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Treatment of venous thromboembolism in elderly patients in the era of direct oral anticoagulants

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SHORT TITLE

DOACs for treatment of VTE in the elderly

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CONFLICT OF INTEREST

Tobias Tritschler reports having received travel and congress fees from Pfizer.

ABSTRACT

The incidence of venous thromboembolism (VTE) and VTE-related morbidity and mortality increase with advancing age. Over the past decade, substantial advances in treatment of VTE have been made, most notably the introduction of direct oral anticoagulants (DOACs) which offer simple treatment regimens across a broad spectrum of VTE patients and have become the first-choice anticoagulants in many VTE patients. Even though elderly patients are underrepresented in clinical trials, extrapolation of overall study results to the elderly subpopulation appears justified for acute VTE treatment and for the choice of anticoagulant agent. In the elderly, DOACs are not only associated with a lower risk of bleeding but they even appear to be more efficacious than vitamin K antagonists in preventing recurrent VTE during the acute treatment period. The most challenging aspect of VTE management in elderly patients is determination of optimal treatment duration. The risk of bleeding increases with advancing age but also several risk factors for recurrent VTE after stopping anticoagulation are more frequent in the elderly. Clinical decision rules estimating risk of recurrent VTE and bleeding have limited utility in elderly patients. Shared decision making considering patient preferences and values is therefore crucial to help determine individual treatment duration in elderly patients.

KEY WORDS

Direct oral anticoagulants; Elderly; Pulmonary embolism; Treatment; Venous thromboembolism.

INTRODUCTION

Venous thromboembolism (VTE), defined as pulmonary embolism (PE) or deep vein thrombosis (DVT), is a common disease in the elderly population. The incidence of VTE increases exponentially with age and is 4-12 per 1000 person-years in persons aged 80 years and older, which reflects a 5 to 10-fold higher risk of developing VTE compared to persons aged 40 to 50 years [1]. While the incidence of DVT has remained stable or even decreased over time [2, 3], the incidence of PE has increased in both the younger and the elderly population in recent decades [3]. The latter is partly related to the widespread use of sensitive multi-detector computed tomography pulmonary angiography resulting in more frequent diagnosis of smaller, potentially insignificant PE than the use of single-detector computed tomography or ventilation-perfusion scan [4-6]. Not only the incidence of VTE but also clinical presentation, prognostic factors, and outcome rates differ between younger and older patients with acute VTE [7, 8]. Furthermore, evidence regarding optimal treatment of VTE in the elderly including first-choice anticoagulant agent and duration of anticoagulation is limited because elderly patients were underrepresented in clinical trials [7, 9]. As a consequence, the 2016 American College of Chest Physician (ACCP) and the 2019 European Society of Cardiology guidelines do not make specific recommendations for elderly patients, but only acknowledge the higher risk of bleeding in this population [10, 11].

Over the past decade, substantial advances in treatment of VTE have been made [12], most notably the introduction of direct oral anticoagulant (DOACs) which offer simple treatment regimens across a broad spectrum of VTE patients. In light of the significant proportion of elderly among patients with VTE and their distinct risk of VTE-related outcomes, in this review, we summarize evidence of VTE treatment with DOACs

in elderly patients and we discuss situations in which other anticoagulants may be preferred.

DEFINITION OF THE ELDERLY AND ANALYSES FOR THIS REVIEW

The US Census Bureau defines the elderly as the population aged 65 years and older; most other developed countries have accepted similar definitions. Definitions for the elderly in studies in the field of VTE are more heterogenous. Subgroup analyses of many recent pivotal randomized controlled trials used age 75 years as cut-off; in recent cohort studies cut-offs ranged from 60 to 80 years. In this review, we will report results using the definition of the pertinent reference.

Amongst previously published evidence, we will also report pooled risk ratios of phase III DOAC trials for VTE treatment by age. Relative risks with corresponding 95% confidence intervals (CI) were calculated based on crude event numbers reported in the trial publications in which the intention-to-treat population was used for efficacy outcomes and the safety population for bleeding outcomes. If not available in the original publication, event numbers were extracted from a meta-analysis that published subgroup analyses based on additional information from the corresponding authors and sponsors of the study [13]. Pooled relative risks were calculated using the Mantel-Haenszel method. The between-study variance was estimated using the DerSimonian-Laird method, and heterogeneity reported with the I^2 statistic. All analyses were performed in R, version 3.6.1 [14], by using the *meta* package, version 4.9-7 [15].

PHARMACOKINETICS AND PHARMACODYNAMICS OF DIRECT ORAL ANTICOAGULANTS

DOACs specifically target single steps in the coagulation pathway by direct inhibition of activated factor X (rivaroxaban, apixaban, and edoxaban) or thrombin (dabigatran). Rivaroxaban at doses of 15 or 20 mg daily requires to be taken with food as this increases its bioavailability (66% without food; 80-100% with food), which is not required for other DOACs [16]. Dabigatran is a pro-drug and it should not be crushed before ingestion as this results in a 75% increase of its bioavailability [16]. Rivaroxaban, apixaban, and edoxaban can be administered in crushed form if patients are unable to swallow tablets [17-19]. DOACs have a dual mode of elimination consisting of hepatic metabolization and renal excretion at different degrees depending on drug. The proportion of renal clearance to non-renal clearance of the absorbed DOAC is 27% for apixaban, 35% for rivaroxaban, 50% for edoxaban, and 80% for dabigatran [16]. Elimination half-lives in persons with normal kidney function range from 5-9 hours (rivaroxaban) to 12-17 hours (dabigatran). DOAC exposure increases with age but this association is confounded by the influence of age on the kidney function. For instance, the area under the concentration-time curve for a single dose of rivaroxaban 10 mg increased in average by 41% in healthy elderly persons (weighted mean age 77 years) compared to younger persons (weighted mean age 32 years) which was, however, at least partially explained by the lower creatinine clearance in the elderly persons (weighted mean clearance 55 mL/min versus 121 mL/min) [20]. Similarly, point estimates of edoxaban trough levels in patients with atrial fibrillation were higher in the elderly, irrespective of dose regimen [21], and edoxaban trough concentrations in patients on edoxaban 60 mg daily for atrial fibrillation showed an inverse relationship to

kidney function [22]. Despite being higher on average, DOAC exposure and trough levels in the elderly were within the observed interindividual variability of the overall study populations [20, 21, 23-26]. Accordingly, dose adjustment based on age was not required in any of the phase III DOAC trials for VTE treatment. Of note, the product monograph of dabigatran recommends adjusting the dose of dabigatran to 110 mg twice daily for VTE treatment in patients aged 80 years and older, and in those aged 75 years and older with one or more risk factors for bleeding. Dabigatran at 110 mg twice daily has not been assessed for VTE treatment in a clinical trial, but the recommended dose reduction might be justified by results from the pooled analysis of phase III trials for treatment of acute VTE which showed that the bleeding risk reduction with dabigatran was influenced by age. Compared to vitamin K antagonists (VKAs), dabigatran was associated with a reduced risk of bleeding in younger patients but this effect was inverse in patients above 85 years in whom VKAs were associated with a lower risk of bleeding than dabigatran [27].

DOACs have fewer food and drug interactions compared with VKAs; still, such interactions have to be considered before prescribing a DOAC [16]. This is particularly important in elderly patients since number of medications and co-morbidities increase with age. The most relevant drug-drug interactions leading to clinically significant alteration in DOAC plasma levels concern drugs metabolized by cytochrome P450 3A4 in patients on apixaban and rivaroxaban or potent P-glycoprotein inhibitors in patients on any DOAC. There are no studies indicating that drug-drug interactions differ between elderly and younger patients, but there is insufficient evidence to draw any firm conclusions [28].

In essence, predictable pharmacodynamics and pharmacokinetics allow for a fixed-dose regimen across all patients eligible for DOAC treatment. Edoxaban is the only DOAC for acute VTE treatment requiring dose adjustment in certain circumstances including any one of: impairment of kidney function (i.e., creatinine clearance of 30-50 mL/min), body weight below 60 kg, and concomitant treatment with potent P-glycoprotein inhibitors. Whether the dose adjustment of dabigatran in elderly patients as recommended in the product monograph is appropriate for treatment of acute VTE has not been evaluated in a clinical trial but may be justified by a secondary analysis of the RE-COVER trials. On the other hand, inappropriate dose reduction of DOACs during initial and long-term VTE treatment occurs more frequently in elderly patients and is associated with an increased risk of recurrent VTE [29].

TREATMENT OF ACUTE VENOUS THROMBOEMBOLISM

The choice of treatment for acute VTE depends on clinical presentation, site of VTE, and benefits and risks of anticoagulation, which should be carefully weighed when determining the optimal therapeutic approach.

Thrombolysis

Hypotension is associated with increased short-term mortality in patients with acute PE [30, 31]. Guidelines recommend systemic thrombolysis in such patients to achieve rapid improvement of pulmonary obstruction and subsequent reduction of the risk of PE-related death [10, 11]. This benefit comes at the cost of an increased risk of bleeding, which is higher in patients above 75 years than in younger patients (13% vs 3% for major bleeding; 1.4% vs 0.5% for intracranial bleeding) [32, 33]. The 2016 ACCP

guidelines therefore specify that age over 75 years is a relative contraindication to thrombolysis while the 2019 ESC guidelines do not make age-specific recommendations [10, 11]. Data from the Nationwide Inpatient Sample between 1999 and 2008 indicate that unstable elderly patients are less likely to undergo systemic thrombolysis than younger patients regardless of presence of co-morbidities [34]. Whether this represents undertreatment or appropriate withholding of systemic thrombolysis due to an unacceptably high bleeding risk remains to be determined.

In normotensive PE patients, primary thrombolysis is not recommended in any age group [10, 11]. The PEITHO trial randomized hemodynamically stable PE patients with increased troponin and right ventricular dysfunction on imaging to systemic thrombolysis plus heparin or placebo plus heparin [35]. The risk of death or hemodynamic deterioration in patients over 75 years was similar between thrombolysis and placebo (4.3% vs 6.7%), but thrombolysis was associated with an increased risk of major bleeding (11.1% vs 0.6%) [35]. Preliminary evidence indicates that bleeding risk could be mitigated by reduced-dose or catheter-directed thrombolysis,[36, 37] but methodologically rigorous trials are required before such treatment can be recommended.

In patient with iliofemoral DVT, catheter-directed thrombolysis in addition to anticoagulation reduced the risk of post-thrombotic syndrome at 2 and 5 years of follow-up in the CAVENT trial [38, 39]. These results were not confirmed in two recent trials [40, 41]. The ATTRACT trial which randomized 692 patients with a proximal DVT to receive pharmacomechanical thrombolysis (i.e., catheter-directed lysis, mechanical thrombus removal, or both) plus anticoagulation or anticoagulation alone, showed no difference between the treatment arms with regard to occurrence of recurrent VTE,

mortality, post-thrombotic syndrome, and quality of life between 6 and 24 months after diagnosis [40]. Similar results were seen in the smaller CAVA trial [41]. The lack of efficacy and moreover, the increased risk of major bleeding with the addition of catheter-directed thrombolysis to anticoagulation (3.3% vs. 0%, 1.7% vs. 0.3%, and 5% vs. 0% in the CAVENT, ATTRACT and CAVA trial, respectively) [38, 40, 41], support current guideline recommendations to consider thrombolysis only if the limb is threatened [10]. Given the increased risk of bleeding in elderly patients, this conservative approach can likely be extrapolated to patients aged over 75 years who were excluded from the CAVENT and ATTRACT trial and underrepresented in the CAVA trial (median age, 52 years; interquartile range, 38-67 years).

Oral anticoagulants for acute treatment

In normotensive patients with VTE, anticoagulation is the mainstay of treatment. The choice of the optimal anticoagulant agent mainly depends on VTE etiology, kidney function, and co-medications. In patients without cancer or severe kidney disease, DOACs are the first-choice anticoagulant [10, 11]. Since there are no head-to-head DOAC trials, one DOAC cannot be recommended over another [42]. DOACs for acute VTE treatment have been compared to VKA therapy in six phase 3 trials using a non-inferiority study design. The proportion of participants over 75 years ranged from 10% to 15% across these studies (Table 1), indicating underrepresentation of the elderly population as epidemiologic studies show this age group represents approximately 25% of the VTE population [43]. While the overall risk of recurrent VTE did not differ between elderly and younger patients, concerns of a higher risk of bleeding in elderly patients were confirmed in the DOAC trials; there was an almost 3-fold higher risk of major

bleeding in patients aged over 75 years compared to younger patients, irrespective of treatment allocation (Figures 1A and 2A). In patients over 75 years, the risk of recurrent VTE was consistently lower in patients on a DOAC compared to those on a VKA with a pooled overall relative risk reduction of 44% (95% confidence interval [CI], 0.38-0.82; I^2, 0%; Figure 1B) [13]. This risk reduction was not seen in younger patients (risk ratio, 0.99; 95% CI, 0.85-1.17; I^2, 0%). Similar to younger patients, DOACs were associated with a lower risk of major bleeding than VKAs in elderly patients (risk ratio, 0.51; 95% CI, 0.30-0.85; I^2, 60%; Figure 2B) [13]. In summary, the risk of bleeding increased with age for both VKAs and DOACs, but DOACs were associated with a lower risk of bleeding compared with VKAs. Subgroup analyses of the Hokusai-VTE trial also indicated that efficacy of edoxaban as well as its lower risk of bleeding compared to VKA therapy was preserved in elderly patients with multimorbidity and polypharmacy [44]. In a large US claims database study, frail patients, defined as per the Johns Hopkins Claims-Based Frailty Indicator score, were less likely to experience recurrent VTE on rivaroxaban than on a VKA with no difference in the risk of bleeding [45]. Post-marketing phase IV trials and DOAC registries confirmed that DOACs are safe and effective alternatives to VKAs for treatment of VTE in routine clinical practice [46]. Interestingly, the mean age of patients enrolled in those studies (range 56-62 years) was similar to that of patients enrolled in the large phase III randomized controlled trials (range 55-58 years) [27, 46-51].

In cancer patients, the choice of anticoagulant agent is less obvious and should be individualized incorporating patient preferences and values, cancer type, additional risk factors for bleeding, and co-medications [52]. In recent randomized controlled trials, DOACs for treatment of cancer-associated VTE were associated with a higher risk of

bleeding (risk ratio, 1.74; 95% CI, 1.05-2.88) and possibly a lower risk of recurrent VTE (risk ratio, 0.65; 95% CI, 0.42-1.01) compared to treatment with low-molecular-weight heparin [53]. The Hokusai-VTE cancer study is the only randomized controlled trial assessing DOACs versus low-molecular-weight heparin for cancer-associated VTE which reported results on the subgroup of patients by age (<65 versus ≥65 years, and <75 years versus ≥75 years) [54]. The primary composite outcome of recurrent VTE or major bleeding did not differ by age [54]. Similar to the findings in the entire study cohort, in patients aged 65 years or older, the risk of recurrent VTE appeared to be lower (6.9% vs 9.9%) and the risk of major bleeding (8.0% vs 4.2%) to be higher with edoxaban than with dalteparin [54].

Given that DOAC clearance depends on renal function, patients with severe renal failure (i.e., creatine clearance <25-30 mL/min) have been excluded from phase III DOAC trials. Therefore, VKAs remain the anticoagulants of choice in these patients. Although chronic kidney disease becomes more prevalent with increasing age, severe renal failure remains relatively rare in the general elderly population as 3.2% of persons aged 75 years or older have an estimated glomerular filtration rate below 30 mL/min [55, 56]. Retrospective data suggest that apixaban may be associated with lower risks of bleeding, thromboembolic events, and mortality compared to VKAs in patients with atrial fibrillation and end stage kidney disease [57]. Whether these benefits hold true for treatment of VTE in a randomized study is uncertain. Results of the ongoing VERDICT study (ClinicalTrials.gov identifier: NCT02664155) will address whether reduced doses of apixaban and rivaroxaban for treatment of VTE in patients with moderate to severe kidney disease (i.e., 15-50 mL/min) are non-inferior to standard of care (i.e., parenteral anticoagulant plus a VKA). While awaiting more data in patients with severe kidney

disease, we consider DOACs efficacious and safe in patients with non-severe kidney disease. Even though the risk of bleeding increases with declining kidney function, DOACs were associated with a lower risk of bleeding than VKAs in patients with non-severe kidney disease without a difference in treatment efficacy [13, 58].

EXTENDED TREATMENT OF VENOUS THROMBOEMBOLISM

Duration of treatment

Once the acute phase of VTE treatment (i.e., first 3 months after diagnosis) is completed, determination of whether to continue or stop anticoagulation is based on balancing the risks of bleeding and recurrent VTE on and off anticoagulant treatment, including associated case-fatality rates. The risk of recurrent VTE is mainly determined by the etiology of VTE. Patients with a strong, transient provoking factor (e.g. major surgery) are at low risk of recurrence and treatment should be stopped after 3 months [10]. Patients with unprovoked VTE are at high risk of recurrence and continuing treatment is recommended, unless the risk of bleeding is high [10]. Continuing treatment reduces the risk of recurrent VTE by 80-90% while patients are on anticoagulants but does not reduce the risk of recurrence once therapy is discontinued [59]. Whether the risk of a recurrent VTE after stopping anticoagulation is higher in the elderly remains controversial [60-68]. In contrast, the risk of major bleeding was consistently shown to be about 2 to 3-fold higher in patients aged above 75 years regardless of anticoagulant drug used (Figure 2A) [13, 63, 69]. Similarly, patients with VTE in the context of active cancer are at high risk of recurrence and as such, extended treatment is recommended for cancer-associated VTE, unless the risk of bleeding outweighs the benefit of anticoagulation [10]. This recommendation is mainly based on expert opinion, given that

only few prospective studies have assessed extended anticoagulant treatment in cancer patients [70-74]. There is only one randomized controlled trial that aimed to assess anticoagulation versus placebo for extended treatment of cancer-associated VTE but it was prematurely terminated due to slow recruitment [74].

Although the risk of recurrence after stopping anticoagulation is overall high in patients with a first unprovoked VTE (10% in the first year, 25% at 5 years, and 36% at 10 years) [75], efforts have been made to identify a subgroup of patients with a low enough risk to justify stopping anticoagulation after 3-6 months. Because the risk of bleeding and possibly the risk of recurrent VTE increase with age, it is uncertain whether the generally recommended threshold of an acceptable recurrence risk of 5% in the first year after stopping treatment can be applied in the elderly population [76]. Four clinical decision rules (HERDOO2, Vienna Prediction Model, DASH, PIT-STOP) have been developed to help clinicians determine the risk of recurrence after a first unprovoked VTE [65-67, 77]. The only rule which has been validated in a management study is the HERDOO2 rule. It allows to identify women at low risk of recurrence based on age, D-dimer levels, signs of post-thrombotic syndrome, and body mass index [78]. Subgroup analyses of the study, however, indicated that among women classified as low-risk, the risk of recurrence was substantially higher in women above 50 years (5.7 events per 100 patient-years) than in women below 50 years (2.0 events per 100 patient-years) [78]. Furthermore, the proportion of patients identified at low risk of recurrence is smaller in the elderly given that not only age 65 years or older but also other score criteria are more frequent in the elderly: advanced age is a risk factor for post-thrombotic syndrome [79, 80] and normal D-dimer values are rare in elderly patients with an unprovoked VTE [81]. In elderly patients, both the Vienna Prediction Model and the DASH score showed

poor discriminative power in external validation studies [82, 83], limiting their utility to identify a subgroup of elderly patients at low risk of recurrence. No elderly-specific data are available for the PIT-STOP model which includes age, sex, site of VTE, and D-dimer to generate estimates of recurrent VTE on a continuous scale [77].

Not only assessment of the risk of recurrent VTE but also estimation of the risk of bleeding is difficult in elderly patients. Several scores have been developed to estimate the risk of bleeding in patients on anticoagulants; most of them in cohorts of patients with atrial fibrillation. When applied in elderly patients with VTE, the Outpatient Bleeding Risk Index, ACCP, HAS-BLED, RIETE, HEMORR$_2$HAGES and ATRIA scores showed only poor to moderate discriminative abilities (c-statistics ranging from 0.49 to 0.60) when [84, 85]. The VTE-BLEED score was specifically developed to estimate the risk of bleeding in patients on anticoagulant treatment beyond 6 months of VTE diagnosis [86], but it lacks validation in elderly patients. Seiler et al. have recently proposed a new bleeding score which was derived in a cohort of VTE patients aged 65 year or older and treated with a VKA [87]. Independent risk factors for major bleeding included in the score were previous major bleeding, active cancer, low physical activity, anemia, thrombocytopenia, concomitant antiplatelet drug use, and poor INR control [87]. However, its use cannot be recommended before external validation studies are available, and inclusion of variables specific for VKA treatment may make it less useful for patients on DOACs.

Overall, no validated clinical decision rules are available that help clinicians assess the risk of recurrent VTE and bleeding in elderly patients with VTE. Therefore, shared decision making which incorporates information on consequences of continuing or

stopping anticoagulation, and patient preferences and values should be highly encouraged in elderly patients.

Anticoagulants for extended treatment

When opting for anticoagulant treatment beyond 3 months, the same anticoagulant options are available as for acute treatment and guidelines do not suggest to change anticoagulant after the first 3 months [10, 11]. VKAs, dabigatran, rivaroxaban and apixaban have been specifically evaluated in randomized controlled trials for secondary prevention of VTE in patients without cancer. As in the trials for acute VTE treatment, the proportion of elderly study participants was below 20% in phase III DOAC trials for extended treatment (Table 1). Compared to placebo, active treatment reduced the risk of recurrent VTE and increases the risk of bleeding in both younger and elderly patients (Figure 3 and 4). The RE-MEDY trial is the only study that specifically compared VKA therapy to a DOAC for extended VTE treatment. Overall, dabigatran was non-inferior to VKA therapy for preventing recurrent VTE and associated with a lower risk of major and clinically relevant non-major bleeding (hazard ratio, 0.54; 95% CI, 0.41-0.71) [88]. Only 9% of study participants were 75 years or older, and in those 239 patients no recurrent VTE occurred in either treatment arm. Subgroup analysis for bleeding events were not reported. Rivaroxaban and apixaban are also approved at reduced doses (i.e., 10 mg daily for rivaroxaban and 2.5 mg twice daily for apixaban) during extended VTE treatment, because they are superior to aspirin and placebo, respectively, for secondary prevention of recurrent VTE [89, 90]. Point estimates of risk of recurrent VTE appear to be similar in the subgroup of elderly patients, but a limited number of elderly participants and low event rates preclude judgment on statistical significance (Figure 3). Low-dose aspirin reduces the risk of recurrent VTE by about one third compared to placebo [91]. There is, however, little role for aspirin for extended VTE treatment [92], because

reduced dose rivaroxaban was more efficacious and not associated with a higher risk of bleeding than aspirin in the EINSTEIN CHOICE trial [89].

Based on the few prospective studies reporting on extended anticoagulant treatment for cancer-associated VTE, it seems reasonable to suppose that there is no need to change the choice of anticoagulant after the first 3 months [70-74]. None of these studies reported subgroup analysis by age.

CONCLUSION

The incidence of VTE increases with age and elderly patients are at higher risk of VTE-related morbidity and mortality. Even though elderly patients are underrepresented in clinical trials, extrapolation of study results from younger patients to the elderly appears justified for acute VTE treatment and for the choice of anticoagulant agent. Subgroup analyses of phase III DOACs trials indicate that during the acute VTE treatment phase, DOACs are not only associated with a lower risk of bleeding but even appear to be more efficacious than VKAs in preventing recurrent VTE in the elderly.

The most challenging aspect of VTE management in elderly patients is determination of optimal treatment duration. The risk of bleeding increases with age but also several risk factors for recurrent VTE are more frequent in the elderly. Clinical decision rules to help estimating risk of recurrence and bleeding have only limited utility in elderly patients and therefore, shared decision making considering also patient preferences and values is essential in determining individualized treatment duration in the elderly.

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AUTHOR CONTRIBUTIONS

Tobias Tritschler performed the meta-analysis and wrote the manuscript. All authors reviewed and revised the manuscript before approving the submission of the final manuscript.

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Table 1. Phase 3 trials of direct oral anticoagulants for acute and extended treatment of VTE in the subgroup of elderly patients

Study	Design	Proportion of patients >75 y	Intervention	Control	Treatment duration	Primary efficacy outcome	Primary safety outcome
Acute VTE Treatment							
RE-COVER pooled [27, 47]	Double-blinded	529/5,107 (10%)	LMWH for ≥5 days, then dabigatran 150 mg bid	LMWH for ≥5 days, then VKA (INR 2-3)	6 months	Recurrent VTE	Not specified
EINSTEIN pooled [48, 49]	Open-label	1,283/8,281 (15%)	Rivaroxaban 15 mg bid for 21 days, then 20 mg od	LMWH for ≥5 days, then VKA (INR 2-3)	3, 6, or 12 months[b]	Recurrent VTE	Clinically relevant bleeding[a]
AMPLIFY [50]	Double-blinded	749/5,244 (14%)	Apixaban 10 mg bid for 7 days, then 5 mg bid	LMWH for ≥5 days, then VKA (INR 2-3)	6 months	Recurrent VTE	Major bleeding
Hokusai-VTE [51]	Double-blinded	1,104/8,240 (13%)	LMWH for ≥5 days, then edoxaban 60 mg od[c]	LMWH for ≥5 days, then VKA (INR 2-3)	3, 6, or 12 months[b]	Recurrent VTE	Clinically relevant bleeding[a]
Extended VTE Treatment							
RE-MEDY [88]	Double-blinded	259/2,856 (9%)	Dabigatran 150 mg bid	VKA (INR 2-3)	6-36 months	Recurrent VTE	Not specified
RE-SONATE [88]	Double-blinded	452/1,343 (33%)[d]	Dabigatran 150 mg bid	Placebo	12 months	Recurrent VTE	Not specified
EINSTEIN-EXT [48]	Open-label	188/1,196 (16%)	Rivaroxaban 20 mg od	Placebo	6-12 months	Recurrent VTE	Major bleeding
EINSTEIN-CHOICE [89]	Double-blinded	394/3,365 (12%)	Rivaroxaban 20 mg od; Rivaroxaban 10 mg od	Aspirin 100 mg od	6-12 months	Recurrent VTE	Major bleeding
AMPLIFY-EXT [90]	Double-blinded	329/2,482 (13%)	Apixaban 5 mg bid; Apixaban 2.5 mg bid	Placebo	12 months	Recurrent VTE and all-cause death	Major bleeding

Abbreviations: bid, twice daily; LMWH; low-molecular-weight heparin; INR, international normalized ratio; od, once daily; VKA, vitamin K antagonist; VTE, venous thromboembolism.

[a] Clinically relevant bleeding was defined as major bleeding or clinically relevant non-major bleeding.

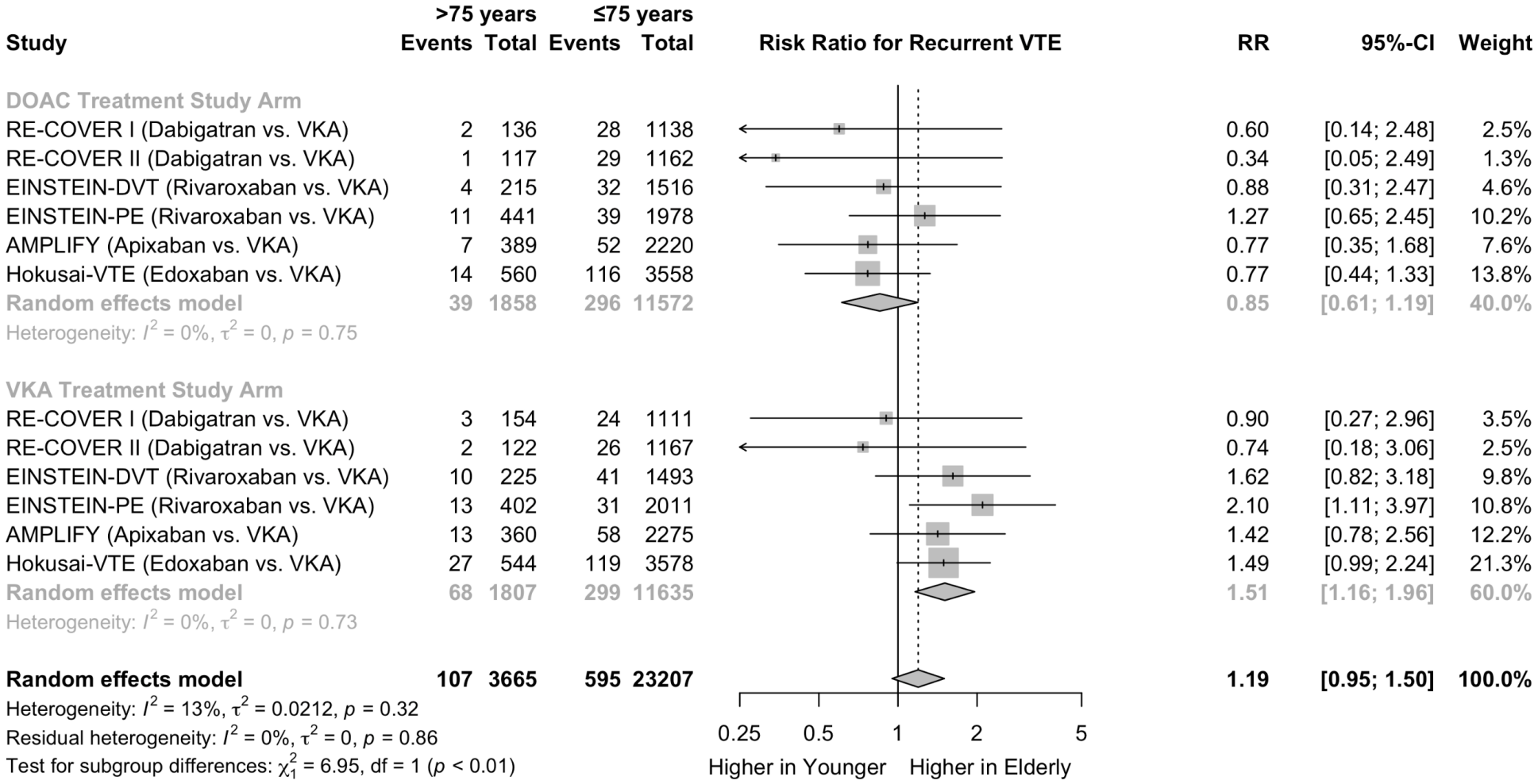
[b] Treatment duration at discretion of the physician.

[c] Dose adjustment (edoxaban 30 mg, od) in patients with a creatinine clearance of 30-50 mL/min or a body weight <60 kg, and in patients receiving concomitant treatment with potent P-glycoprotein inhibitors.

[d] Subgroup analysis for age <65 vs ≥65 years, because subgroup analysis for ≤75 vs >75 years not reported.

Figure 1. Recurrent VTE in DOAC phase 3 trials for acute VTE treatment

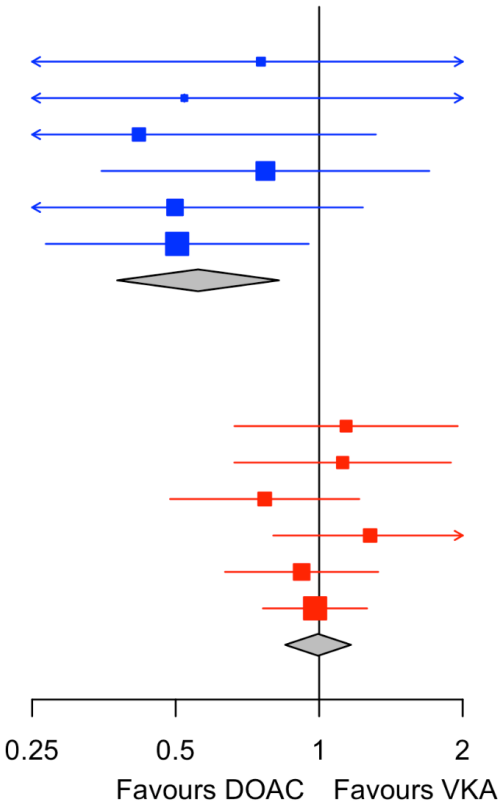
A. Association of recurrent VTE with age over 75 years by treatment arm



Abbreviations: CI, confidence interval; RR, risk ratio; VKA, vitamin K antagonist; VTE, venous thromboembolism.

B. Recurrent VTE by age

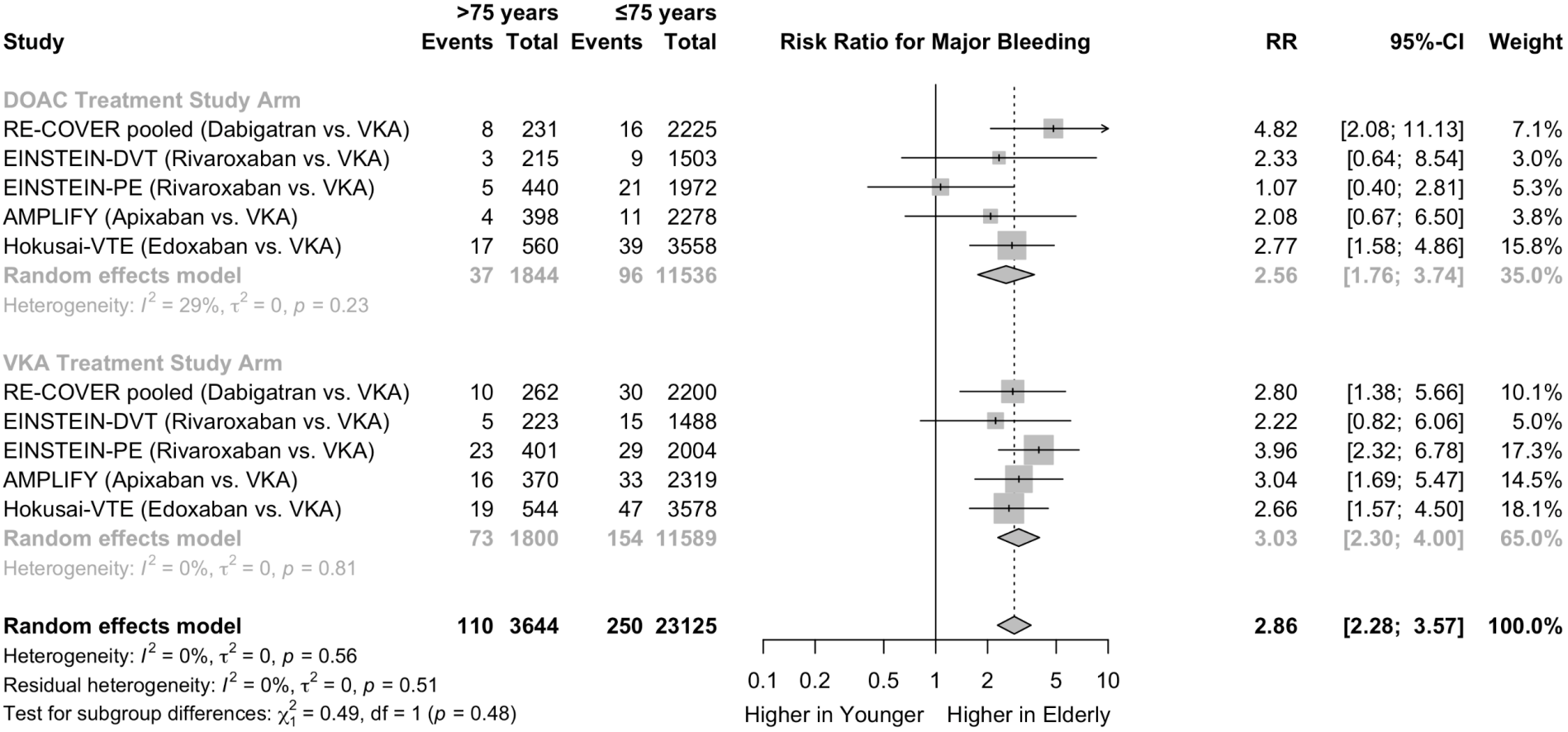
Study	Intervention	Control	Intervention Events	Intervention Total	Control Events	Control Total	RR	95%-CI
Age >75 years								
RE-COVER	Dabigatran	VKA	2	136	3	154	0.75	[0.13; 4.45]
RE-COVER II	Dabigatran	VKA	1	117	2	122	0.52	[0.05; 5.67]
EINSTEIN-DVT	Rivaroxaban	VKA	4	215	10	225	0.42	[0.13; 1.31]
EINSTEIN-PE	Rivaroxaban	VKA	11	441	13	402	0.77	[0.35; 1.70]
AMPLIFY	Apixaban	VKA	7	389	13	360	0.50	[0.20; 1.24]
Hokusai-VTE	Edoxaban	VKA	14	560	27	544	0.50	[0.27; 0.95]
Random effects model			**39**	**1858**	**68**	**1807**	**0.56**	**[0.38; 0.82]**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.95								
Age ≤75 years								
RE-COVER	Dabigatran	VKA	28	1138	24	1111	1.14	[0.66; 1.95]
RE-COVER II	Dabigatran	VKA	29	1162	26	1167	1.12	[0.66; 1.89]
EINSTEIN-DVT	Rivaroxaban	VKA	32	1516	41	1493	0.77	[0.49; 1.21]
EINSTEIN-PE	Rivaroxaban	VKA	39	1978	31	2011	1.28	[0.80; 2.04]
AMPLIFY	Apixaban	VKA	52	2220	58	2275	0.92	[0.63; 1.33]
Hokusai-VTE	Edoxaban	VKA	116	3558	119	3578	0.98	[0.76; 1.26]
Random effects model			**296**	**11572**	**299**	**11635**	**0.99**	**[0.85; 1.17]**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.71								
Heterogeneity: I^2 = 3%, τ^2 = 0.0026, p = 0.41								
Test for subgroup differences: χ^2_1 = 7.26, df = 1 (p < 0.01)								



Abbreviations: CI, confidence interval; DOAC, direct oral anticoagulant; RR, risk ratio; VKA, vitamin K antagonist; VTE, venous thromboembolism.

Figure 2. Major bleeding in DOAC phase 3 trials for acute VTE treatment

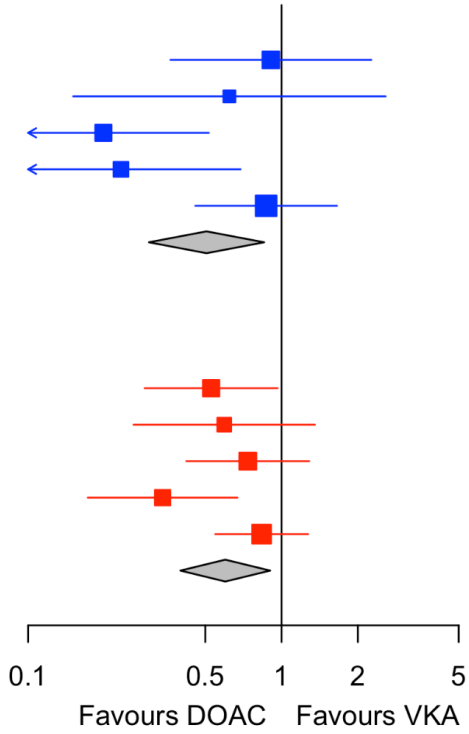
A. Association of major bleeding with age over 75 years by treatment arm



Abbreviations: CI, confidence interval; RR, risk ratio; VKA, vitamin K antagonist.

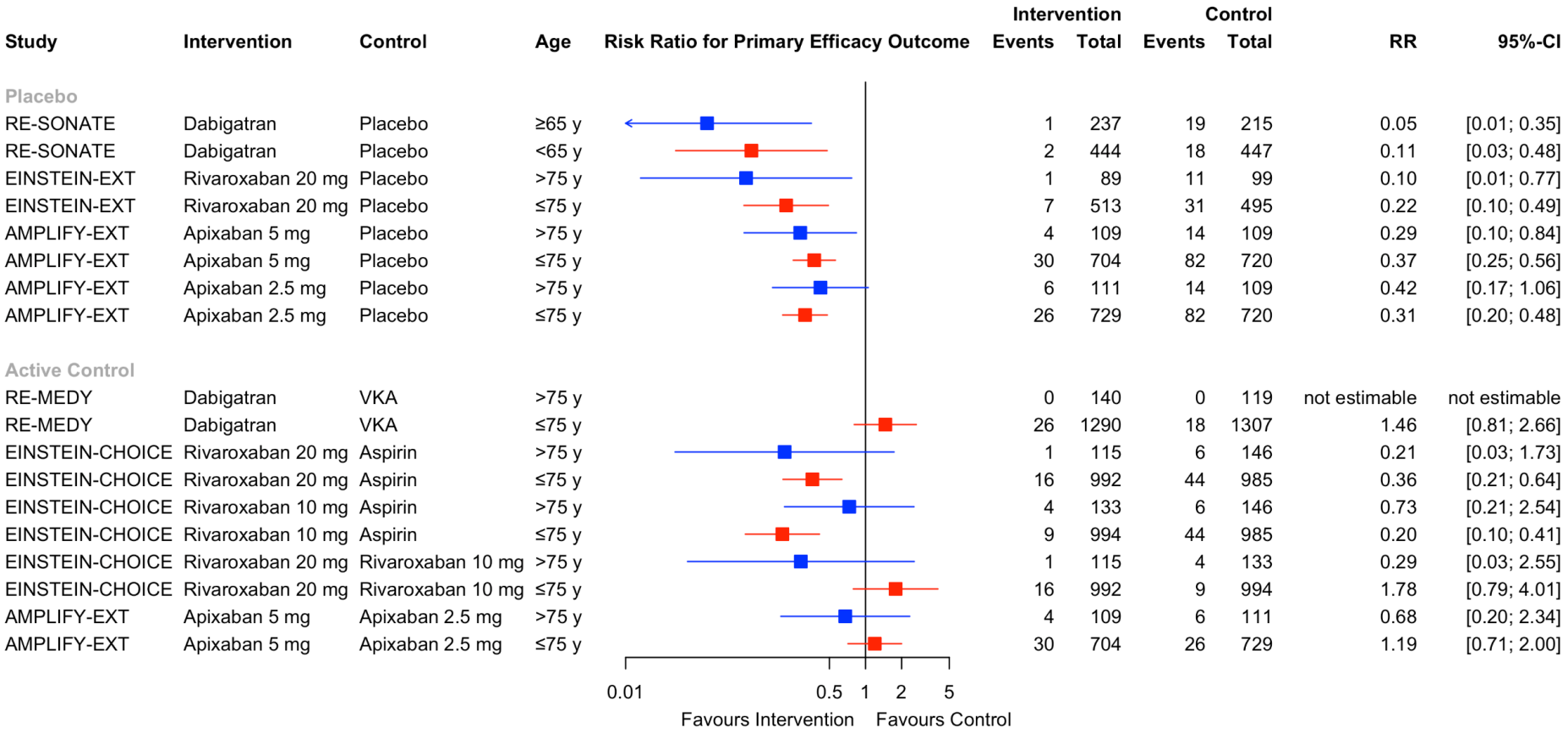
B. Major bleeding by age

Study	Intervention	Control	Intervention Events	Intervention Total	Control Events	Control Total	RR	95%-CI
Age >75 years								
RE-COVER pooled	Dabigatran	VKA	8	231	10	262	0.91	[0.36; 2.26]
EINSTEIN-DVT	Rivaroxaban	VKA	3	215	5	223	0.62	[0.15; 2.57]
EINSTEIN-PE	Rivaroxaban	VKA	5	440	23	401	0.20	[0.08; 0.52]
AMPLIFY	Apixaban	VKA	4	398	16	370	0.23	[0.08; 0.69]
Hokusai-VTE	Edoxaban	VKA	17	560	19	544	0.87	[0.46; 1.65]
Random effects model			**37**	**1844**	**73**	**1800**	**0.51**	**[0.30; 0.85]**
Heterogeneity: I^2 = 60%, τ^2 = 0.1209, p = 0.04								
Age ≤75 years								
RE-COVER pooled	Dabigatran	VKA	16	2225	30	2200	0.53	[0.29; 0.96]
EINSTEIN-DVT	Rivaroxaban	VKA	9	1503	15	1488	0.59	[0.26; 1.35]
EINSTEIN-PE	Rivaroxaban	VKA	21	1972	29	2004	0.74	[0.42; 1.29]
AMPLIFY	Apixaban	VKA	11	2278	33	2319	0.34	[0.17; 0.67]
Hokusai-VTE	Edoxaban	VKA	39	3558	47	3578	0.83	[0.55; 1.27]
Random effects model			**96**	**11536**	**154**	**11589**	**0.60**	**[0.40; 0.90]**
Heterogeneity: I^2 = 28%, τ^2 = 0.1209, p = 0.24								
Heterogeneity: I^2 = 44%, τ^2 = 0.1001, p = 0.07								
Test for subgroup differences: χ^2_1 = 0.25, df = 1 (p = 0.61)								



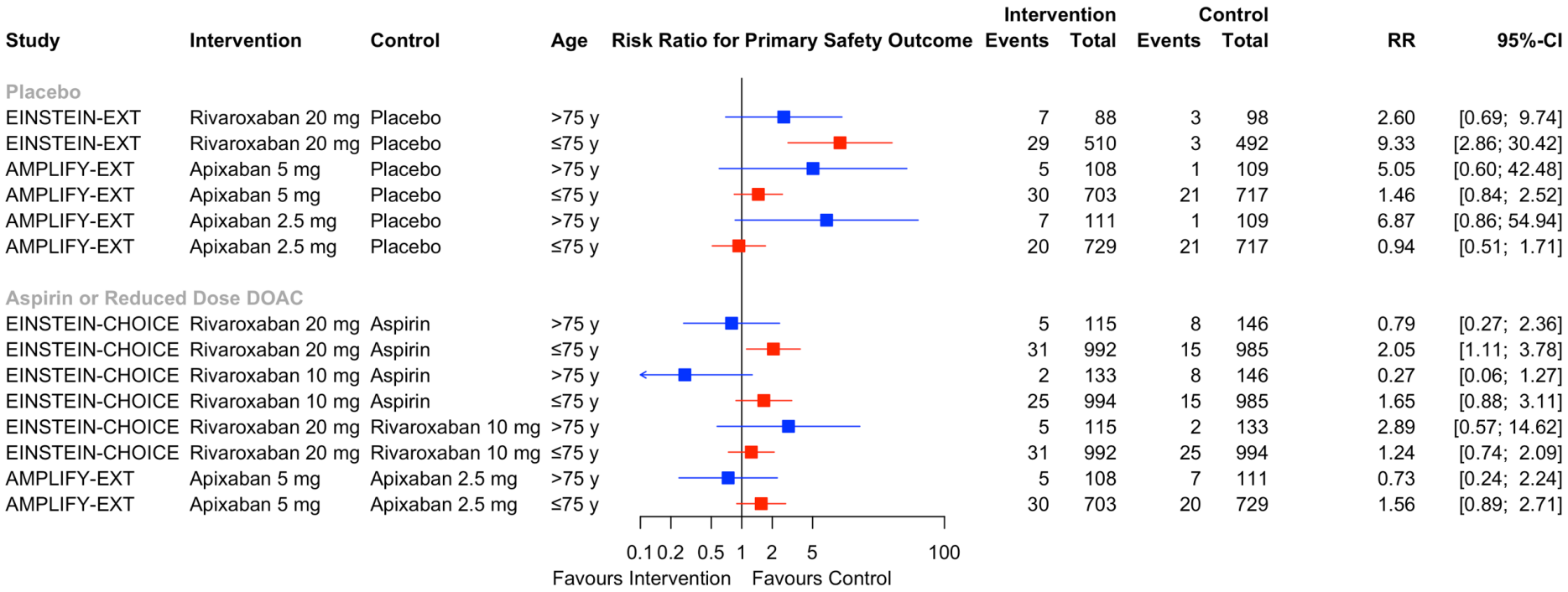
Abbreviations: CI, confidence interval; DOAC, direct oral anticoagulant; RR, risk ratio; VKA, vitamin K antagonist.

Figure 3. Primary efficacy outcome in DOAC phase 3 trials for extended VTE treatment by age



Abbreviations: CI, confidence interval; RR, risk ratio; VKA, vitamin K antagonist.

Figure 4. Primary safety outcome in DOAC phase 3 trials for extended VTE treatment by age



Abbreviations: CI, confidence interval; DOAC, direct oral anticoagulant; RR, risk ratio.