# Meta-Analysis of Direct-Acting Oral Anticoagulants Compared With Warfarin in Patients >75 Years of Age

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**Older patients with atrial fibrillation (AF) are at higher risk of thromboembolic events and oral anticoagulant (OAC)-related bleeding complications. This meta-analysis evaluates the efficacy and safety of direct-acting OACs (DOACs) compared with warfarin in older patients with nonvalvular AF. PubMed, Embase, and Cochrane Central databases were searched for randomized controlled trials assessing the efficacy and safety of DOACs compared with warfarin in AF patients who were >75 years old. Treatment effects and relevant standard errors were calculated from the available data. These values were imputed in software R to perform meta-analysis through generic inverse variance method. Additionally, we performed a network meta-analysis to compare the relative efficacy and safety of each OAC. Five substudies of randomized controlled trials, comprising 28,135 older participants, were included in the analysis. DOACs as a group were found to have superior efficacy compared with warfarin in reducing stroke or systemic embolization (hazard ratio 0.76, 95% confidence intervals 0.67 to 0.86, p <0.01). The rate of major bleeding was similar, but intracranial hemorrhage was significantly lower in patients randomized to a DOAC (hazard ratio 0.48, 95% confidence intervals 0.34 to 0.67, p <0.01). Apixaban was the only DOAC that significantly reduced all 3 outcomes of systemic embolization, major bleeding, and intracranial hemorrhage compared with warfarin (by 29%, 36%, and 66%, respectively). In conclusion, DOACs were found to be safer and more effective than warfarin for the treatment of nonvalvular AF in older patients. Apixaban appears to provide the best combination of efficacy and safety in this population.**  **(Am J Cardiol 2019;123:2051−2057)**

Atrial fibrillation (AF) is a frequently encountered condition in older adults.[1,2] Long-term anticoagulation with warfarin has been shown to reduce the risk of stroke and systemic embolization (SSE) in AF,[3] yet fewer than half of the anticoagulation-eligible patients with AF are prescribed an oral anticoagulant (OAC).[4] Much of this underutilization is seen in the older population, in whom the risk of bleeding also increases with the use of an OAC. Over 40% of the patients included in the pivotal randomized controlled trials (RCTs) of these agents were >75 years of age,[5−8] and post hoc analyses of these trials have demonstrated the safety and efficacy of direct-acting OACs (DOACs).[9−12] However, none of the reported trials have compared the relative efficacy and safety of the individual DOACs to each other in older patients with AF. In addition, an analysis of DOACs as a class versus warfarin in this subgroup might yield additional valuable information. Accordingly, the objectives of this meta-analysis were to answer these questions by pooling the data from available RCTs in AF patients >75 years of age.

## Methods

A literature search was performed in PubMed, Embase, and Cochrane Central through December 12, 2018. The keywords utilized were "nonvitamin K antagonist oral anticoagulants" or "direct oral anticoagulants" or "dabigatran" or "rivaroxaban" or "apixaban" or "edoxaban" AND "stroke" or "systemic embolism" or "major bleeding" or "intracranial hemorrhage," with the limits for humans and RCTs activated. No restriction for language or publication year was used. The studies were electronically and manually deduplicated before title and abstract screening by 2 independent investigators (AM and SY). (see Figure 1) Once identified, full manuscripts were extracted and were considered for inclusion if they had comparative data for older patients >75 years of age who were treated with DOACs or warfarin. We adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines throughout all the stages of design and implementation (Appendix Table 1). The relevant data regarding the investigator's name, publication year, study design, population characteristics, treatments, and length of follow-up were collected from the final list of studies. The outcomes of interest were SSE, major bleeding, and intracranial hemorrhage (ICH). The odds ratios with their corresponding confidence intervals (CIs) were used to calculate the relative treatment effects and standard errors. Software R version 3.5.1 (R Development Core Team, 2010) was used with random-effects DerSimonian-Laird estimator for tau[2] to generate the pooled hazard ratio (HR) with 95% CI. A frequentist

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Funding: None.

See page 2057 for disclosure information.

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0002-9149/
https://doi.org/10.1016/j.amjcard.2019.02.060

network meta-analysis was performed. The details of statistical analyses are explained in the online supplementary appendix.

## Results

Our initial search yielded 1,409 articles. After electronic deduplication, 1,113 studies remained. A further title and the abstract review led to the exclusion of the least relevant articles, and 13 articles were selected for the final full-text review (Figure 1). On full-text review, 5 RCTs, including 27,639 older patients with nonvalvular AF randomized to a DOAC or warfarin, were selected for meta-analysis.[9–13] Table 1 shows the baseline characteristics in the trials.

Figure 2 depicts the forest plot of the comparison between DOACs and warfarin for the outcome of SSE. In patients >75 years of age, DOACs significantly reduced the risk of SSE by 24% (HR 0.76, 95% CI 0.67 to 0.86, p <0.01). Heterogeneity was low among the trials for this end point ($I^2 = 0\%$).

Figure 3 shows the forest plot of the comparison between DOACs and warfarin for the outcome of major bleeding. There was no significant difference between DOACs and warfarin for the outcome of major bleeding (HR 0.95, 95% CI 0.74 to 1.23, p = 0.69). Significant heterogeneity was noticed among the trials for this end point ($I^2 = 84\%$). The source of significant heterogeneity is possibly the differential effects of various DOACs on the

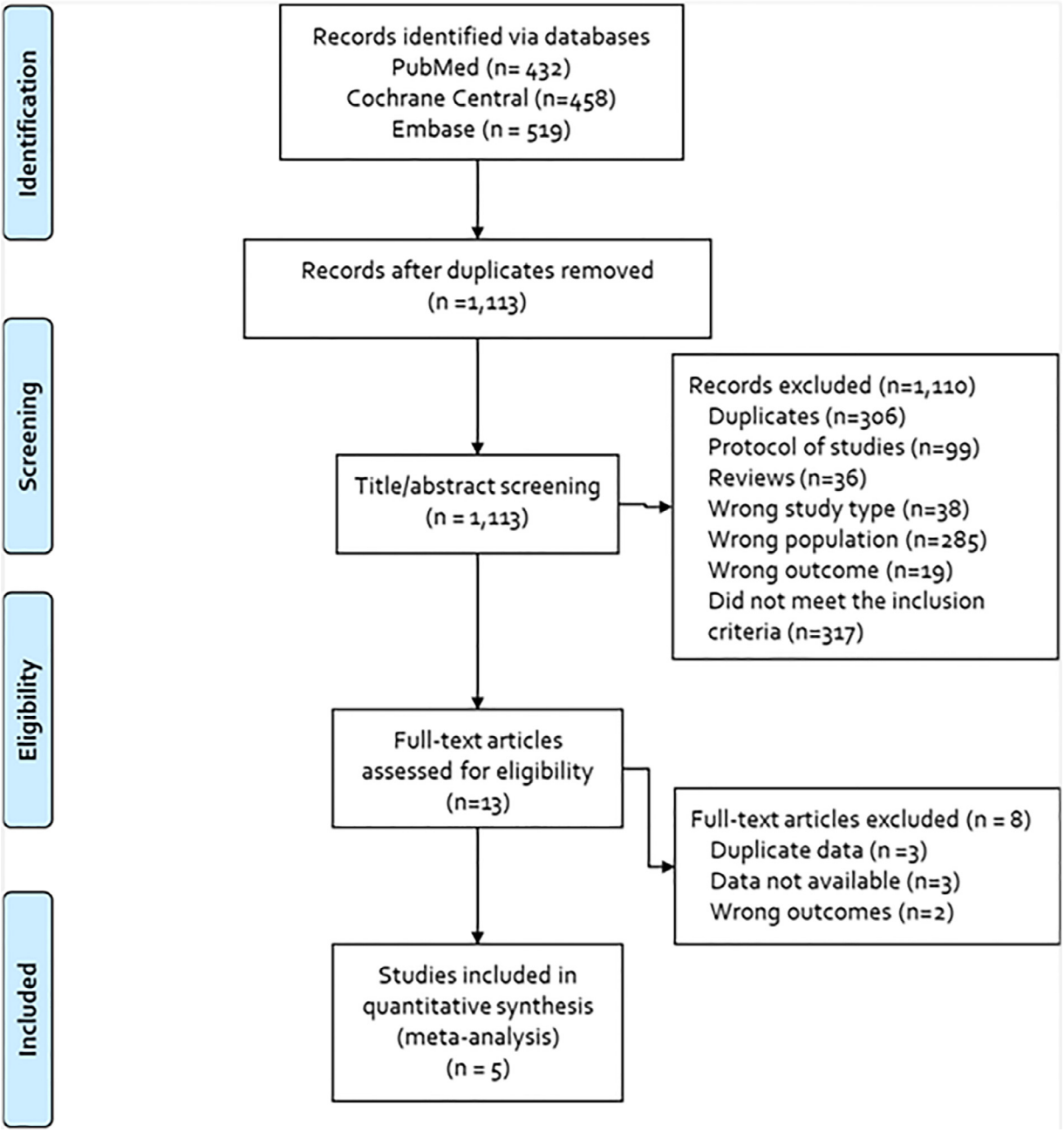


Figure 1. PRISMA diagram for search strategy and studies selection.

Table 1
Baseline characteristics in randomized trials for treatment of atrial fibrillation in patients >75 years of age

| | RE-LY, 2009 | ARISTOTLE, 2011 | ROCKET AF, 2011 | ENGAGE AF-TIMI, 2013 | J-ROCKET AF, 2012 |
|---|---|---|---|---|---|
| Study design | Open label RCT | Double blind RCT | Double blind RCT | Double blind RCT | Double blind RCT |
| Post hoc studies in older | Eikelboom et al.[11] | Halvorsen et al.[12] | Halperin et al.[9] | Kato et al.[10] | Hori et al.[13] |
| Interventions vs Warfarin | Dabigatran 110 and 150 mg | Apixaban 2.5-5 mg | Rivaroxaban 20 mg | Edoxaban 60 mg | Rivaroxaban 15 mg |
| Number of Participants | 7,258 | 5,678 | 6,229 | 8,474 | 498 |
| Median Follow-up (years)* | 2.0 | 1.8 | 1.9 | 2.8 | 1.9 |
| Median TTR | 67%* | 66%* | 58%* | 70% | 65%* |
| Mean CHADS2 score | 2.2* | 2.7 | 3.7 | 2.9 | 3.25* |
| Mean HAS-BLED score* | NA | NA | 2.8 | 3.2 | NA |
| Median age (years) | NA | NA | 79 | NA | 79 (mean) |
| Female | 36.4%* | 42.2% | 46.2% | 45.0% | 27.2% |
| Hypertension | 78.9%* | 83.0% | 92.7% | 93.0% | 82.3% |
| Heart failure | 31.9%* | 24.3% | 58.6% | 45.0% | 46.7% |
| Previous stroke, TIA or systemic embolization | 20.0%* | 21.8% | 41.6% | 25.0% | 51.4% |
| Diabetes Mellitus | 23.3%* | 21.1% | 33.8% | 28.0% | 30.7% |

RCT = randomized controlled trial; TTR = time in therapeutic range; TIA = transient ischemic attack; NA = not available
* For the overall study cohort.

outcome of bleeding because some DOACS are more commonly known to be associated with higher risk of bleeding such as rivaroxaban.

The forest plot of the comparison between DOACs and warfarin for the outcome of ICH is shown in Figure 4. DOACs significantly reduced the ICH risk by 52% compared with warfarin (HR 0.47, 95% CI 0.34 to 0.67; p <0.01). There was a moderate amount of heterogeneity for this end point ($I^2 = 46\%$).

Funnel, bias and Baujat plots were made as shown in the supplementary online material for all outcomes. There was a lack of small study effects due to the reasonable spread of the studies. Detailed analysis demonstrated a lack of a significantly influential study.

Figure 5 displays the efficacy of individual DOACs compared with each other and with warfarin among older patients with AF using a network meta-analysis model. Each of the DOACs had similar efficacy for the prevention of SSE. Apixaban and dabigatran 150 mg demonstrated superior efficacy to warfarin.

Figure 6 displays the results of the network meta-analysis for the end point of major bleeding. Apixaban was associated with lower rates of major bleeding than all the other DOACs, and along with edoxaban 60 mg was associated with significantly lower rates of major bleeding compared with warfarin.

Figure 7 displays the results of the network meta-analysis for the end point of ICH. Rivaroxaban was associated with an increased risk of ICH compared with each of the other DOACs, which were otherwise similar to each other. All of the DOACs except rivaroxaban were superior to warfarin for the risk of ICH. Figure 8 is the central diagram depicting an overall summary of the results of this study.

Table 2 shows the rankings for each of the OACs for the 3 analyzed outcomes in the older AF patients. This metric suggests that apixaban provides the best combination of efficacy and safety when compared with other DOACs and to warfarin.

## Discussion

In this comprehensive meta-analysis of data from RCTs evaluating the safety and efficacy of DOACs compared with warfarin, we report novel and important findings in the subgroup of older AF patients. First, DOACs as a class were superior to warfarin with respect to both efficacy and safety; second, individual DOACs demonstrated similar efficacy to each other in the prevention of SSE; third,

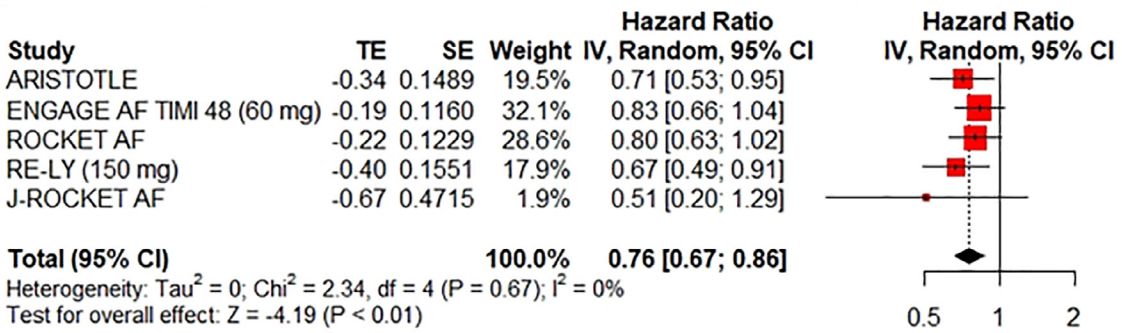


Figure 2. Stroke or systemic embolization with DOACs compared with warfarin in patients >75 years with AF.

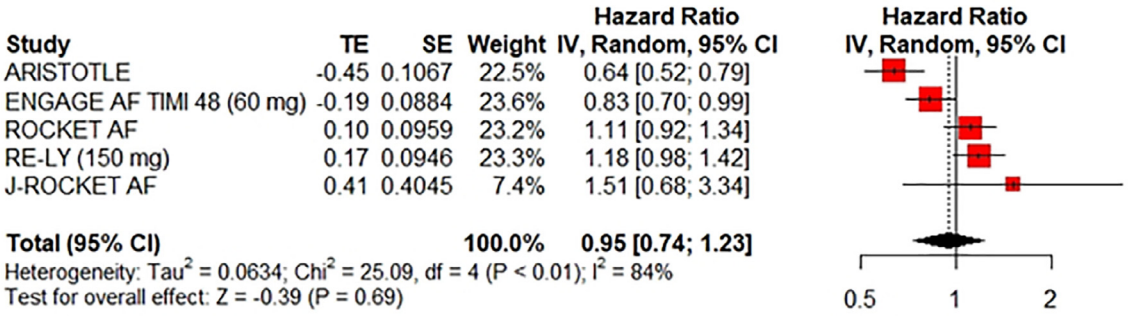


Figure 3. Major bleeding with DOACs compared with warfarin in patients >75 years with AF.

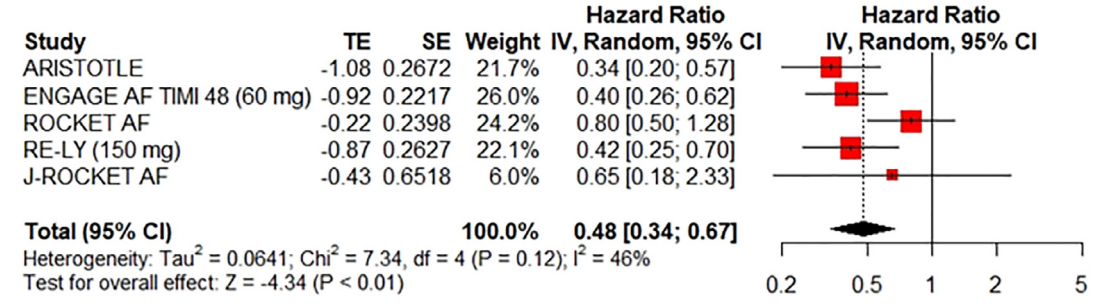


Figure 4. Intracranial hemorrhage with DOACs compared with warfarin in patients >75 years with AF.

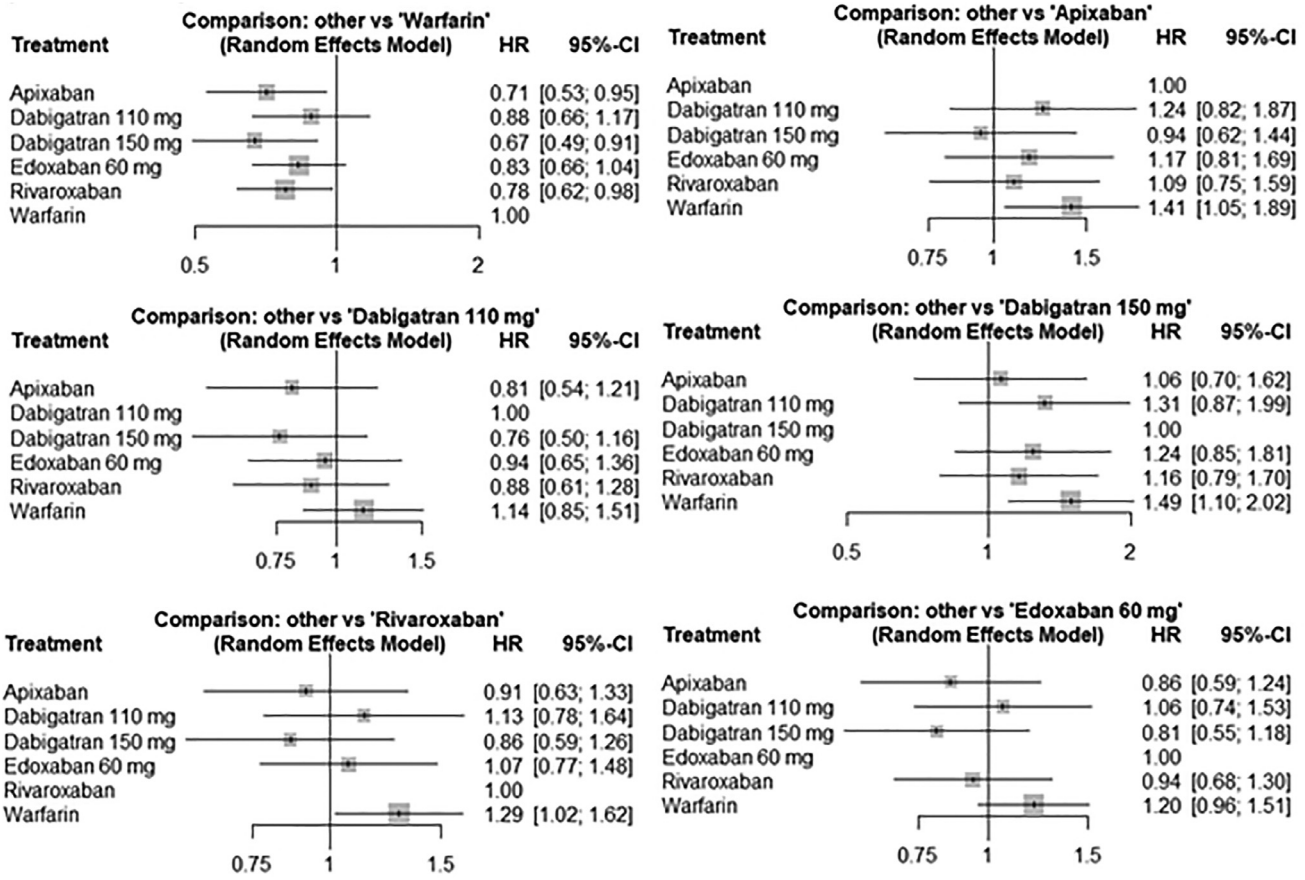


Figure 5. Relative comparison of oral anticoagulants for stroke or systemic embolization in patients >75 years with AF.

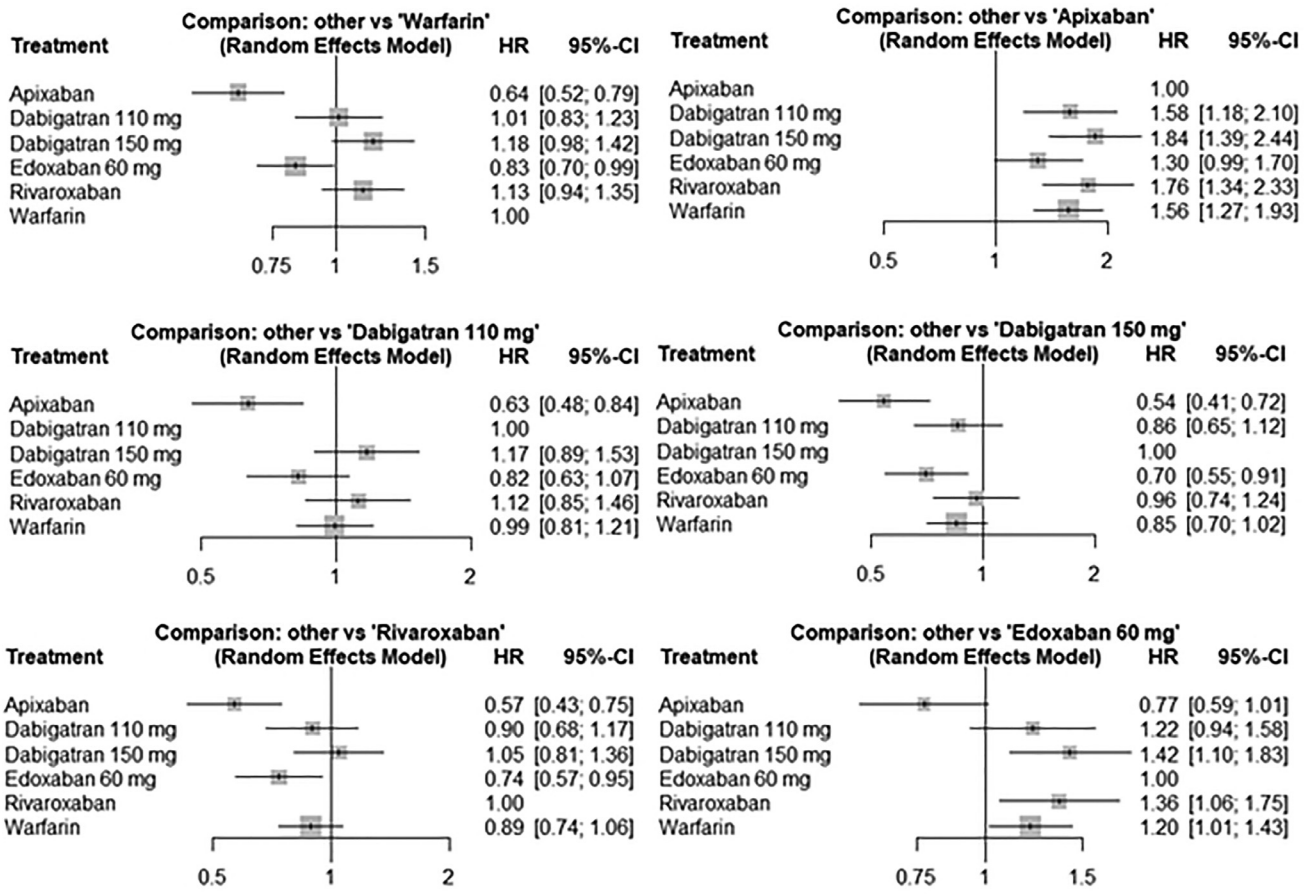


Figure 6. Relative comparison of oral anticoagulants for major bleeding in patients >75 years with AF.

apixaban was associated with the lowest risk of major bleeding; fourth, apixaban, edoxaban, and dabigatran were associated with lower rates of ICH than either rivaroxaban or warfarin; and last, apixaban appeared to offer the most favorable combination of efficacy and safety in older patients with nonvalvular AF.

The implications of our findings are substantial. Historically, warfarin has been substantially underutilized in the older population with AF, despite its proved efficacy in stroke prevention. This reluctance to prescribe warfarin has largely been attributed to concerns regarding the risk of bleeding, due in part to the unpredictability of warfarin's anticoagulant effects. Increasing age complicates this matter, with additional difficulties relating to poor adherence, cognitive impairment, decreased risk, drug interactions, and polypharmacy.[14] DOACs, as we have shown, are both more effective and safer than warfarin in older patients, and in particular are associated with a marked reduction in the most feared complication of anticoagulation, which is ICH.

Additional benefits of DOACs include rapid onset and offset, limited dietary, and drug interactions, and no requirement for routine monitoring. DOACs also simplify the practice of bridging anticoagulation which can substantially reduce the length of hospital stays in older patients. Furthermore, the recent development of specific and highly effective reversal agents for certain DOACs may serve to enhance prescriber comfort with these agents.[15–17] Taken together, these benefits of DOACs may be expected to encourage greater adoption of OAC use among older patients with AF.

Our findings are consistent with those of a previous meta-analysis assessing the efficacy and safety of DOACs in older patients.[18] However, this previous analysis had significant limitations: (1) inclusion of studies of both AF and venous thromboembolism; (2) inclusion of short-term phase II trials; and (3) inclusion of comparators other than warfarin. Our current analysis overcomes each of these limitations, thereby providing a more robust evaluation of the comparison of DOACs and warfarin in older patients with AF. Also, to the best of our knowledge, we are the first to use network meta-analysis techniques to perform individual DOAC comparisons in this patient population.

A significant limitation of our study is the absence of trials with head-to-head comparisons between different DOAC agents; therefore, all the comparisons made between them were indirect. Nevertheless, our study using the accepted techniques of network meta-analysis adds essential information to a significant gap in the literature, particularly considering that direct head-to-head trials are unlikely to be initiated in the foreseeable future. One trial included in the analysis used an open-label design; this along with other differences in study design, and different mechanism of action of dabigatran compared with other DOACs may affect the cross-study comparisons. For our network

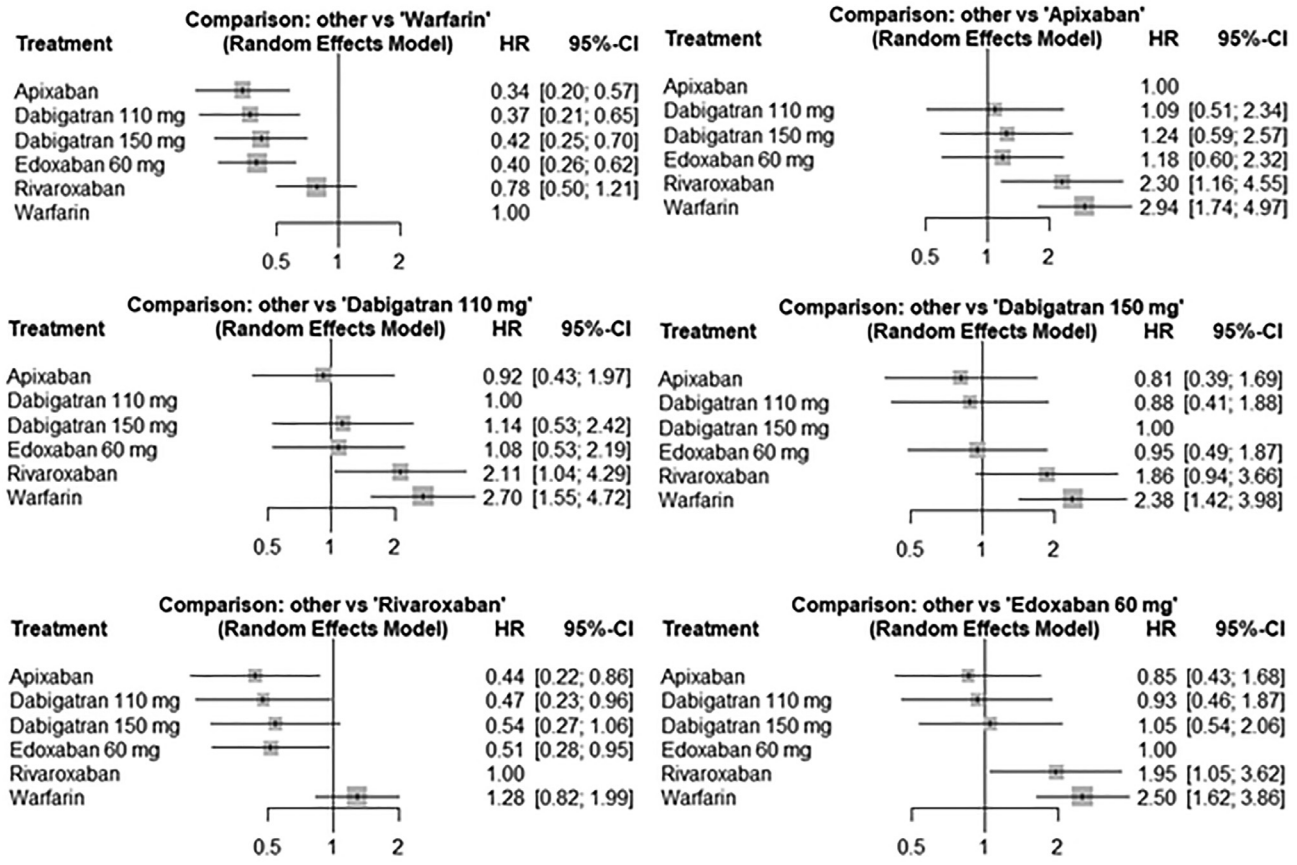


Figure 7. Relative comparison of oral anticoagulants for intracranial hemorrhage in patients >75 years with AF.

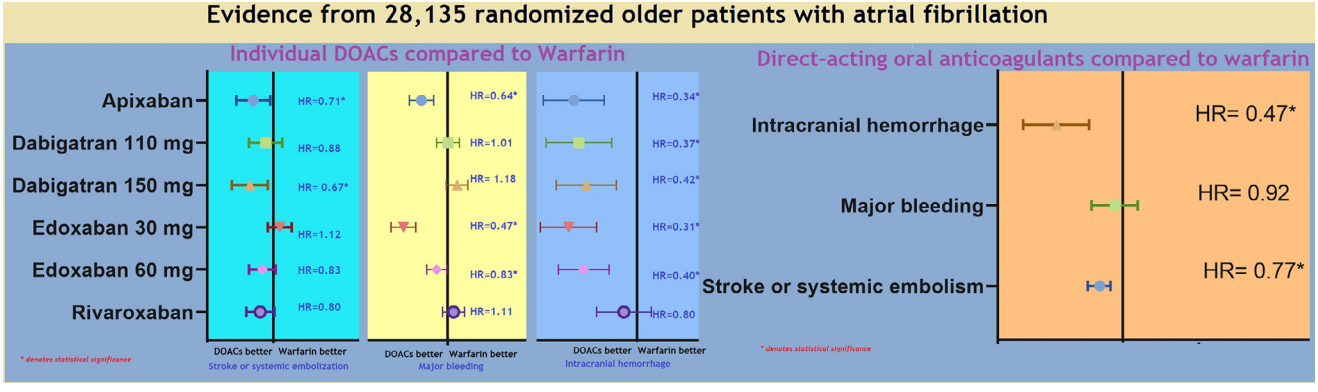


Figure 8. Central summary diagram.

Table 2
Ranking of oral anticoagulants based on p scoring system in patients >75 years of age with atrial fibrillation

| | Stroke or systemic embolization | Major bleeding | Intracranial hemorrhage |
|---|---|---|---|
| Apixaban | 2 (74%) | 1 (99%) | 1 (79%) |
| Dabigatran 150 mg | 1 (83%) | 6 (11%) | 4 (61%) |
| Edoxaban 60 mg | 4 (45%) | 2 (79%) | 3 (65%) |
| Rivaroxaban | 3 (58%) | 5 (19%) | 5 (19%) |
| Dabigatran 110 mg | 5 (34%) | 4 (44%) | 2 (72%) |
| Warfarin | 6 (6%) | 3 (48%) | 6 (0.3%) |

analysis, we had to assume transitivity despite a lack of relevant detailed data on demographics and comorbidities. Our results represent the best available evidence especially because a dedicated trial with a head-to-head comparison among DOACs is unlikely. Finally, although our analyses are based on RCTs, they are post hoc subgroup analyses, and therefore our findings must be considered as hypothesis-generating.

In conclusion, DOACs appear to reduce the risk of SSE to a greater extent than warfarin in patients >75 years of age with nonvalvular AF, whereas also being associated

with a markedly reduced risk of ICH. When compared with other DOACs and with warfarin, apixaban appears to offer the best combination of efficacy and safety. Dedicated randomized trials in older patients with AF are required to confirm these findings.

## Disclosures

None of the authors have any conflicts of interest or funding sources to disclose.

## Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2019.02.060.


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