c Median

^d Reported in aggregate for all trial arms

95% CI 0.74–1.13, $p = 0.42$). The secondary end points of death (HR 0.89, 95% CI 0.80–0.99, $p = 0.047$) and major bleeding (HR 0.69, 95% CI 0.60–0.80, $p < 0.001$) favored apixaban. The rates of gastrointestinal bleeding were similar in the apixaban and warfarin groups (HR 0.89, 95% CI 0.70–1.15, $p = 0.37$). Selected results of this trial are also displayed in Table 1. Although the results of subgroup analyses were generally consistent with treatment effects seen for the overall study population, significant interactions suggested greater reduction in bleeding with apixaban among those without diabetes mellitus and moderate or severe renal impairment.

Finally, edoxaban was assessed in ENGAGE AF-TIMI 48 (Effective aNticoagulation with factor xA next GEneration in AF—Thrombolysis In Myocardial Infarction study 48), a double-blind trial [20]. In this trial, 21,105 patients with AF and moderate or high risk of stroke

were randomized to receive two once-daily regimens of edoxaban (60 or 30 mg) or warfarin (target INR 2.0–3.0). The primary efficacy end point was stroke or systemic embolism, whereas the principal safety end point was major bleeding. Primary comparisons in a modified intention-to-treat population favored both the 60-mg dose (HR 0.79, 97.5% CI 0.63–0.99, $p < 0.001$ for non-inferiority) and the 30-mg dose of edoxaban (HR 1.07, 97.5% CI 0.87–1.31, $p = 0.005$ for non-inferiority). A prespecified superiority analysis using the intention-to-treat population showed trends in favor of the 60-mg dose of edoxaban versus warfarin (HR 0.87, 95% CI 0.73–1.04, $p = 0.08$) and against the 30-mg dose of edoxaban versus warfarin ($p = 0.10$). Other end points that favored edoxaban significantly were the rate of major bleeding (HR 0.80, 95% CI 0.71–0.91 for the 60-mg dose and HR 0.47, 95% CI 0.41–0.55 for the 30-mg dose) and the rates of death from cardiovascular

causes (HR 0.86, 95% CI 0.77–0.97 for the 60-mg dose and HR 0.85, 95% CI 0.76–0.96 for the 30-mg dose). The rates of the key secondary end point (a composite of stroke, systemic embolism, or death from cardiovascular causes) favored only the 60-mg dose of edoxaban (HR 0.87, 95% CI 0.78–0.96). Gastrointestinal bleeding was significantly more frequent with the 60-mg dose of edoxaban than with warfarin. Selected results of this trial are presented in Table 1. A prespecified analysis of stroke rates indicated that patients receiving 60 mg of edoxaban showed significantly lower stroke rates (HR 0.8, 95% CI 0.65–0.98), whereas patients receiving 30 mg of edoxaban showed similar stroke rates (HR 1.10, 95% CI 0.91–1.32) compared with warfarin [21]. However, both doses of edoxaban were significantly more effective than warfarin in reducing the rates of hemorrhagic stroke and other types of intracranial bleeding [20].

In summary, compared with warfarin, the four NOACs discussed above significantly reduce the risk of hemorrhagic stroke (Table 1). Only dabigatran (at the dose of 150 mg twice daily) was found to significantly reduce the risk of ischemic stroke. More recently, a meta-analysis included the four larger pivotal trials discussed above (RE-LY, ROCKET AF, ARISTOTLE, and ENGAGE AF-TIMI 48) [22]. NOACs were found to significantly reduce the risks of stroke or systemic embolism (RR 0.81, 95% CI 0.73–0.91), all-cause mortality (RR 0.90, 95% CI 0.85–0.95), and intracranial hemorrhage (RR 0.48, 95% CI 0.39–0.59). The benefit regarding strokes was mainly driven by a reduction in hemorrhagic stroke (RR 0.49, 95% CI 0.38–0.64). Conversely, NOACs significantly increased the risk of gastrointestinal bleeding (RR 1.25, 95% CI 1.01–1.55).

Indirect Comparisons Among New Oral Anticoagulants

Given the availability of at least four NOACs, each with a different efficacy and safety performance versus warfarin, the question arises as to whether any of these agents is preferable to others, especially considering that individual

randomized trials disclosed nuances whose practical value remain uncertain, especially with regard to non-composite end points (e.g., the rate of ischemic stroke alone) and to subgroups with a preferential benefit (e.g., patients in primary or secondary prevention of stroke or transient ischemic attack). Unfortunately, there are no published data with direct comparisons between NOACs.

An adjusted indirect comparison of apixaban, dabigatran (150 mg twice daily), and rivaroxaban using data from four randomized trials on one of these agents versus warfarin [15, 18, 19, 23] suggested that dabigatran decreases the risks of stroke or systemic embolism, as well as ischemic and hemorrhagic strokes versus rivaroxaban, with no differences in mortality. Furthermore, the study suggested that apixaban decreases the risk of major and gastrointestinal bleedings versus dabigatran and major bleeding versus rivaroxaban, but increases the risk of systemic embolism versus rivaroxaban [24]. Another indirect meta-analysis comparing the outcomes of the three pivotal trials for apixaban, dabigatran, and rivaroxaban [15, 18, 19] drew very similar conclusions [25]. The same authors of the previous study assessed the results separately in primary and secondary prevention and found that, for patients with prior stroke, apixaban, dabigatran, and rivaroxaban had essentially similar efficacy for the main outcomes; however, hemorrhagic stroke, vascular death, major bleeding, and intracranial bleeding were less common with twice-daily dabigatran 110 mg than with rivaroxaban. For patients with no prior stroke, all three drugs showed few differences. Apixaban was superior to twice-daily dabigatran 110 mg for disabling or fatal stroke, but inferior to twice-daily dabigatran 150 mg for stroke; however, apixaban was superior to twice-daily dabigatran 150 mg for bleeding. No significant differences were observed for the efficacy and safety endpoints between twice-daily dabigatran 150 mg and rivaroxaban. Finally, no significant differences were found in efficacy end points between apixaban and rivaroxaban, but the former led to less major bleeding [26]. Ideally, all these hypothesis-generating results should be confirmed in randomized trials directly comparing the NOACs of interest.

Where the NOACs have been evaluated in postmarketing studies in routine clinical practice, the real-world data generally support the efficacy and safety profiles observed in their respective pivotal randomized trials [27–29].

One of the largest independent real-world studies was conducted by the US FDA with an analysis of the Medicare database [27], which included over 134,000 Medicare beneficiaries, all aged ≥ 65 years, with 37,587 person-years of follow-up. The study showed that dabigatran was associated with reduced risks of ischemic stroke, intracranial hemorrhage, and death, and an increased risk of gastrointestinal hemorrhage, when compared with warfarin in elderly patients with non-valvular AF. Overall, the independent results of the US FDA Medicare study are consistent with the results of the pivotal RE-LY trial, indicating that dabigatran has a favorable risk profile, thus leading to no changes to the current recommendations for its use. A nationwide cohort study in Denmark ($N = 61,678$) assessed safety and efficacy of apixaban, dabigatran, rivaroxaban, and warfarin. No significant differences were observed in the rates of stroke between NOACs and the warfarin groups. However, the rates of major bleeding and mortality were significantly lower in the dabigatran and apixaban groups compared with the warfarin group [28]. A retrospective cohort study analyzed the safety data of NOACs and warfarin in patients ($N = 44,057$) with nonvalvular AF from a US administrative claims database. The rates of risk of major bleeding were consistent with the findings from pivotal randomized trials that compared NOACs with warfarin [29]. These real-world studies are important to support understanding of the real drug safety profiles of approved medicines in routine clinical practice.

Absolute Measures of Efficacy

Measures of relative benefits from medical interventions, such as RRs, odds ratios, and HRs, do not immediately provide the estimated benefit to be derived by an individual patient, something best done by considering the

expected absolute benefit. This can be computed by considering the patient's estimated baseline risk of an outcome of interest (in the absence of intervention) and the relative benefit derived from clinical trials or meta-analyses. The absolute risk reduction (ARR) is the difference in the rates of the outcome of interest in the presence and in the absence of the intervention in clinical trials or meta-analyses. The number needed to treat (NNT) is the number of patients who must be treated in order to prevent one case of the outcome of interest, thus representing the expected absolute benefit [30]. Mathematically, the NNT is the reciprocal of the ARR ($NNT = 1/ARR$). An absolute measure of harm [the number needed to harm (NNH)] may be computed in the same way as the NNT if the ARR is replaced by the absolute risk increase. Thus, the NNH is the reciprocal of the absolute risk increase. The computation of the NNT and the NNH only makes sense when there are statistically significant advantages (i.e., superiority) or disadvantages (i.e., inferiority), respectively, for the use of intervention regarding outcomes of interest in comparison with no use of the intervention (i.e., control).

Considering the pooled results of the meta-analysis discussed previously, the NNT to prevent one death from the use of an NOAC instead of warfarin is 244, and the corresponding NNT for cardiovascular mortality is 500. NNTs are more favorable for the outcomes of stroke or systemic embolism (137) and major bleeding (157). For the latter, there was significant heterogeneity in a random-effects model. A subgroup analysis examining each NOAC separately showed that dabigatran and apixaban led to significant reductions in the rate of major bleeding, whereas rivaroxaban and edoxaban did not [14]. No NNHs were computed in this meta-analysis. Table 2 displays selected NNTs and NNHs based on the individual analysis of each pivotal study of these four agents, with the caveat that such metrics cannot be computed for agents that have not proven a statistically significant difference against warfarin in selected outcomes. For the sake of comparison, the NNT for the use of aspirin as primary

Table 2 Selected absolute measures from pivotal phase 3 trials of four new anticoagulants (yearly NNT or NNH in head-to-head comparisons with warfarin within each trial) [15, 18–20]

Features and results	Dabigatran 110 mg ^a	Dabigatran 150 mg ^a	Rivaroxaban 20 mg	Apixaban 5 mg ^a	Edoxaban 30 mg	Edoxaban 60 mg
Primary end point	N/A	167 ^b	N/A	303 ^b	N/A	N/A
Ischemic stroke	N/A	175 ^b	N/A	N/A	192 ^c	N/A
Hemorrhagic stroke	385 ^b	357 ^b	333 ^b	434 ^b	323 ^b	476 ^b
Intracranial bleeding	189 ^b	227 ^b	250 ^b	213 ^b	169 ^b	217 ^b
Gastrointestinal bleeding	N/A	204 ^c	100 ^c	N/A	244 ^b	357 ^c

N/A refers to situations where neither superiority nor inferiority was demonstrated, thus precluding computation of NNTs and NNHs

NNH numbers needed to harm, NNT numbers needed to treat

^a Twice-daily doses; for apixaban, see the text for the explanation regarding the criteria for the 2.5-mg dose

^b NNT

^c NNH

prevention of non-fatal myocardial infarctions has been estimated at 200 [31].

Applying NNT to a Country

The economic factors that are not considered in this review but discussed elsewhere [6] must also be taken into account, especially in developing countries, where warfarin may continue to have a role in selected patients [32]. A simple exercise using Brazilian data, for example, may illustrate this point. The population of Brazil is approximately 200 million, with nearly 10% of the population aged ≥ 60 years [33]. A population-based study of residents aged ≥ 65 years living in an economically deprived area of São Paulo determined the prevalence of AF at 2.4% [34]. Based on this information, we estimate that 480,000 individuals in Brazil have AF. Considering that nearly 75% of these individuals would have an indication to receive anticoagulation [12], 360,000 users of warfarin potentially exist. The NNT for NOACs with proven superiority to warfarin may be used to compute the annual number of strokes that could be prevented. If dabigatran (150 mg twice daily) and apixaban were used instead of warfarin in Brazil, they could prevent 2156 and 1188 strokes, respectively, every year

[15, 16, 19]. These rough estimates ignore the burden of AF in people younger than 60 years of age, the different prevalence of AF between males and females [2], the potentially different effect of individual agents on patients at moderate and at high risk, and the percentage of individuals with moderate and high risk for stroke who should receive anticoagulants according to guidelines.

Limitations

The main limitation of this review is that, in the absence of head-to-head trials, all the data are hypothesis generating. In addition, it should be noted that the use of the NNT is not without drawbacks or controversy [35, 36]. Two problems with the NNT are immediately apparent in the analysis of the four phase 3 trials of the currently available NOACs [15, 18–20]. The first problem relates to the slightly different patient populations investigated in each trial; in that regard, the direct comparison of NNTs may be misleading because this absolute measure clearly reflects the baseline risk of patients, which was different across studies. For example, the mean CHADS₂ score [Congestive heart failure, Hypertension, Age ($> 65 = 1$ point, $> 75 = 2$ points), Diabetes, and Stroke/

TIA: a prediction for estimating the risk of strokes] was higher in ROCKET AF (3.5) and ENGAGE AF-TIMI 48 (2.8) than in RE-LY (2.1 for the lower dose and 2.2 for the higher dose) and ARISTOTLE (2.1). Likewise, the percentage of patients with a previous stroke or transient ischemic attack (and, in some cases, systemic embolism) was higher in ROCKET AF (55%) and ENGAGE AF-TIMI 48 (28%) than in RE-LY (20%) and ARISTOTLE (19%). Patients with a higher baseline risk derive more absolute benefit from an intervention with a given relative impact than patients with a lower baseline risk undergoing the same intervention. The second problem relates to different results in the control arm across the trials. Notably, the quality of anticoagulation, as indicated by the mean percentage of time the INR remained in the therapeutic range, was higher in ENGAGE AF-TIMI 48 (65%) and in RE-LY (64%) than in ARISTOTLE (62%) and in ROCKET AF (55%). Since the NNT is a function of the difference between the rates of the outcomes of interest with NOACs and with warfarin, differing results in control arms influence the computed NNTs.

CONCLUSIONS

Encouraging progress has been achieved with the introduction of NOACs that, overall, have displayed a superior efficacy and improved safety in comparison with warfarin [15, 18–20]. As noted earlier, differences exist in the efficacy and safety profile among the four currently available NOACs. Careful analysis of trial results so far indicates that the choice among the available agents is not easy. Despite the limitations of the NNT, this may be a valid metric to be considered by a clinician faced with four different agents to be used instead of warfarin in patients with AF plus moderate or high stroke risk. In addition, economic as well as health factors should be considered, as they play a major role. In the example of applying NNT to Brazilian data, around 2156 and 1188 stroke events could be prevented per year by using dabigatran or apixaban, respectively, instead of warfarin [6, 32].

Regardless of these limitations, the number of patients with AF in whom a stroke could be prevented by the use of NOACs instead of warfarin would only increase, accompanying the expected increase in prevalence of AF in Brazil and elsewhere. It is hoped that future studies on the efficacy, safety, and economic performance of NOACs will further allow for rational choices within this important therapeutic class.

ACKNOWLEDGEMENTS

Funding. No funding or sponsorship was received for this study. The article processing charges were funded by Boehringer Ingelheim.

Editorial Assistance. The authors acknowledge editorial assistance provided by PAREXEL, with funding from Boehringer Ingelheim.

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published. All authors had full access to all of the data in this study and take complete responsibility for the integrity of the data and accuracy of the data analysis.

Disclosures. José Francisco Kerr Saraiva is a principal investigator and national coordinator leader of clinical trials from Amgen, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Janssen, Novartis, Novo Nordisk, Pfizer, and Sanofi. José Francisco Kerr Saraiva also serves on the speakers' bureau of AstraZeneca, BMS-Pfizer, Boehringer Ingelheim, and Novo Nordisk.

Compliance with Ethics Guidelines. This article is based on previously conducted studies, and does not involve any new studies of human or animal subjects performed by any of the authors.

Open Access. This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 International License (<http://creativecommons.org/licenses/by-nc/4.0/>), which permits any noncommercial use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made.

REFERENCES

1. Chugh SS, Havmoeller R, Narayanan K, et al. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. *Circulation*. 2014;129:837–47.
2. Go AS, Hylek EM, Phillips KA, et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. *JAMA*. 2001;285:2370–5.
3. Lip GY, Brechin CM, Lane DA. The global burden of atrial fibrillation and stroke: a systematic review of the epidemiology of atrial fibrillation in regions outside North America and Europe. *Chest*. 2012;142:1489–98.
4. Rahman F, Kwan GF, Benjamin EJ. Global epidemiology of atrial fibrillation. *Nat Rev Cardiol*. 2014;11:639–54.
5. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke*. 1991;22:983–8.
6. Furie KL, Goldstein LB, Albers GW, 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;43:3442–53.
7. Gage BF, Waterman AD, Shannon W, et al. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA*. 2001;285:2864–70.
8. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. Analysis of pooled data from five randomized controlled trials. *Arch Intern Med*. 1994;154:1449–57.
9. Camm AJ, Kirchhof P, Lip GY, et al. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Eur Heart J*. 2010;31:2369–429.
10. Friberg L, Rosenqvist M, Lindgren A, et al. High prevalence of atrial fibrillation among patients with ischemic stroke. *Stroke*. 2014;45:2599–605.
11. Ogilvie IM, Newton N, Welner SA, Cowell W, Lip GY. Underuse of oral anticoagulants in atrial fibrillation: a systematic review. *Am J Med*. 2010;123:638–45.
12. Mohammed MA, Marshall T, Nirantharakumar K, Stevens A, Fitzmaurice D. Patterns of warfarin use in subgroups of patients with atrial fibrillation: a cross-sectional analysis of 430 general practices in the United Kingdom. *PLoS One*. 2013;8:e61979.
13. Wang C, Yang Z, Wang C, et al. Significant under-use of warfarin in patients with nonvalvular atrial fibrillation: results from the China National Stroke Registry. *J Stroke Cerebrovasc Dis*. 2014;23:1157–63.
14. Dentali F, Riva N, Crowther M, et al. Efficacy and safety of the novel oral anticoagulants in atrial fibrillation: a systematic review and meta-analysis of the literature. *Circulation*. 2012;126:2381–91.
15. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2009;361:1139–51.
16. Connolly SJ, Ezekowitz MD, Yusuf S, Reilly PA, Wallentin L. Newly identified events in the RE-LY trial. *N Engl J Med*. 2010;363:1875–6.
17. Diener HC, Connolly SJ, Ezekowitz MD, et al. Dabigatran compared with warfarin in patients with atrial fibrillation and previous transient ischaemic attack or stroke: a subgroup analysis of the RE-LY trial. *Lancet Neurol*. 2010;9:1157–63.
18. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med*. 2011;365:883–91.
19. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2011;365:981–92.
20. Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2013;369:2093–104.
21. Giugliano RP, Ruff CT, Rost NS, et al. Cerebrovascular events in 21 105 patients with atrial fibrillation randomized to edoxaban versus warfarin: effective anticoagulation with factor Xa next

- generation in atrial fibrillation-thrombolysis in myocardial infarction 48. *Stroke*. 2014;45:2372–8.
22. Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anti-coagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet*. 2014;383:955–62.
 23. Ezekowitz MD, Reilly PA, Nehmiz G, et al. Dabigatran with or without concomitant aspirin compared with warfarin alone in patients with nonvalvular atrial fibrillation (PETRO Study). *Am J Cardiol*. 2007;100:1419–26.
 24. Baker WL, Phung OJ. Systematic review and adjusted indirect comparison meta-analysis of oral anti-coagulants in atrial fibrillation. *Circ Cardiovasc Qual Outcomes*. 2012;5:711–9.
 25. 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.
 26. Rasmussen LH, Larsen TB, Graungaard T, Skjoth 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.
 27. Graham DJ, Reichman ME, Wernecke M, et al. Cardiovascular, bleeding, and mortality risks in elderly Medicare patients treated with dabigatran or warfarin for nonvalvular atrial fibrillation. *Circulation*. 2015;131:157–64.
 28. Larsen TB, Skjoth F, Nielsen PB, Kjaeldgaard JN, Lip GY. Comparative effectiveness and safety of non-vitamin K antagonist oral anticoagulants and warfarin in patients with atrial fibrillation: propensity weighted nationwide cohort study. *BMJ*. 2016;353:i3189.
 29. Adeboyeje G, Sylwestrzak G, Barron JJ, et al. Major bleeding risk during anticoagulation with warfarin, dabigatran, apixaban, or rivaroxaban in patients with nonvalvular atrial fibrillation. *J Manag Care Spec Pharm*. 2017;23:968–78.
 30. Laupacis A, Sackett DL, Roberts RS. An assessment of clinically useful measures of the consequences of treatment. *N Engl J Med*. 1988;318:1728–33.
 31. Baigent C, Blackwell L, Collins R, et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. *Lancet*. 2009;373:1849–60.
 32. Bista D, Chalmers L, Bereznicki L, Peterson G. Potential use of NOACs in developing countries: pros and cons. *Eur J Clin Pharmacol*. 2014;70:817–28.
 33. Censo Demográfico. 2010. <http://www.ibge.gov.br/home/estatistica/populacao/censo2010/>. Accessed 30 Aug 2016.
 34. Kawabata-Yoshihara LA, Scazufca M, Santos IS, et al. Atrial fibrillation and dementia: results from the Sao Paulo ageing and health study. *Arq Bras Cardiol*. 2012;99:1108–14.
 35. Chatellier G, Zapletal E, Lemaitre D, Menard J, Degoulet P. The number needed to treat: a clinically useful nomogram in its proper context. *BMJ*. 1996;312:426–9.
 36. Cook RJ, Sackett DL. The number needed to treat: a clinically useful measure of treatment effect. *BMJ*. 1995;310:452–4.