New Oral Anticoagulants in Elderly Adults: Evidence from a Meta-Analysis of Randomized Trials

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OBJECTIVES: To evaluate the efficacy and safety of new oral anticoagulants (NOACs) in elderly adults.

DESIGN: Meta-analyses of randomized clinical trials (RCTs).

SETTING: PubMed, Cochrane Library, EMBASE, Web of Science, and CINAHL databases were searched from January 1, 2001, through March 30, 2013.

PARTICIPANTS: Elderly population (≥75) in RCTs comparing NOACs (rivaroxaban, apixaban, and dabigatran) with conventional therapy.

MEASUREMENTS: Two authors reviewed the trials, and odds ratios (ORs) were calculated using a random effects model.

RESULTS: Ten RCTs included 25,031 elderly participants. Risk of major or clinically relevant bleeding was not significantly different between NOACs and conventional therapy in elderly adults (OR = 1.02, 95% confidence interval = 0.73–1.43). Similar results were observed when comparing NOACs and pharmacologically active agents. In atrial fibrillation (AF) trials, NOACs were more effective than conventional therapy in prevention of stroke or systemic embolism in an elderly population with AF. In non-AF trials, NOACs also had a significantly lower risk of venous thromboembolism (VTE) or VTE-related death than conventional therapy in elderly adults. Analysis for individual NOACs showed that the NOAC was noninferior or more effective than conventional therapy for efficacy and safety outcomes.

CONCLUSION: In participants of clinical trials aged 75 and older, NOACs did not cause excess bleeding and were associated with equal or greater efficacy than conventional therapy. **J Am Geriatr Soc 62:857–864, 2014.**

Key words: new anticoagulants; elderly; meta-analysis

The prevalence of arterial and venous thromboembolic diseases increases with age.[1–3] For individuals aged 80 to 90, risk of atrial fibrillation (AF) related stroke also increases with age; in the Framingham Study, 23.5% of strokes in individuals aged 80 and older were attributable to AF.[4] Age 75 and older is considered a risk factor in stroke risk-stratification schemes and contributes 1 point toward a maximum risk score of 6 in the cardiac failure, hypertension, age, diabetes, stroke ($CHADS_2$) scheme.[5,6] In the CHA_2DS_2-VASc score, aged 75 and older contributes 2 points toward a maximum score of 9.[5,7] The prevalence of other risk factors, including hypertension, prior stroke, diabetes mellitus, and heart failure is also higher in elderly adults.[3,8] Aging is regarded as one of the strongest and most prevalent risk factor for venous thromboembolism (VTE).[2,9] Previous studies have showed that conventional risk factors, malignant disease, and the presence of comorbidities in elderly adults increase the risk of VTE and bleeding and might complicate anticoagulation treatment.[2,9] Anticoagulants such as heparin and vitamin K antagonists remain the mainstay for the treatment of arterial and venous thromboembolic diseases, although they have potential limitations.[10,11] Recently, new oral anticoagulants (NOACs) such as rivaroxaban, dabigatran, and apixaban have been developed as an alternative to conventional anticoagulants,[12,13] but the efficacy and safety profiles of NOACs have not been established in elderly adults,[1,3,14] and there are particular concerns regarding bleeding with NOACs in elderly adults. The suggested predisposing factors are low body mass index in frail and the oldest-old adults, altered body composition of muscle and fatty tissue, and high frequency of renal impairment.[3,14] Recent reports suggest a higher potential risk of bleeding with NOACs in older individuals.[15–17] No randomized trial has specifically randomized elderly adults to compare NOACs with vitamin K antagonists or

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low-molecular-weight heparin (LMWH) as the population of primary interest.

The objectives of the present meta-analysis were to evaluate the efficacy and safety of NOACs in elderly adults based on existing trials of stroke prevention in individuals with AF and with VTE and acutely medically ill individuals. For the meta-analysis for major or clinically relevant bleeding, all trials were analyzed for this safety endpoint. Only AF trials were included in the meta-analysis for the stroke and systemic embolism endpoint; non-AF trials examined for the VTE efficacy meta-analysis.

MATERIALS AND METHODS

Data Sources and Searches

A systematic search of relevant articles published through March 30, 2013, was performed in the PubMed, Cochrane Library, EMBASE, Web of Science, and CINAHL databases. The search terms and corresponding Medical Subject Headings "new oral anticoagulants," "oral thrombin inhibitors," "oral factor Xa inhibitors," "apixaban," "dabigatran," and "rivaroxaban" were used.

Study Selection

Studies were included in the meta-analysis if they were randomized clinical trials (RCTs) of participants comparing NOACs (rivaroxaban, apixaban, dabigatran) with conventional therapy (vitamin K antagonists, LMWH, aspirin, placebo) and reporting specific data for elderly adults. The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement was followed.[18]

Data Extraction and Quality Assessment

Two authors (PS, SC) independently reviewed the trials for eligibility and risk of trial bias and extracted data. The risk of bias was assessed using the Cochrane Collaboration tool.[19] When more than one dose of the study drug was used in a single trial, the data related to particular outcome for all doses were added. Separate sensitivity analyses were performed for two doses of dabigatran (150 and 110 mg twice a day).

Data Synthesis and Analysis

Outcome Measures

The safety outcome was major or clinically relevant bleeding. The efficacy outcome of interest was VTE or VTE-related death and stroke or systemic embolism. For trials reporting only major bleeding, the same data were used for major or clinically relevant bleeding. The definition of major bleeding was according to the International Society on Thrombosis and Haemostasis (ISTH) criteria.[20] Data from individual trials with the longest follow-up were incorporated into the analysis. In trials that did not report raw event rates or sample size, the event rates or sample sizes were calculated using mean or median follow-up period, and the results were rounded off to whole numbers for the analysis, and the intention-to-treat principle was used whenever applicable.

Statistical Analysis

Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for each trial and pooled in random-effects models. The statistical analysis was performed according to recommendations from the Cochrane Collaboration and the PRISMA statement.[18] The I^2 statistic was calculated to identify the proportion of inconsistency between trials.[21] I^2 less than 25% was considered to indicate low heterogeneity and I^2 greater than 75% to indicate high heterogeneity.

Publication bias was tested using the Egger regression test and through visual inspection of the asymmetry in funnel plots. A two-tailed alpha level of .05 was set as the threshold for statistical significance. The analysis was performed using RevMan 5.2.4 software (Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen, Denmark).

Subgroup Analysis and Sensitivity Analysis

Subgroup analyses were performed based on the individual NOAC evaluated, the indication for anticoagulation, the conventional therapy (warfarin, LMWH, LMWH followed by VKA). Sensitivity analyses were performed for various subgroups based on study design, blinding, different doses of dabigatran, and risk of bias.

Follow-Up Adjusted Analysis

To adjust for the different lengths of follow-up for individual trials and to account for censored data, the rate of major or clinically relevant bleeding as person years was used to calculate the log rate ratio of NOACs versus conventional therapy in individual trials. A random-effects Poisson regression model was used, and data from trials with the longest follow-up were used for this analysis.

RESULTS

The results of the literature search are presented in Figure 1. Ten randomized trials included a total of 25,031 elderly adults.[22–30] Five of the identified trials evaluated rivaroxaban, three apixaban, and two dabigatran. The indications for anticoagulation are listed in Table 1. Two trials were for treatment of acute VTE or pulmonary embolism and three for extended treatment of VTE. Four trials included individuals with AF, and one was for thromboprophylaxis in medically ill individuals. Only one trial with acute coronary syndrome reported data related to elderly adults, although the definition of safety outcome was different (thrombolysis in myocardial infarction bleeding instead of bleeding according to the ISTH criteria) and hence was excluded from the present analysis.[31] Another study for extended treatment of VTE did not report group-specific data for the elderly population.[29]

The basic baseline demographic characteristics of participants in the included trials are summarized in Table 1. The length of follow-up ranged from 35 days to 2 years. The risk of bias assessment showed overall good quality of the included trials, but reporting bias was common. Most of the trials with dabigatran did not report the bleeding

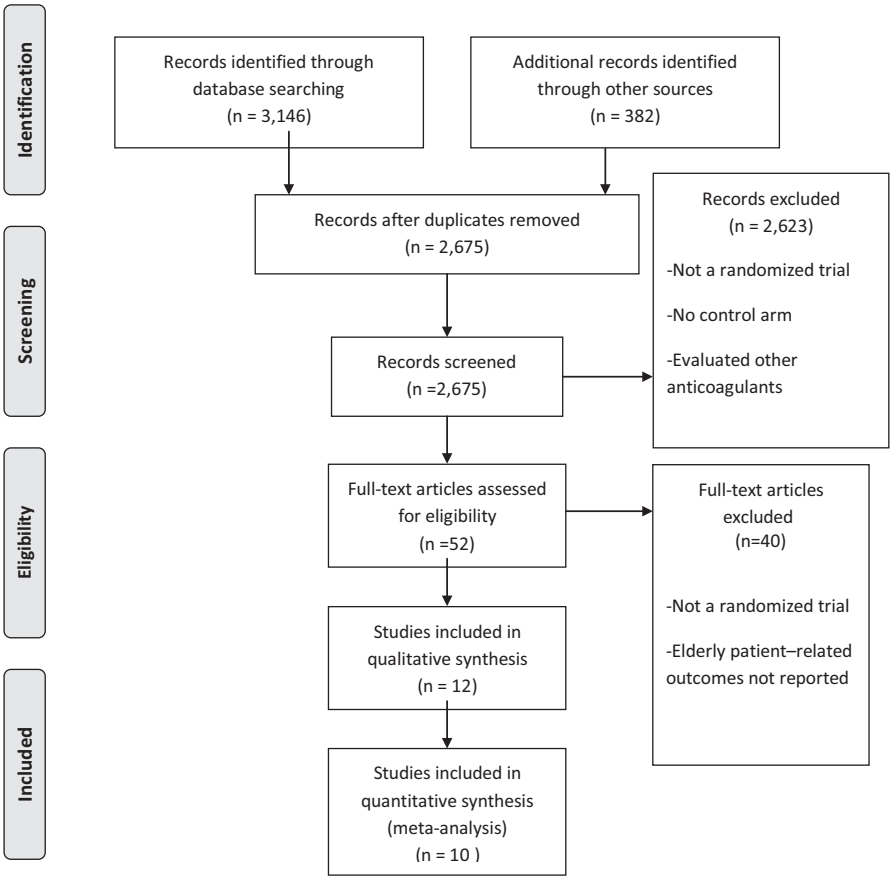

Figure 1. Search strategy and study selection according to the PRISMA checklist.

outcomes related to an elderly subgroup. Variables that might influence bleeding risk in elderly adults such as renal function and body mass index (BMI) were also not reported.

NOAC Use in Elderly Adults (≥75)

NOACs did not cause greater major or clinically relevant bleeding than conventional therapy in individuals aged 75 and older (6.4% with NOAC vs 6.3% with conventional anticoagulants; OR = 1.02, 95% CI = 0.73–1.43) (Figure 2). Similar results were observed with NOACs and pharmacologically active agents (6.4% vs 6.3%; OR = 0.98, 95% CI = 0.70–1.37). These results showed high heterogeneity (I^2 = 86%, P < .001), which the AF trials mainly contributed, although separate analysis for acute VTE trials did not show any heterogeneity (Supporting Information). NOACs also did not cause extra bleeding for treatment of acute VTE or pulmonary embolism, extended treatment of VTE, or AF except thromboprophylaxis for acutely ill medical individuals.

Risk of stroke and systemic embolism was significantly lower with NOACs than conventional therapy or pharmacologically active agents (3.3% vs 4.7%; OR = 0.65, 95% CI = 0.48–0.87; absolute risk reduction (ARR) = 1.4%, number needed to treat (NNT) = 71) (Figure 3).

NOAC also resulted in a significantly lower risk of VTE or VTE-related death than conventional therapy (3.7% vs 7.0%; OR = 0.45, 95% CI = 0.27–0.77; ARR = 3.3%, NNT = 30) (Figure 4) and pharmacologically active agents (3.9% vs 6.6%; OR = 0.61, 95% CI = 0.45–0.81; ARR = 2.6%, NNT = 38).

Effects of Individual NOACs

Rivaroxaban

Rivaroxaban did not cause greater major or clinically relevant bleeding than conventional therapy in elderly adults (4.5% vs 4.5%; OR = 1.18, 95% CI = 0.64–2.19). Rivaroxaban was noninferior to or more effective than conventional therapy in prevention of stroke or systemic embolism and VTE or VTE-related death.

Apixaban

The risk of major or clinically relevant bleeding was not higher with apixaban (5.1% vs 7.3%; OR = 0.80, 95% CI = 0.43–1.51) (Figure 2). Risk of stroke or systemic embolism and VTE or VTE-related death was equal to or lower than with apixaban than with conventional therapy.

Dabigatran

Safety data on dabigatran was more limited. Major or clinically relevant bleeding was similar with dabigatran and conventional therapy (9.3% vs 8.7%; OR = 1.07, 95% CI = 0.90–1.28) (Figure 2). Dabigatran was more effective than conventional agents in the prevention of

Table 1. Characteristics of Randomized Clinical Trials

Trial (Reference)	Intervention	Control	NOAC Group According to Age, n	Control Group According to Age, n	Age, NOAC/ Conventional Therapy[a]	Male,%, NOAC/ Conventional Therapy[a]	Follow-Up
Atrial fibrillation							
ROCKET-AF (2011)[25]	Rivaroxaban 20 mg once daily	Warfarin	>75 = 3,082[b]	>75 = 3,082[b]	73/73[d]	60.3/60.3	590 days (median)
ARISTOTLE (2011)[27]	Apixaban 5 mg twice daily	Warfarin	>75 = 2,743 65–75 = 3,504	>75 = 2,752 65–75 = 3,660	70/70[d]	64.5/65	1.8 years (median)
AVERROES (2011)[28]	Apixaban 5 mg twice daily	Aspirin 81–324 mg/d	>75 = 909 65–75 = 1,090	>75 = 983 65–75 = 942	70 ± 9/ 70 ± 10[c]	59/58	1.1 years
RE-LY (2009)[30]	Dabigatran 150 mg twice daily	Warfarin	>75 = 4,828 [b]	>75 = 2,360 [b]	71.4/71.6[d]	63.8/63.3	2.0 years (median)
Acute VTE or pulmonary embolism							
EINSTEIN (2010)[22]	Rivaroxaban 15 mg twice daily for 3 weeks, followed by 20 mg once daily	Enoxaparin/ VKA	>75 = 215 65–75 = 371	>75 = 225 65–75 = 382	55.8 ± 16.4/ 56.4 ± 16.3[c]	57.4/56.3	3, 6, or 12 months
EINSTEIN PE (2012)[23]	Rivaroxaban 15 mg twice daily for 3 weeks, followed by 20 mg once daily	Enoxaparin/ VKA	>75 = 441 65–75 = 517	>75 = 402 65–75 = 532	57.9 ± 7.3/ 57.5 ± 7.2[c]	54.1/51.7	3, 6, or 12 months
Extended treatment of VTE							
EINSTEIN-Extension (2012)[22]	Rivaroxaban 20 mg daily	Placebo	>75 = 89 65–75 = 153	>75 = 99 65–75 = 121	58.8/57.1[d]	73.1/74.2	6 or 12 months
AMPLIFY-EXT (2013)[26]	Apixaban 5 and 2.5 mg twice daily	Placebo	>75 = 220 65–75 = 318	>75 = 109 65–75 = 172	56.4/57.1[d]	58/56.5	12 months
RE-MEDY (2013)[29]	Dabigatran 150 mg twice daily (N = 1,430)	Warfarin	>75 = 140 65–75 = 303	>75 = 119 65–75 = 288	55.4 ± 15.0/ 53.9 ± 15.3[c]	60.9/61.1	6 to 36 months
Medically ill participants							
MAGELLAN (2013)[24]	Rivaroxaban 10 mg once daily	Enoxaparin 40 mg/d for 10 ± 4 days and oral placebo for 35 ± 4 days	>75 = 1,084 65–75 = 862	>75 = 1,149 65–75 = 842	71.0/71.0[d]	55.6/52.7	35 days

NOACs = new oral anticoagulants; VTE = venous thromboembolism; VKA = vitamin K antagonist.
[a]For overall population (including elderly and younger adults).
[b]Data for participants aged 65–75 not reported.
[c]Mean ± standard deviation.
[d]Median.

stroke or systemic embolism (3.2% vs 4.3%; OR = 0.75, 95% CI = 0.58–0.96 ARR = 1.1%, NNT = 95).

Subgroup Analysis According to Type of Conventional Anticoagulant

NOACs did not cause greater bleeding than warfarin (6.5% vs 7.1%; OR = 0.76, 95% CI = 0.51–1.12) or LMWH or LMWH followed by VKA (6.9% vs 5.3%; OR = 1.27, 95% CI = 0.54–2.98).

Sensitivity Analysis

The summary effect estimates were consistent with the primary analyses when analyses were repeated using a fixed-effects model. Sensitivity analyses with two different doses of dabigatran (110 and 150 mg twice a day) showed results similar to the primary analysis. Sensitivity analyses with various subgroups based on study design, blinding, and risk of bias also showed consistent results, similar to the current study's primary analysis.

Follow-Up Adjusted Analysis

The follow-up adjusted analysis showed that risk of major or clinically relevant bleeding was not significantly different with NOACs and conventional therapy in elderly adults (OR = 1.17, 95% CI = 0.73–1.9).

Publication Bias

There was no evidence of small study effects (publication bias) according to visual inspection of funnel plots and the Egger test.

DISCUSSION

There are several important findings in this meta-analysis of randomized trials evaluating the efficacy and safety of NOACs in elderly adults. First, NOACs did not lead to greater major or clinically relevant bleeding than conventional therapy and pharmacologically active agents in elderly adults. NOACs significantly reduced the risk of

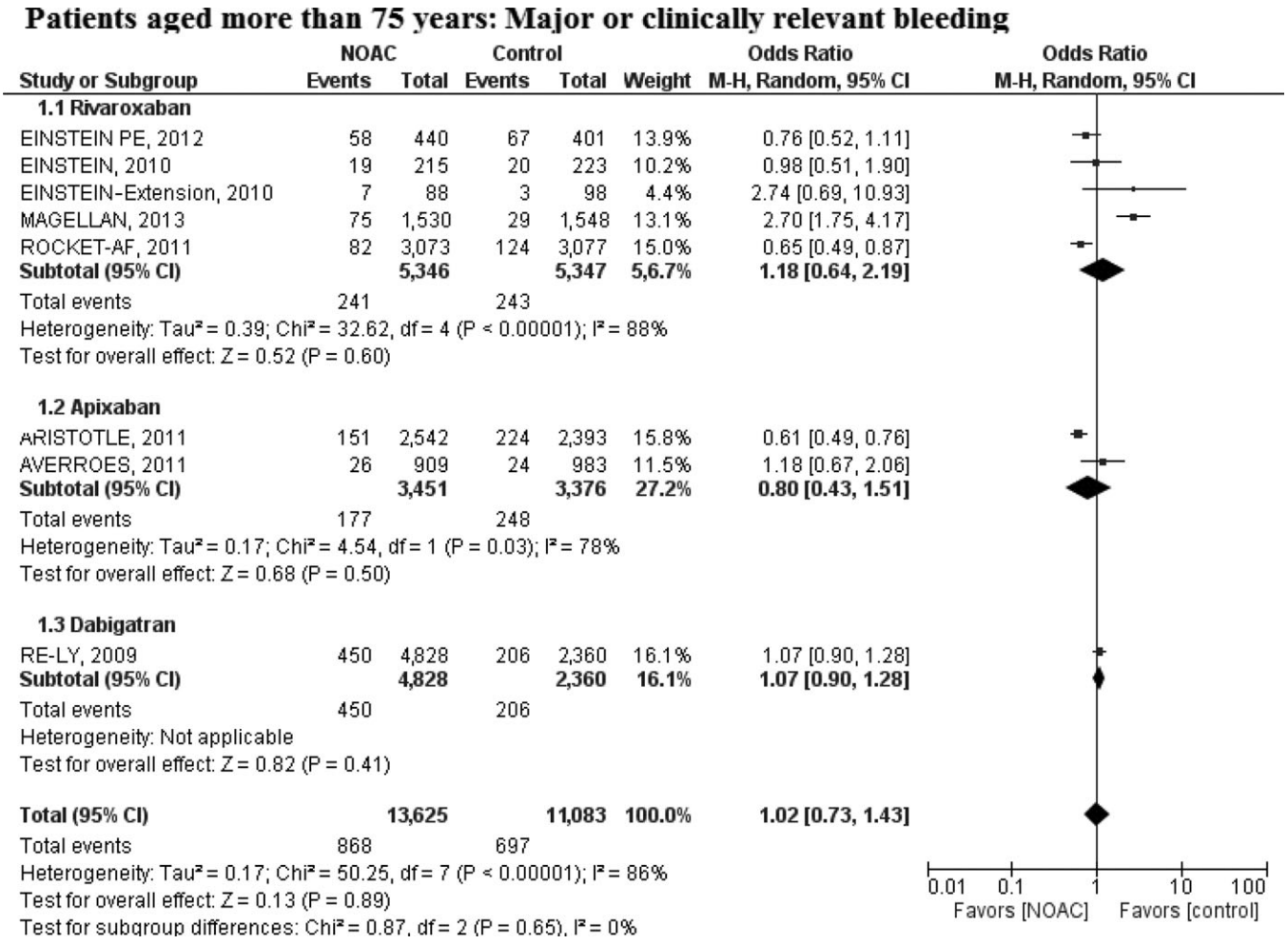

Figure 2. New oral anticoagulants versus conventional therapy for participants aged 75 and older: major or clinically relevant bleeding. CI = confidence interval.

stroke or systemic embolism in elderly adults with AF. NOACs were also more effective than conventional therapy for the reduction of the risk of VTE or VTE-related death.

A similar profile was also found for the effectiveness of the individual NOACs. Rivaroxaban, apixaban, and dabigatran were more or as effective and safe as conventional therapy or pharmacologically active agents.

Concerns About Bleeding

Several recent reports have raised concerns regarding the safety profile of NOACs in the elderly population.[15–17] Reports initially suggested that NOACs may cause more bleeding events, including life-threatening or fatal bleeding in elderly adults.[15,16] Case reports suggest that major bleeding events can occur with even a modified (lower) dose of NOACs in elderly adults.[15] A 2-month audit conducted by the Haematology Society of Australia and New Zealand identified 78 episodes of bleeding in dabigatran-treated individuals, and participant age was one of the four major factors that contributed to these episodes.[16] Two-thirds of the participants were aged 80 and older, and 58% had moderate or severe renal impairment.

One of the major arguments for the findings[16] was that the mean age of the trial population (RE-LY trial) was lower (71), and data from that trial may not be extrapolated into clinical practice in this case, but the current analysis for individuals aged 75 and older, including data from 10 RCTs, did not show excess bleeding with NOACs or with dabigatran specifically (data pooled from 2 RCTs). The data also showed that NOACs are significantly more effective than conventional therapy in this population.

Recent detailed analysis of bleeding related to rivaroxaban and apixaban in elderly adults in two large randomized trials also did not show excess bleeding with these drugs.[32,33] The reasons frequently suggested for the greater risk of bleeding in elderly adults are renal function impairment, low body weight, drug interactions, and unavailability of reliable coagulation tests to monitor blood level of NOACs.[1,14] Almost all previous articles reporting greater bleeding in elderly adults included individuals who had comorbidities, mainly coexisting renal failure,[15,16] but all of the reports were from small observational studies or case reports, and no randomized data are available. A possible explanation for the contrasting results of the current study might be that the chances of bleeding with NOACs

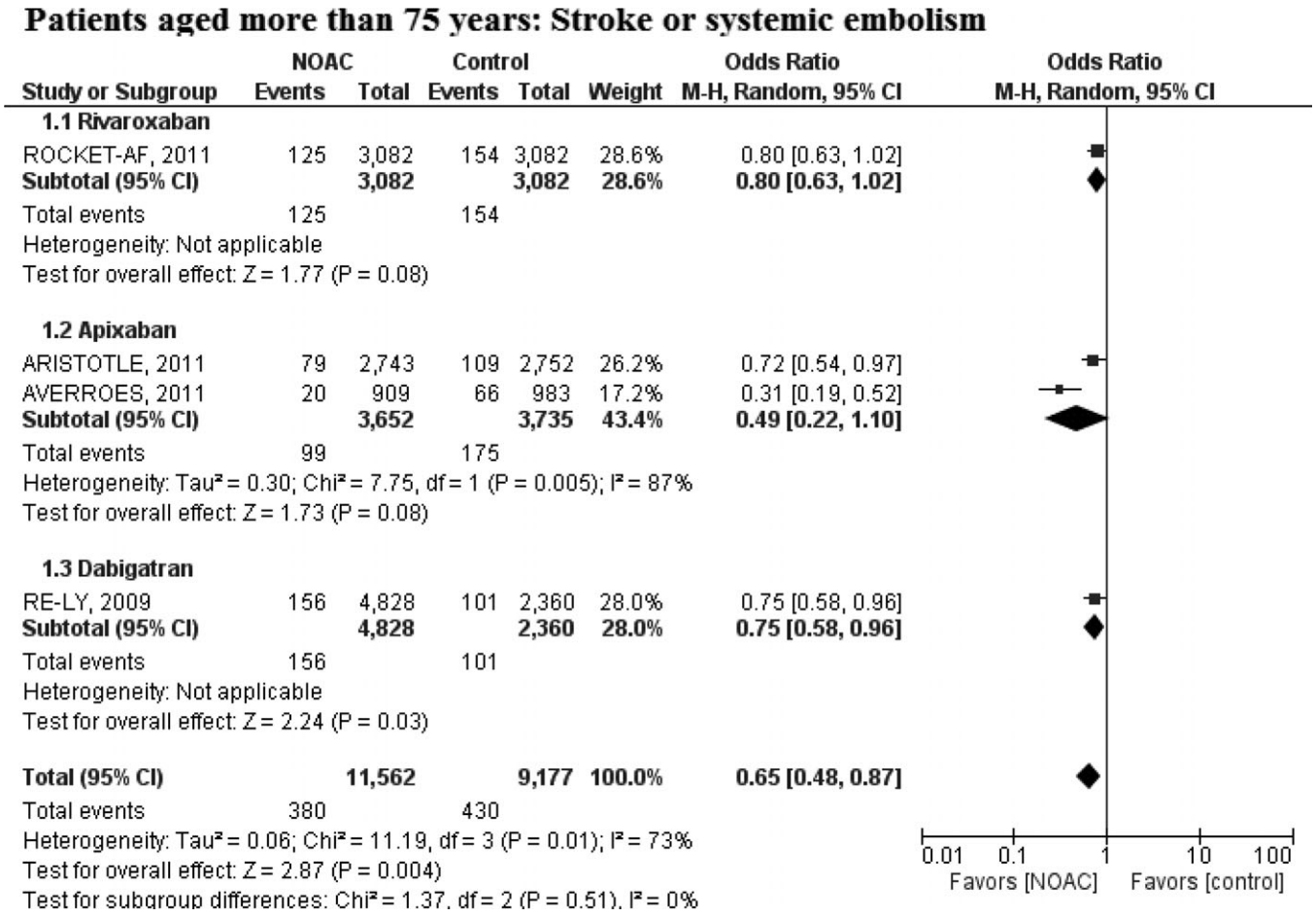

Figure 3. New oral anticoagulants versus conventional therapy for participants aged 75 and older: stroke or systemic embolism.

are more related to associated comorbidities than the age of the individual per se.

Implications for Practice

The benefit of antithrombotic therapy is well established in elderly adults, including those who are at high risk of falling or bleeding.[10,11] The current study suggests that NOACs are more effective than conventional anticoagulants in elderly adults. Old age per se should not be a criterion for withholding anticoagulation with NOACs.

The recommended dose of apixaban is lower (2.5 vs 5 mg) in elderly adults with at least one comorbidity in addition to older age (i.e., a lower dose is recommended in those with ≥2 of aged ≥80, body weight ≤60 kg, or serum creatinine ≥1.5 mg/dL).[3] For individuals with AF, 110 mg of dabigatran twice a day is recommended for aged 80 and older in the European Union, rather than a 150-mg twice-a-day regular dose, although the Food and Drug Administration (FDA) does not recommend a routine dose modification for dabigatran in elderly adults.[3,34] Dose modification for rivaroxaban is also not recommended for elderly adults, but a lower dose of dabigatran and rivaroxaban is recommended in individuals with moderate renal impairment.[3,34]

A recent FDA postmarketing report of bleeding with dabigatran did not identify any unrecognized risk factors for bleeding.[35] A large propensity score–matched nationwide cohort study from Denmark supports the FDA report (which does not adjust for comorbidities).[36] Another report showed no greater risk of bleeding with dabigatran in VKA-naive individuals.[37]

These arguments do not contradict the fact that caution should still be taken with NOACs in elderly adults with other comorbidities (mainly renal impairment) and very low body weight. Lack of a reversal agent for the anticoagulant effects of NOAC should also be kept in mind while prescribing these agents.[3] Thus, an individualized case-by-case approach might be best for elderly adults, with proper judgment of risk of bleeding and associated comorbidities rather than a generalized "one drug fits all" approach. Prospective, randomized controlled trials of NOACs in elderly populations are also needed.

LIMITATIONS

The current results are subject to the intrinsic limitations of meta-analyses: pooling of data from different trials with different study protocols, definitions of efficacy and safety outcomes, and baseline participant characteristics. The participant population in the included trials was healthier, with less comorbidity, better cognitive and physical function, and less polypharmacy, which is different from the typical elderly adult population in practice. Although

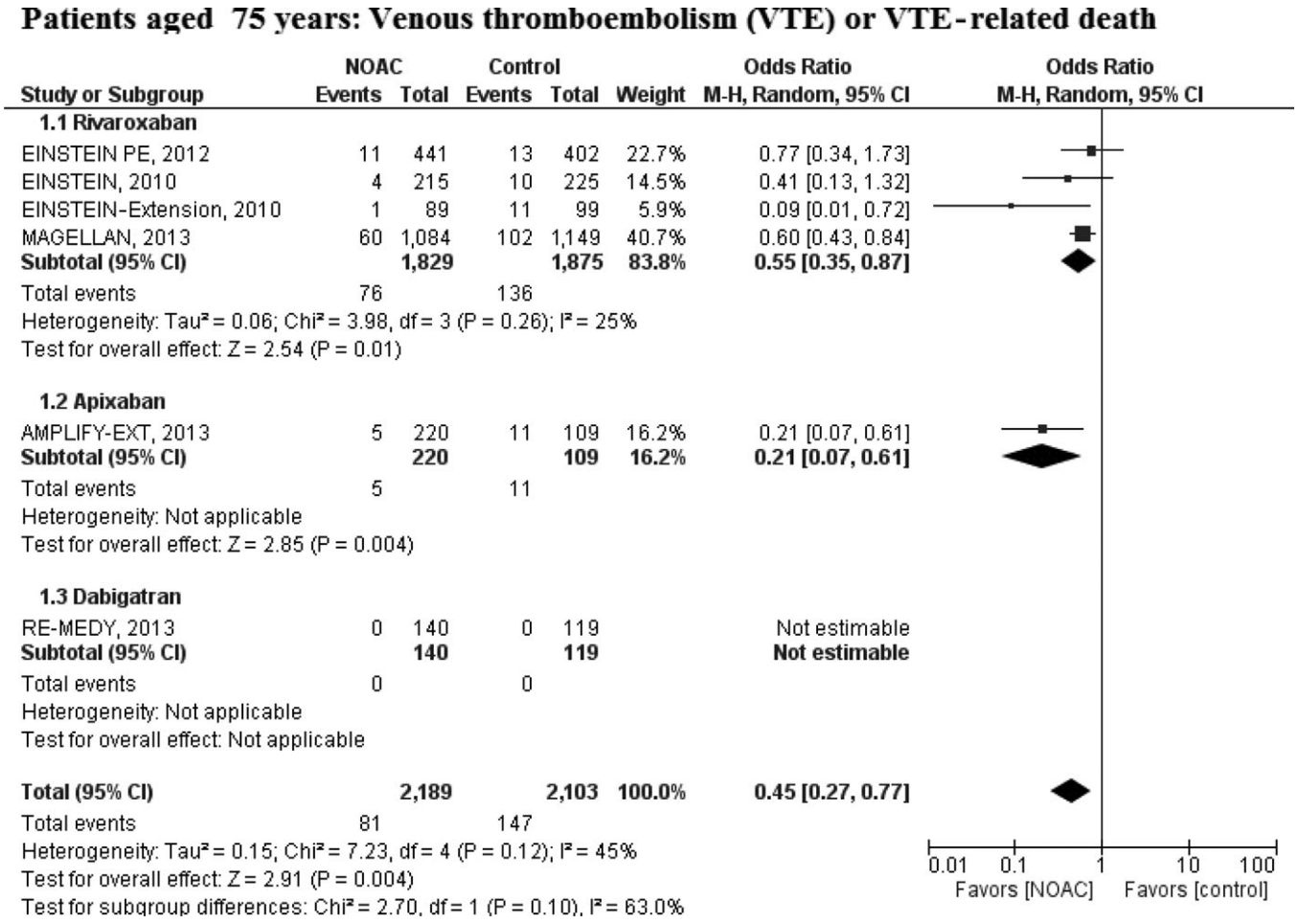

Figure 4. New oral anticoagulants versus conventional therapy for participants aged 75 and older: venous thromboembolism (VTE) or VTE-related death.

NOACs as a whole were studied, there are some pharmacological differences between the direct thrombin inhibitors and oral Factor Xa inhibitors. For data reported as percentage per year, number of events was calculated using mean or median follow-up, which was rounded off to whole numbers, although these values might vary slightly from the exact numbers in the original trials. Also, some of the results had wide CIs and a high degree of statistical heterogeneity, although most of the indication-wise analyses showed no or insignificant heterogeneity, and the high heterogeneity of the primary analyses can be explained. Safety data for dabigatran were inconsistently reported for the elderly population in included RCTs. Full details of the baseline demographic characteristics of the elderly participants were not reported.

CONCLUSION

In elderly adults enrolled in randomized trials, bleeding with NOACs was not different from that with conventional anticoagulants. NOACs might be more effective than conventional agents in this population. An individualized approach matching the particular NOAC to the participant profile, taking into consideration the risk of bleeding and other comorbidities, should be taken rather than a generalized "one drug fits all" approach in elderly adults.

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Conflict of Interest: Gregory Y. H. Lip has served as a consultant for Bayer, Astellas, Merck, AstraZeneca, Sanofi, BMS/Pfizer, and Boehringer Ingelheim and has been on the speakers bureau for Bayer, BMS/Pfizer, Boehringer Ingelheim, and Sanofi.

Author Contributions: Partha Sardar and Saurav Chatterjee designed the study; performed the literature search; and acquired, analyzed, and interpreted the initial data. Partha Sardar and Shobhana Chaudhari drafted the initial manuscript. Shobhana Chaudhari and Gregory Y. H. Lip provided critical review of the analysis and assisted in data analysis, data interpretation, and writing the manuscript for important intellectual content. Gregory Y. H. Lip provided study supervision. Partha Sardar is the guarantor.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Figure S1. New oral anticoagulants versus pharmacologically active conventional therapy for participants aged 75 and older: major or clinically relevant bleeding.

Figure S2. New oral anticoagulants versus conventional therapy: indication-specific analysis for major or clinically relevant bleeding in participants aged 75 and older.

Figure S3. New oral anticoagulants versus pharmacologically active conventional therapy for participants aged 75 and older: venous thromboembolism (VTE) or VTE-related death.

Figure S4. New oral anticoagulants versus conventional therapy: indication-specific analysis for venous thromboembolism (VTE) or VTE-related death in participants aged 75 and older.

Figure S5. Follow-up adjusted analysis for major or clinically relevant bleeding.

Table S1. Risk of bias assessments for included randomized clinical trials.

Table S2. Efficacy and safety of new oral anticoagulants with two different doses of dabigatran versus conventional therapy.

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