Meta-Analysis of Safety and Efficacy of Direct Oral Anticoagulants Versus Warfarin According to Time in Therapeutic Range in Atrial Fibrillation

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Among atrial fibrillation (AF) patients, it is unclear whether the efficacy and safety of direct oral anticoagulants (DOAC) relative to warfarin is consistent across various levels of international normalized ratio (INR) control. To determine the efficacy and safety of DOAC agents compared with warfarin for patients with various levels of anticoagulation control as reflected by their time in therapeutic range (TTR), we conducted a systematic review and meta-analysis of published randomized controlled trials of DOAC versus (vs) warfarin which reported outcomes stratified by TTR. Based on reported center-based TTR (cTTR) ranges, degrees of INR control were categorized into 3 cTTR strata: low (<60%), intermediate (60% to 66%), and high (>66%). Pooled hazard ratios (HR) and 95% confidence intervals (CI) were determined for stroke or systemic embolism (SSE), major bleeding, and intracranial hemorrhage (ICH). Across all cTTR strata, DOAC-treated patients had lower risk of SSE versus warfarin, with a HR of 0.73 (95% CI 0.61 to 0.88) for the low, 0.76 (95% CI 0.59 to 0.98) intermediate; and 0.78 (95% CI 0.63 to 0.96) high cTTR subgroups. Compared with warfarin, DOAC-treated patients had lower risk of major bleeding in the low and intermediate cTTR strata, and similar risk in the highest cTTR stratum (HR 1.00, 95% CI 0.80 to 1.26). Patients treated with DOAC had lower risk of ICH compared with warfarin (HR 0.55, 95% CI; 0.40 to 0.74) which was observed across all cTTR strata. In conclusion, regardless of the degree of INR control, DOAC agents are preferable over warfarin as stroke prevention therapy for patients with AF.
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Based on randomized trials, current guidelines recommend the use of direct oral anticoagulants (DOAC) over warfarin as stroke prevention therapy for atrial fibrillation (AF) patients with thromboembolic risk factors.[1−5] Although this recommendation is commonly implemented among AF patients initiated with OAC, it is less so for those already treated with warfarin.[6−9] Among patients treated with warfarin, rates of switching to DOAC agents were low in contemporary studies, at typically <20%.[7−9] The notion that patients with "stable" international normalized ratios (INR) levels have low risk of bleeding and stroke may contribute to this inertia. We conducted a systematic review and meta-analysis to examine whether the benefit of DOAC agents over warfarin is consistent across varying degrees of INR control, using time in therapeutic range (TTR) to determine whether anticoagulation control is satisfactory. We hypothesize that the rates of thromboembolism, major bleeding, and intracranial hemorrhage (ICH) are lower among DOAC-treated patients than those treated with warfarin, irrespective of INR control.

Methods

We systematically searched OVID versions of MEDLINE (1946 to August 1, 2019) and EMBASE (1980 to August 1, 2019) for citations mentioning any of the approved DOAC agents (dabigatran, rivaroxaban, apixaban, edoxaban) and "atrial fibrillation," "auricular fibrillation," or "atrial flutter." These citations were limited to "randomized controlled trials" (RCT) for MEDLINE and EMBASE, and limited to "conference abstract" or "conference paper" or "conference proceeding" for EMBASE. These 2 searches were combined and duplicates were removed. We only included clinical trials randomizing adult subjects with AF or atrial flutter to any of the approved DOAC agents versus warfarin, which reported separate outcomes in TTR subgroups. Full text reviews were conducted to determine whether a citation meets inclusion criteria. In addition, we conducted a web-based search for regulatory documents (e.g., Food and Drug Administration [FDA] of the United States and the European Medicines Agency [EMA]), which might contain additional pertinent information. The literature search was

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performed by 2 reviewers (JJL and ACTH) who consulted with a third reviewer as needed. This project was performed in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement.[10] Research ethics approval was not sought for conduct of this study given that it was a meta-analysis of published data. Study data and statistical methodology are available upon request to the corresponding author.

Details of the publication (trial authors and acronym, enrolment period, year of publication), inclusion/exclusion criteria, demographics and risk factors of the enrolled patients, description of the interventions used, and outcome definitions and events were compiled using a standardized form by 2 reviewers (JJL and ACTH). Risk of bias in randomized controlled trials (RCT), including blinding of participants, method of sequence generation and allocation concealment, intention-to-treat analysis, early trial stopping for efficacy before the planned enrollment was completed, and loss to follow-up, was also assessed.[11]

The primary efficacy endpoint was the time to first occurrence of stroke or systemic embolism (SSE). The primary safety endpoint was the time to first occurrence of major bleeding (as prespecified by the included trials). A secondary safety endpoint was the time to first occurrence of ICH.

Hazard ratios (HR) from each trial were pooled on the logarithmic scale using the generic inverse variance method. Individual trial and summary results were reported with 95% confidence intervals (CI). Differences between pooled HRs were evaluated using z tests. For trials which studied various DOAC doses in pre-specified arms, we included the higher dose arm in the primary analysis. This was the case for patients treated with edoxaban (60 mg daily or 30 mg daily if the dose reduction criteria were met) and dabigatran (150 mg twice daily). We analyzed our results with random effects models as they provided wider, more conservative CIs if heterogeneity was present. Statistical heterogeneity among trials was assessed using I^2: the percentage of total variability across studies attributable to heterogeneity rather than chance. Cut-offs for heterogeneity were defined according to published guidelines as low ($I^2 = 0\%$ to 49%), moderate ($I^2 = 50\%-74\%$) and high ($I^2 \geq 75\%$).

We performed an interaction test to assess for effect modification between the highest and lowest TTR strata. We considered an interaction p value of <0.10 to be statistically significant. In a sensitivity analysis, we analyzed patients treated with all DOAC dosing regimens. We did not perform statistical testing for funnel plot asymmetry due to the small number of studies that met inclusion criteria (<10) which would have insufficiently distinguished chance from real asymmetry. Analyses were performed using Review Manager (RevMan version 5.2; Cochrane Collaboration, Oxford, UK). Event rates were reported as percentages (%) if available. Statistical significance, defined as a 2-sided alpha <0.05, was assessed with the Chi-square test.

Results

Our search of the published literature identified 2,246 records. From our web-based search, we identified 4 regulatory documents from the FDA, which contained additional pertinent data for our analysis. This meta-analysis derived data from 4 phase III RCTs: Randomized evaluation of long-term anticoagulation therapy (RE-LY), Apixaban for reduction in stroke and other thromboembolic events in AF (ARISTOTLE), Rivaroxaban once daily oral direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation (ROCKET-AF), and Effective anticoagulation with factor Xa next generation in atrial fibrillation−Thrombolysis in Myocardial Infarction 48 (ENGAGE AF-TIMI 48).[1−4] In total, data from 11 records were included in this meta-analysis, which included the 4 RCTs, 3 sub-analyses of RCTs, and 4 documents submitted by the drug manufacturer to the FDA.[1−4,12−18] An overview of the literature search and selection process of this meta-analysis, in accordance with the PRISMA strategy, is shown (Figure 1).

Overall, 71,681 patients were enrolled in the 4 RCTs which compared a DOAC to warfarin. The RE-LY trial studied 2 doses of dabigatran (110 mg and 150 mg twice daily).[1] The ENGAGE AF TIMI-48 trial studied 60 mg and 30 mg daily doses of edoxaban, with doses reduced to 30 mg daily or 15 mg daily, respectively, if dose-reduction criteria were present.[4] The primary dosing regimen was 5 mg twice daily in the ARISTOTLE (apixaban) trial (2.5 mg twice daily if dose reduction criteria were present) and 20 mg daily in the ROCKET-AF (rivaroxaban) trial (15 mg daily if dose reduction criteria were present).[2,3] In all 4 trials, warfarin was used as the comparator drug. Three trials had a double-blind, double-dummy design (ARISTOTLE, ROCKET-AF, and ENGAGE AF TIMI-48) while RE-LY had an open-label design with outcomes assessed by adjudicators who were blinded to treatment assignment. Baseline characteristics of patients in the 4 trials are presented in Supplementary Tables 1 and 2. The studies were of high methodologic quality (Supplementary Table 3).

Subanalyses of each of the 4 pivotal RCTs comparing a DOAC agent to warfarin reported outcomes according to center-based TTR (cTTR).[12−18] The cTTR analyses had been published in manuscript form for the ARISTOTLE, RE-LY, and ROCKET-AF trials.[12−14] Outcomes in relation to cTTR from the ENGAGE AF TIMI-48 trial were obtained from a publicly accessible report provided by the manufacturer to the FDA.[18] In contrast to quartiles of cTTR used in the original trials (Table 1), we realigned the cTTRs into low, intermediate, and high strata. By categorizing into 3 groups, we could align cTTRs reported in the trials into similar threshold values that were consistent across studies (Table 2). This approach allowed us to present findings with consistent values among the low, intermediate, and high groups.

Overall, the risk of SSE was reduced among DOAC-treated patients when compared with those treated with warfarin (HR 0.75, 95% CI 0.67 to 0.85). Across all cTTR strata, patients treated with DOACs had lower risk of SSE compared with warfarin-treated patients (Figure 2). Low study heterogeneity was observed across the 3 cTTR strata ($I^2 < 50\%$). No significant interaction was observed between the low and high cTTR subgroups ($P_{interaction} = 0.63$).

The use of DOAC agents was associated with a 19% reduction in the risk of major bleeding compared with warfarin, which was not statistically significant (HR 0.81, 95% CI; 0.66 to 1.00). In the low and intermediate cTTR groups,

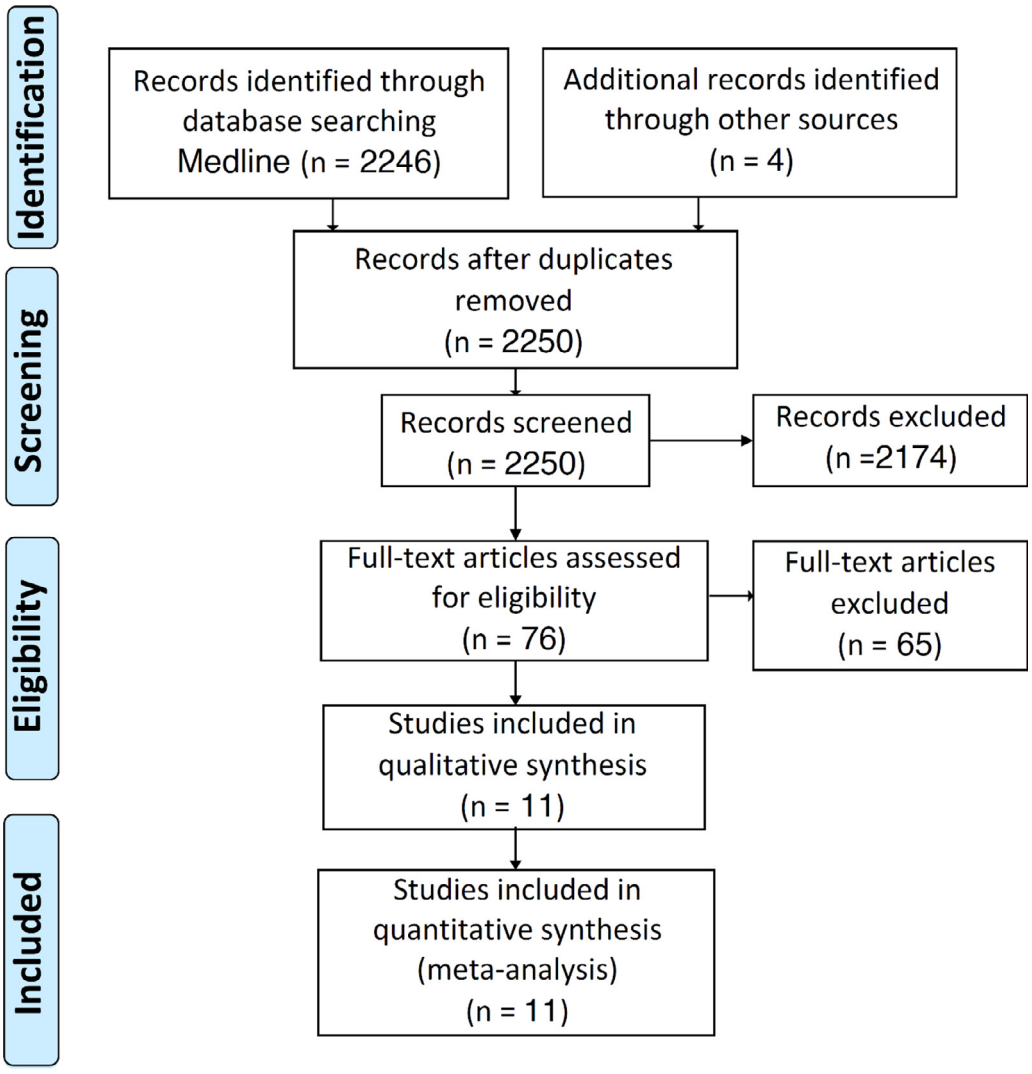

Figure 1. PRISMA flow diagram. PRISMA = preferred reporting items for systematic reviews and meta-analyses.

Table 1
Center-based time in therapeutic range (cTTR) in the ARISTOTLE, RE-LY, ROCKET-AF, and ENGAGE AF TIMI-48 trials, divided by quartiles

Trial name	Quartile			
	1	2	3	4
ARISTOTLE[13]	24.3%–60.5%	60.6%–66.3%	66.4%–71.1%	71.2%–83.2%
RE-LY[12]	≤57.0%	57.1%–65.5%	65.6%–72.6%	≥72.7%
ROCKET-AF[14]	≤50.6%	50.7%–58.5%	58.6%–65.7%	≥65.8%
ENGAGE AF TIMI-48[18]	≤58.4%	58.5%–66.7%	66.8%–74.2%	≥74.3%

Table 2
Reclassified cTTR groups (low, intermediate, high) based on cTTR quartiles from the ARISTOTLE, RE-LY, ROCKET-AF, and ENGAGE AF-TIMI 48 trials

Trial name	Center-based Time in Therapeutic Range (% cTTR range)		
	Low	Intermediate	High
ARISTOTLE[13]	24.3%–60.5%	60.6%–66.3%	66.4%–83.2%
RE-LY[12]	≤57.0%	57.1%–65.5%	≥65.6%
ROCKET-AF[14]	≤58.5%	58.6%–65.7%	≥65.8%
ENGAGE AF TIMI-48[18]	≤58.4%	58.5%–66.7%	≥66.8%

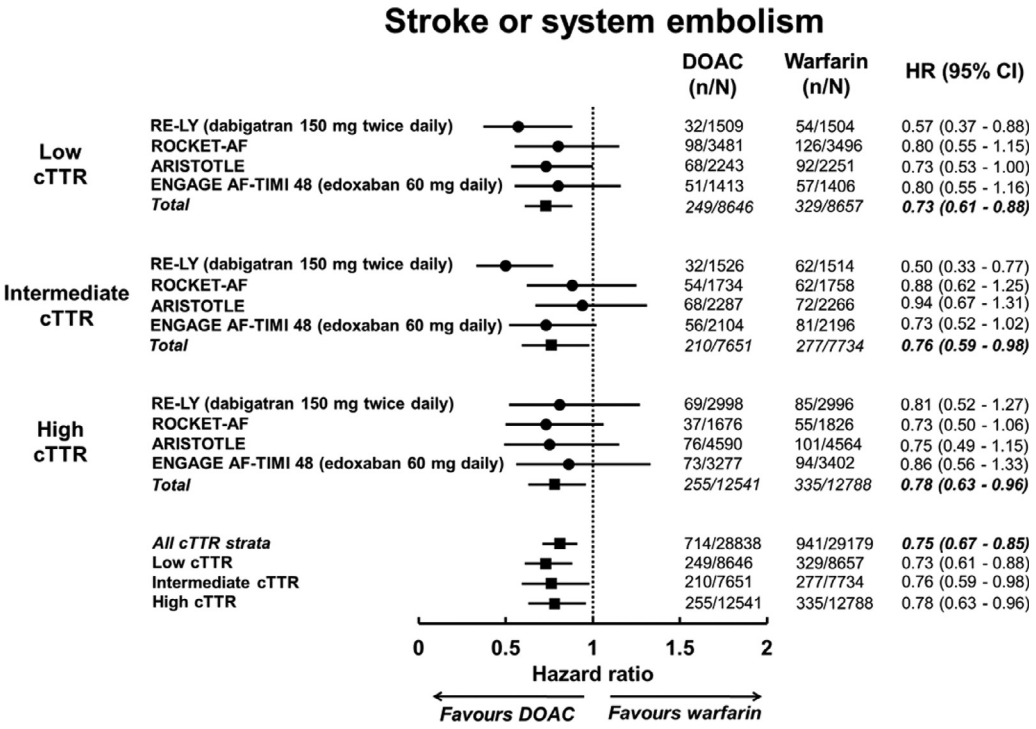

Figure 2. Pooled stroke and systemic embolism risk between patients treated with DOAC and warfarin, stratified by cTTR. CI = confidence interval; cTTR = center-based time in therapeutic range; DOAC = direct oral anticoagulant; HR = hazard ratio.

DOAC use was associated with a reduction in the risk of major bleeding compared with warfarin in the low and intermediate cTTR strata (Figure 3). The risk of major bleeding was similar between DOAC and warfarin in the high cTTR stratum (HR 1.00, 95% CI 0.80 to 1.26; Figure 3). A statistically significant interaction was observed between the low and high cTTR strata ($P_{interaction} = 0.01$). Moderate study heterogeneity was observed across the three cTTR strata, with I^2 values of 47%, 46%, and 69% for the low, intermediate, and high cTTR stratum.

Use of DOAC agents was associated with 45% reduction in the risk of ICH compared with warfarin (HR 0.55, 95%

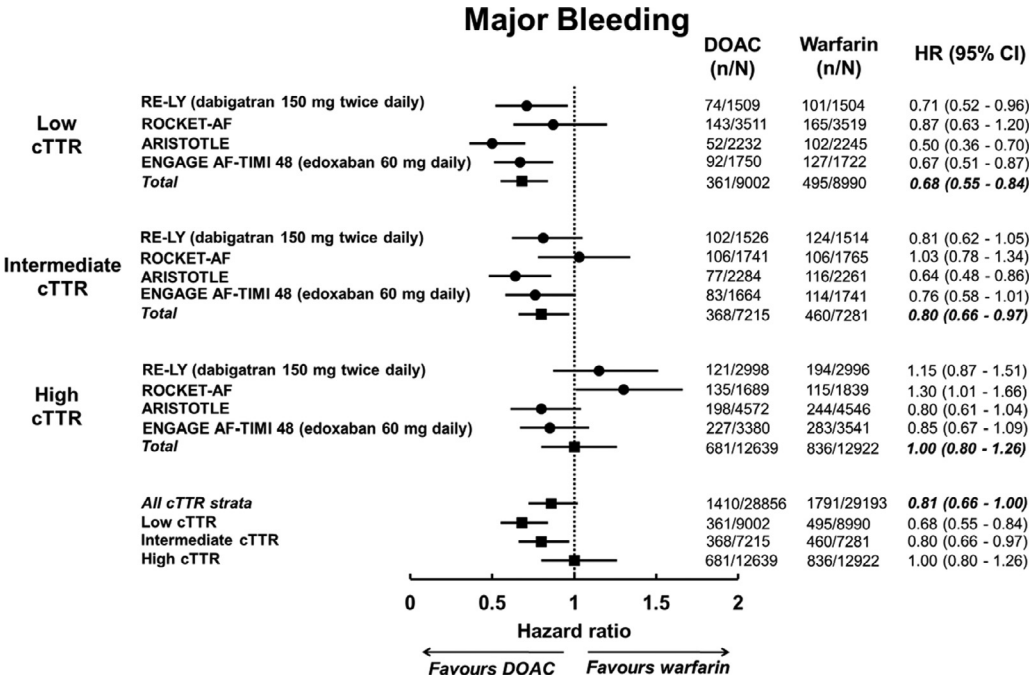

Figure 3. Pooled major bleeding risk between patients treated with DOAC and warfarin, stratified by cTTR. CI = confidence interval; cTTR = center-based time in therapeutic range; DOAC = direct oral anticoagulant; HR = hazard ratio.

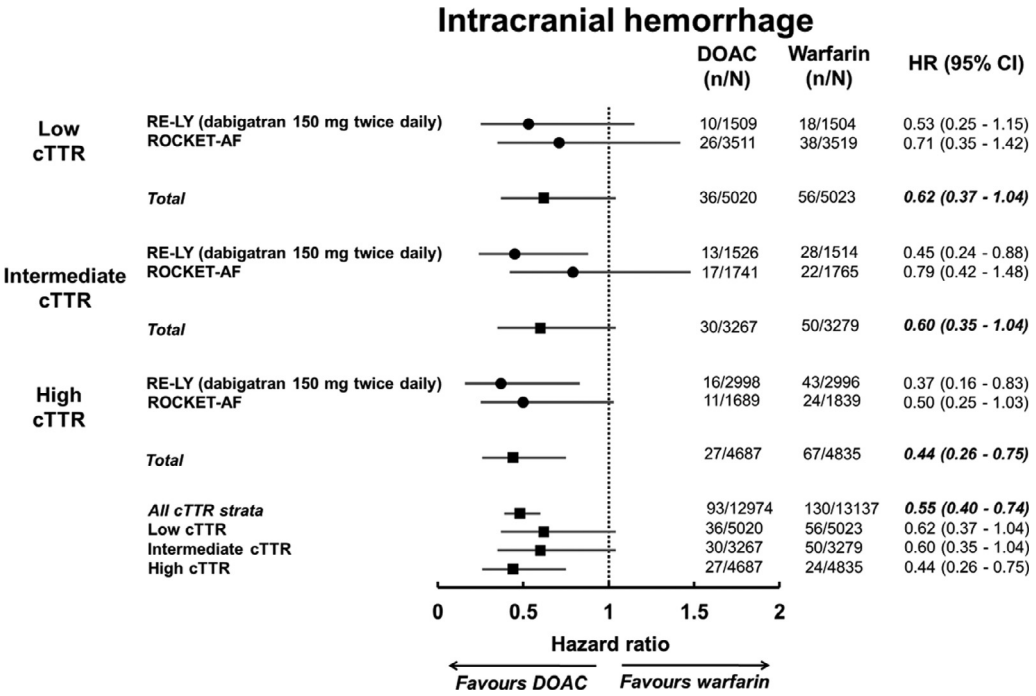

Figure 4. Pooled intracranial hemorrhage risk rates between patients treated with DOAC and warfarin stratified by cTTR. CI = confidence interval; cTTR = center-based time in therapeutic range; DOAC = direct oral anticoagulant; HR = hazard ratio.

CI; 0.40 to 0.74). The RE-LY and ROCKET-AF trials reported ICH outcomes according to cTTR. There was a trend for lower risk of ICH for DOAC agents compared with warfarin in the low and intermediate cTTR strata (Figure 4). A statistically significant reduction of ICH in favor of DOAC was observed in the high cTTR stratum (HR 0.44, 95% CI 0.26 to 0.75; Figure 4). No effect modification was observed between the low and high cTTR subgroups ($P_{interaction} = 0.37$).

We performed sensitivity analyses by including subjects randomized to lower doses of dabigatran (110 mg twice daily) and edoxaban (reduced doses of 30 mg daily or 15 mg daily). Inclusion of the lower-dose arms did not affect the overall benefit of DOAC agents over warfarin in reducing the risk of SSE, major bleeding, and ICH (Supplementary Table 4). The overall results of this sensitivity analyses are consistent with those reported in the primary analysis.

Discussion

Our meta-analysis showed that DOAC agents were superior over warfarin in reducing thromboembolic risk across all cTTR strata. In terms of major bleeding, while DOACs were beneficial over warfarin for patients in the low cTTR stratum, this was not observed among patients in the high cTTR stratum (cTTR ≥66%). There was a trend for lower risk of ICH among patients treated with DOAC when compared with warfarin in the low and intermediate cTTR strata. A statistically significant reduction of ICH risk was observed among DOAC-treated patients in the high cTTR stratum when compared with warfarin. Overall, these results support the finding that DOAC agents are superior to warfarin even among AF patients with good INR control.

Prior studies showed that anticoagulation intensity outside the therapeutic range (INR 2.0 to 3.0) was associated with higher risk of thromboembolism or bleeding.[19,20] In clinical practice, there remains a perception that warfarin-treated patients with good INR control (i.e., high TTR) may not derive as much benefit from DOACs as those with poorer INR control, as reflected by lower TTRs. If so, it can be argued that warfarin-treated patients with good INR control may not require switching to DOAC agents if the magnitude of benefit is similar regardless of the type of oral anticoagulant prescribed. However, our meta-analysis demonstrated consistent thromboembolic protective benefit in favor of DOACs over warfarin across all 3 cTTR strata, even for patients with seemingly good INR control (i.e., cTTR >66%)

Our work differed from a previous meta-analysis on the same topic by Carmo et al.[21] A key distinction between our study and Carmo's analysis was the INR cut-offs employed to define high, intermediate, and low cTTR. The cTTR cut-offs published among the 4 RCTs varied considerably (Table 1). Due to the marked differences in cTTR cut-offs among the 4 trials, it was not possible to simply report the pooled results based on quartiles as presented by the individual trials. We believed that the optimal way to harmonize these cTTR differences was to re-stratify them into tertiles as used in our analysis. On the other hand, the cut-offs employed by Carmo et al. (<60%, ≥60% to 70%, and >70%) resulted in exclusion of 1,676 patients in the highest cTTR (>65.8%) quartile of the ROCKET-AF trial. Our study expands on Carmo's work by demonstrating that re-stratification of cTTRs without excluding any patients enrolled in the 4 RCTs led to more precise estimates of the aggregate data. Furthermore, from an open-access FDA regulatory document, we obtained major bleeding rates from ROCKET-AF.[16] This allowed us to report the pooled

rates of major bleeding between DOAC versus warfarin at varying levels of INR control, a missing aspect in Carmo's analysis.[21]

Of note, we could only examine outcomes in relation to cTTR instead of individual-based TTR (iTTR). Center-based TTR might also reflect practice variations and differences in patient characteristics, potentially introducing confounding. For example, a low cTTR could indicate a site which preferentially enrolled more medically complex patients with greater co-morbidities than sites with high cTTR. If this was the case, then the higher risk of SSE and bleeding observed among warfarin-treated patients with low cTTR would not be entirely explained by having poorer INR control. This concept was supported by Shimada et al. which examined regional differences in clinical outcomes among East Asian patients from Japan, Korea, China, and Taiwan enrolled in the ENGAGE AF TIMI-48 trial.[22] The major finding was that the relative risk reduction of edoxaban over warfarin was greater in Korea, China, and Taiwan than in Japan. After multivariable adjustment, the authors concluded that this difference was related to a higher risk of SSE and bleeding in the warfarin arms of Korea, China, and Taiwan when compared with Japan. The reasons for these heightened event rates were in part related to sicker patients being enrolled, higher composition of warfarin-naïve patients, and lower TTR levels in the 3 countries. Another potential criticism with the use of cTTR is that it is subject to ecological effects and may not necessarily reflect iTTR. However, the ARISTOTLE TTR subanalysis showed a near perfect correlation between cTTR and iTTR after adjustment of a number of baseline factors, suggesting that these 2 measures of INR control could be used interchangeably.[13]

This analysis has a number of important limitations. First, we conducted a post hoc analysis of RCTs. As such, our results are subject to potential confounding and should be considered hypothesis-generating. Second, we did not have access to patient-level data to explore why high degrees of heterogeneity were observed in some analyses, but we do not expect the overall conclusions to be markedly altered by this limitation. Third, we did not have access to ICH outcomes stratified by TTR in 2 RCTs (ARISTOTLE and ENGAGE AF-TIMI 48), which limited our analysis. Finally, our results do not apply to AF patients with bioprosthetic valves, moderate or severe mitral stenosis, or transcatheter-based valve replacements since these patient subsets were under-represented in the RCTs.

In conclusion, this meta-analysis demonstrated that the incremental protective effect on SSE conferred by DOAC agents over warfarin was observed regardless of INR control. Even among patients in the high cTTR stratum, warfarin did not exhibit a better safety profile than DOAC agents in terms of major bleeding and ICH. These findings support the use of DOAC over warfarin for stroke prevention among patients with AF and well-managed INR levels.

Author Contribution

Joseph J. Lee: Conceptualization, Methodology, Investigation, Writing − original draft, Writing − review and editing, Visualization. Andrew C. T. Ha: Conceptualization, Methodology, Formal analysis, Investigation, Writing − original draft, Writing − review and editing, Visualization, Supervision, Project administration, Resources. Paul Dorian: Writing − review and editing. Maya Verma: Writing − review and editing. Shaun G. Goodman: Writing − review and editing. Jan O. Friedrich: Methodology, Formal analysis, Writing − review and editing.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2020.10.064.

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