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Systematic Review/Meta-analysis

Novel Oral Anticoagulants in Patients With Renal Insufficiency: A Meta-analysis of Randomized Trials

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See editorial by Witt and Healey, pages 853-854 of this issue.

ABSTRACT

Background: Recent reports suggest altered antithrombotic efficacy and higher risk of bleeding with new oral anticoagulants (NOACs) in patients with renal insufficiency. A meta-analysis was performed to evaluate the efficacy and safety with recommended doses of NOAC compared with conventional treatment in patients with renal insufficiency.

Methods: PubMed, Cochrane Library, EMBASE, EBSCO, Web of Science, and CINAHL databases were searched from January 1, 2001 through March 23, 2014. Randomized controlled trials that compared NOACs (rivaroxaban, apixaban, and dabigatran) with comparators (vitamin K antagonist/warfarin, low molecular weight heparin, aspirin, placebo) were selected. We defined moderate renal insufficiency as creatinine clearance (estimated glomerular filtration rate [eGFR]) of 30-49 mL/min, and mild renal insufficiency as eGFR 50-79 mL/min.

Results: There were 40,693 patients with renal insufficiency in 10 trials. Compared with other anticoagulants in patients with mild renal insufficiency there was significantly less major or clinically relevant nonmajor bleeding (odds ratio [OR], 0.81; 95% confidence interval [CI],

RÉSUMÉ

Introduction : De récents rapports montrent que les nouveaux anticoagulants (NACO) comportent une perte de l'efficacité antithrombotique et un risque plus élevé d'hémorragie chez les patients souffrant d'insuffisance rénale. Une méta-analyse a été réalisée pour évaluer l'efficacité et l'innocuité des NACO aux doses recommandées par rapport au traitement traditionnel des patients souffrant d'insuffisance rénale.

Méthodes : Les banques de données PubMed, de la Bibliothèque Cochrane, EMBASE, EBSCO, Web of Science et CINAHL ont fait l'objet de recherche du 1er janvier 2001 au 23 mars 2014. Des essais cliniques aléatoires qui comparaient les NACO (rivaroxaban, apixaban et dabigatran) aux comparateurs (antagoniste de la vitamine K/warfarine, héparine de bas poids moléculaire, aspirine, placébo) ont été sélectionnés. Nous avons défini l'insuffisance rénale modérée en fonction de la clairance de la créatinine (taux de filtration glomérulaire estimé [TFGe]) de 30 à 40 ml/min, et l'insuffisance rénale légère de 50 à 79 ml/min.

Résultats : On comptait 40 693 patients souffrant d'insuffisance rénale de 10 essais. Comparativement aux patients souffrant

Patients with renal insufficiency face a higher risk of stroke, systemic thromboembolism, and bleeding[1-3] than those with normal renal function. In patients with nonvalvular atrial fibrillation (AF), chronic kidney disease is recognized as a risk factor for stroke in the **R**enal Dysfunction, **C**ongestive Heart Failure, **H**ypertension, **A**ge, **D**iabetes, **S**troke/Transient Ischemic Attack (R_2CHADS_2) risk scheme[2] and as a risk factor for bleeding in the **H**ypertension, **A**bnormal Renal/Liver Function, **S**troke, **B**leeding History or Predisposition, **L**abile INR, **E**lderly (> 65 Years), **D**rugs/Alcohol Concomitantly (HAS-BLED), **H**epatic or Renal Disease, **E**thanol Abuse, **M**alignancy, **O**lder Age, **R**educed Platelet Count or Function, **R**e-Bleeding, **H**ypertension, **A**nemia, **G**enetic Factors, **E**xcessive Fall Risk, and **S**troke ($HEMORR_2HAGES$), and **A**nticoagulation and **R**isk Factors **i**n **A**trial Fibrillation (ATRIA) scores.[2] Anticoagulant therapy is often indicated when patients with renal insufficiency develop AF, venous thromboembolism (VTE), or other indications.[1-3] The most commonly prescribed anticoagulants in these situations are the vitamin K antagonists (VKAs), unfractionated heparin, or low molecular weight heparin (LMWH), but each has limitations.[1,2,4,5] Use of warfarin in patients with moderate and severe renal insufficiency is associated with an increased risk of bleeding complications; and a clear benefit vs risk of using warfarin in patients with moderate and severe renal insufficiency and AF has not been demonstrated.[6-8] Several novel oral anticoagulants (NOACs) have been approved for clinical use and others are in development.[3,6] The advantages of these agents are convenient oral

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0.72-0.90) and stroke or systemic embolism (OR, 0.70; 95% CI, 0.54-0.92) with NOACs. Using random effects meta-analysis, there was significantly less stroke or systemic embolism (OR, 0.72; 95% CI, 0.57-0.92) and a trend toward less major or clinically relevant nonmajor bleeding (OR, 0.82; 95% CI, 0.59-1.14) with the NOACs among patients with moderate renal insufficiency, and this became statistically significant when evaluated using a fixed effects model. NOACs showed efficiency comparable with conventional anticoagulants for prevention of venous thromboembolism or related mortality.

Conclusions: In patients with renal insufficiency, recommended doses of novel anticoagulants are noninferior and relatively safe compared with conventional anticoagulants.

d'insuffisance rénale légère qui prenaient d'autres anticoagulants, les patients prenant des NACO ont montré significativement moins d'hémorragies majeures ou non majeures cliniquement pertinentes (ratio d'incidence approché [RIA], 0,81; intervalle de confiance [IC] à 95 %, 0,72-0,90), et d'accidents vasculaires cérébraux ou d'embolies systémiques (RIA, 0,70; IC à 95 %, 0,54-0,92). À l'aide de la méta-analyse à effets aléatoires, on a observé beaucoup moins d'accidents vasculaires cérébraux ou d'embolies systémiques (RIA, 0,72; IC à 95 %, 0,57-0,92), et une tendance à avoir moins d'hémorragies majeures ou non majeures cliniquement pertinentes (RIA, 0,82; IC à 95 %, 0,59-1,14) chez les patients souffrant d'insuffisance rénale modérée qui prenaient des NACO. Par conséquent, cela devient statistiquement significatif lors de l'évaluation à l'aide d'un modèle à effets fixes. Les NACO ont montré une efficacité comparable aux anticoagulants traditionnels dans la prévention de la thromboembolie veineuse ou de la mortalité associée.

Conclusions : Chez les patients souffrant d'insuffisance rénale, les nouveaux anticoagulants aux doses recommandées ne sont pas inférieurs aux anticoagulants traditionnels et s'avèrent relativement sûrs.

dosing, predictable pharmacokinetics, avoidance of routine coagulation monitoring, noninferior or superior efficacy and acceptable safety, including a lower risk of intracranial hemorrhage.[5,9,10] Patients with creatinine clearance < 30 mL/min for rivaroxaban and dabigatran and creatinine clearance < 25 mL/min for apixaban were excluded from the randomized trials; clinical experience in patients with renal impairment is limited, and their variable dependence on renal clearance leaves efficacy and safety of NOACs less certain compared with conventional anticoagulants.[3,10-12] Several reports suggest that the NOACs might be associated with a higher risk of bleeding in patients with renal insufficiency,[13,14] and randomized clinical trials (RCTs) have been conducted to evaluate modified dosing regimens in patients with renal impairment.[15,16] Accordingly, we performed a meta-analysis of RCTs focused on the efficacy and safety of NOACs in patients with renal impairment.

Methods

We performed a comprehensive search of the PubMed, Cochrane Systematic Reviews, Cochrane Central Register of Controlled Trials, EMBASE, EBSCO, Web of Science, and CINAHL databases for reports published between January 1, 2001 and March 23, 2014. The search strategy, study selection, and analysis criteria adhered to the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement.[17] We used the following search terms and/or keywords: new oral anticoagulant, oral thrombin inhibitor, oral factor Xa inhibitor, dabigatran, rivaroxaban, and apixaban. Inclusion in this analysis required the following: (1) RCT evaluating dabigatran, rivaroxaban, or apixaban; (2) 1 or more comparator (warfarin or another VKA, LMWH, aspirin, or placebo); and (3) outcomes data in patients with renal impairment. Two reviewers (P.S., S.C.) independently extracted data from trial reports using a standardized protocol, and disagreements were resolved by discussion with a third reviewer (D.M.). Risk of bias was assessed as recommended in the Cochrane Handbook of Systematic Reviews.[18] When more than 1 dose of a drug was administered in a single trial, data related to the outcome for all doses were considered.

The principal efficacy outcomes were stroke or systemic embolism, VTE, or fatal thromboembolism. The primary safety outcome was major or, when reported, clinically relevant nonmajor (CRNM) bleeding. Diagnosis of major bleeding was based on the International Society on Thrombosis and Hemostasis criteria.[19] We defined moderate renal insufficiency as creatinine clearance (estimated glomerular filtration rate [eGFR]) of 30-49 mL/min, and mild renal insufficiency as eGFR 50-79 mL/min (as classified in the original trials and based on European Medicines Agency classification)[20] using the Cockroft-Gault formula. When event rates or sample size was not available, we calculated event rates or sample size using mean or median follow-up data (rounded to whole numbers). The longest available follow-up data from individual trials were analyzed according to intention-to-treat. Data from each trial were combined using a random effects model to estimate pooled odds ratios (ORs) and respective 95% confidence intervals (CIs). Heterogeneity across trials was identified using I^2 statistics, considering $I^2 < 25\%$ as low and $I^2 > 75\%$ as high heterogeneity and the Cochran Q ($P \leq 0.1$) as significant for each outcome. Publication bias was evaluated using the Egger regression test and visual inspection of asymmetry in funnel plots. Statistical analyses were performed using RevMan 5.2.4 software with 2-tailed P values < 0.05 considered significant. Subgroup analyses were based on the individual NOAC agent (rivaroxaban, apixaban, or dabigatran) evaluated, indication for anticoagulation, and comparator. Sensitivity analyses for various subgroups were based on study design, blinding, different doses of dabigatran, and risk of bias.

Results

Trial characteristics

We identified 10 randomized trials that satisfied the inclusion criteria[10,15,16,21-25] (Fig. 1), and analyzed outcome

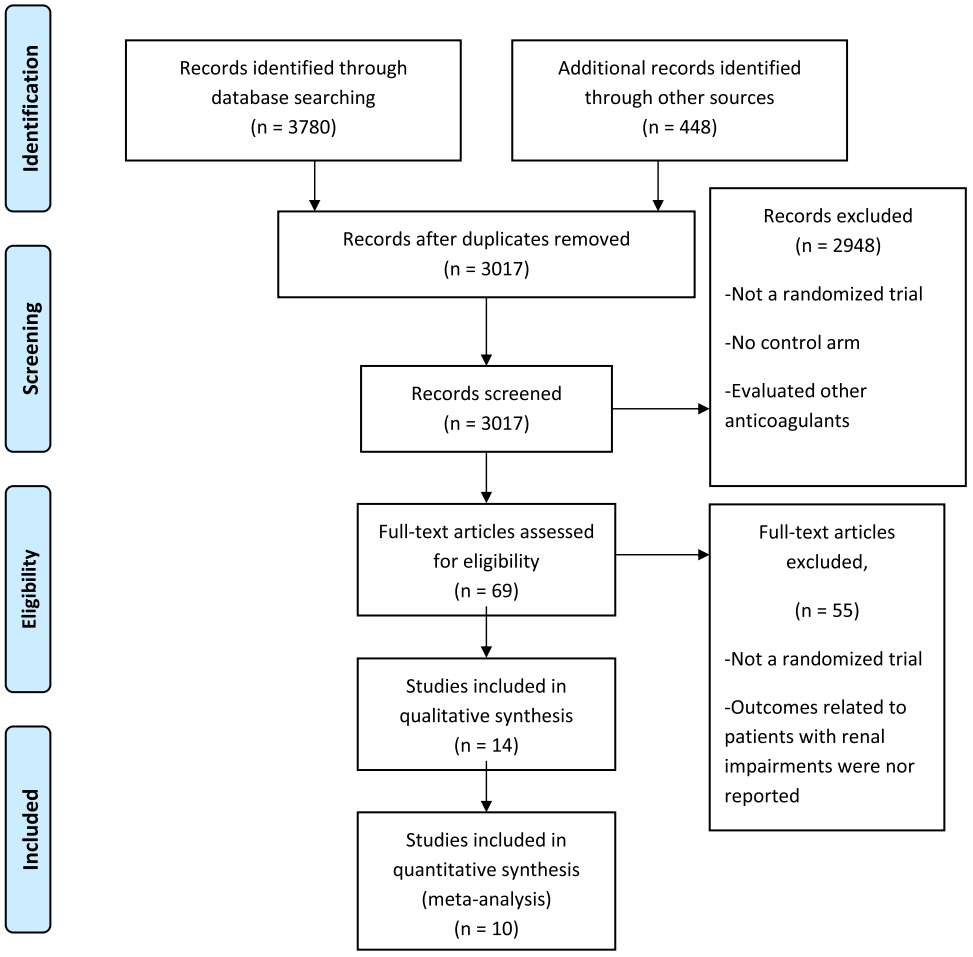

Figure 1. Search strategy and study selection according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist.

data from 40,693 patients. Baseline characteristics are listed in Table 1. Four trials evaluated rivaroxaban, 3 apixaban, and 3 dabigatran. Four trials included patients with AF; 2 addressed treatment of acute deep vein thrombosis or pulmonary embolism, 4 involved extended treatment of VTE. Outcome data (number of events per sample size) related to renal insufficiency were retrieved from a subsequent publication from the **R**andomized **E**valuation of **L**ong-term Anticoagulation Therap**y** (RE-LY) trial.[26] The sole trial involving patients with acute coronary syndromes that reported data specific to participants with impaired renal function[27] defined bleeding according to the **T**hrombolysis **i**n **M**yocardial **I**nfarction (TIMI) rather than the International Society on Thrombosis and Hemostasis criteria, and was excluded from this study. Trials of rivaroxaban and dabigatran excluded patients with creatinine clearance < 30 mL/min, and trials of apixaban excluded those with clearance < 25 mL/min and did not report outcomes separately for participants with creatinine clearance 25-29 mL/min; we combined data (creatinine clearance < 50 mL/min) for analysis of outcomes in patients with moderate renal insufficiency. The estimated creatinine clearance (CrCl) was calculated in most trials using the Cockcroft-Gault formula, and the **A**pixaban **Ver**sus Acetylsalicylic Acid (ASA) to P**r**event Str**o**ke**s** in Atrial Fibrillation Patient**s** Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment (AVERROES) trial based eGFR on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. Follow-up ranged from 3 to 36 months. The risk of bias assessment found selective reporting (reporting bias) common for outcomes data related to renal insufficiency (Supplemental Table S1).

Outcomes in patients with mild renal insufficiency

There were 28,971 patients with mild renal insufficiency included in 10 RCTs, 15,945 in the NOAC groups, and 13,026 patients in comparator groups. The rates of major or CRNM bleeding was significantly lower in those randomized to NOACs than in patients randomized to the conventional agents (4.8% vs 5.5%; OR, 0.81; 95% CI, 0.72-0.90); absolute risk reduction (ARR), 0.7%; number needed to treat (NNT), 143 (Fig. 1). Results were similar for rivaroxaban (OR, 0.78; 95% CI, 0.65-0.95) and apixaban (OR, 0.79; 95% CI, 0.64-0.97), and dabigatran (OR, 0.84; 95% CI, 0.70-1.00; Fig. 2). Sensitivity analyses with 110 and 150 mg twice a day dabigatran (2 different doses) showed results similar to the primary analysis (Supplemental Table S3). In patients with AF, the NOACs were associated with significantly lower rates of stroke or systemic embolism than conventional anticoagulants (2.9% vs 3.8%; OR, 0.70; 95%

Table 1. Characteristics of randomized clinical trials

Trial	Renal impairment-related exclusion criteria	Intervention	Control	NOAC group according to age group, n	Control group, n	Mean age (years) NOAC/comparator*	Men (%) NOAC/comparator*	Follow-up
EINSTEIN, 2010[21]	Creatinine clearance < 30 mL/min	Rivaroxaban; 15 mg twice daily for 3 weeks, followed by 20 mg once daily†	Enoxaparin/VKA	Mild RF = 393 Moderate RF = 121	Mild RF = 399 Moderate RF = 129	55.8 ± 16.4/56.4 ± 16.3	57.4/56.3	3, 6, or 12 months
EINSTEIN-PE, 2012[22]	Creatinine clearance < 30 mL/min	Rivaroxaban; 15 mg twice daily for 3 weeks, followed by 20 mg once daily†	Enoxaparin/VKA	Mild RF = 637 Moderate RF = 211	Mild RF = 593 Moderate RF = 193	57.9 ± 7.3/57.5 ± 7.2	54.1/51.7	3, 6, or 12 months
EINSTEIN-Extension, 2012[21]	Creatinine clearance < 30 mL/min	Rivaroxaban 20 mg daily†	Placebo	Mild RF = 134 Moderate RF = 37	Mild RF = 122 Moderate RF = 49	58.8/57.1	73.1/74.2	6 or 12 months
ROCKET-AF, 2011[15]	Creatinine clearance < 30 mL/min	Rivaroxaban 20 mg daily or 15 mg daily in patients with a creatinine clearance of 30-49 mL/min	Warfarin	Mild RF = 3298 Moderate RF = 1490	Mild RF = 3400 Moderate RF = 1459	73/73‡	60.3/60.3	590 days (median)
AMPLIFY-EXT, 2013[23]	Serum creatinine > 2.5 mg/dL (221 μmol/L) or a calculated creatinine clearance < 25 mL/min	Apixaban 5 mg and 2.5 mg twice daily, 2.5 mg twice daily if serum creatinine ≥ 133 μmol/L and age ≥ 80 years or weight ≤ 60 kg	Placebo	Mild RF = 342 Moderate RF = 92	Mild RF = 194 Moderate RF = 46	56.4/57.1	58/56.5	12 months
ARISTOTLE, 2011[16]	Creatinine clearance < 25 mL/min	Apixaban 5 mg twice daily, 2.5 mg twice daily if serum creatinine ≥ 133 μmol/L and age ≥ 80 years or weight ≤ 60 kg	Warfarin	Mild RF = 3817 Moderate RF = 1502	Mild RF = 3770 Moderate RF = 1515	70/70‡	64.5/65	1.8 years (median)
AVERROES, 2011[24]	serum creatinine > 2.5 mg/dL (221 μmol/L) or a calculated creatinine clearance < 25 mL/min	Apixaban 5 mg twice daily, 2.5 mg twice daily if serum creatinine ≥ 133 μmol/L and age ≥ 80 years or weight ≤ 60 kg	Aspirin 81-324 mg per day	Mild RF = 1176 Moderate RF = 581	Mild RF = 1192 Moderate RF = 564	70 ± 9/70 ± 10	59/58	1.1 years
RE-MEDY, 2013[25]	Creatinine clearance < 30 mL/min	Dabigatran 150 mg twice daily	Warfarin	Mild RF = 328 Moderate RF = 59	Mild RF = 289 Moderate RF = 49	55.4 ± 15.0/53.9 ± 15.3	60.9/61.1	6 to 36 months
RE-SONATE, 2013[25]	Creatinine clearance < 30 mL/min	Dabigatran (at a fixed dose of 150 mg twice daily)	Placebo	Mild RF = 165 Moderate RF = 41	Mild RF = 169 Moderate RF = 30	56.1 ± 15.5/55.5 ± 15.1	55.9/55	Up to 12 months
RE-LY,[10,26]	Creatinine clearance < 30 mL/min	Dabigatran 150 mg twice daily or 110 mg twice daily	Warfarin	Mild RF = 5655 Moderate RF = 2428	Mild RF = 2898 Moderate RF = 1126	71.4/71.6	63.8/63.3	2.0 years (median)

AMPLIFY-EXT, **A**pixaban After the Initial **M**anagement of **Pul**monary Embol**i**sm and Deep Vein Thrombosis With **F**irst-Line Therap**y**-**Ext**ended Treatment; ARISTOTLE, **A**pixaban for **R**eduction **i**n **St**roke and **O**ther **T**hromboembol**i**c **E**vents in Atrial Fibrillation; AVERROES, **A**pixaban **Ver**sus Acetylsalicylic Acid (ASA) to P**r**event Str**oke**s in Atrial Fibrillation Patient**s** Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment; EINSTEIN, Oral Direct Factor Xa Inhibitor Rivaroxaban in Patients With Acute Symptomatic Deep Vein Thrombosis; EINSTEIN-PE, Oral Direct Factor Xa Inhibitor Rivaroxaban in Patients With Acute Symptomatic Pulmonary Embolism; NOAC, new oral anticoagulant; RE-LY, **R**andomized **E**valuation of **L**ong-term Anticoagulation Therap**y**; RF, renal failure; ROCKET-AF, **R**ivaroxaban **O**nce Daily Oral Direct Factor Xa Inhibition **C**ompared With Vitamin **K** Antagonist for Prevention of Stroke and **E**mbolism **T**rial in **A**trial **F**ibrillation; VKA, vitamin K antagonist; VTE, venous thromboembolism.

*For overall population (separate data for renal insufficiency patients was not reported).

†In patients with moderate renal impairment (creatinine clearance of 30-50 mL/min), a dose adaptation is not indicated because of the wide therapeutic window of rivaroxaban and the potential risk for undertreatment with rivaroxaban dosages < 20 mg per day.

‡Median value.

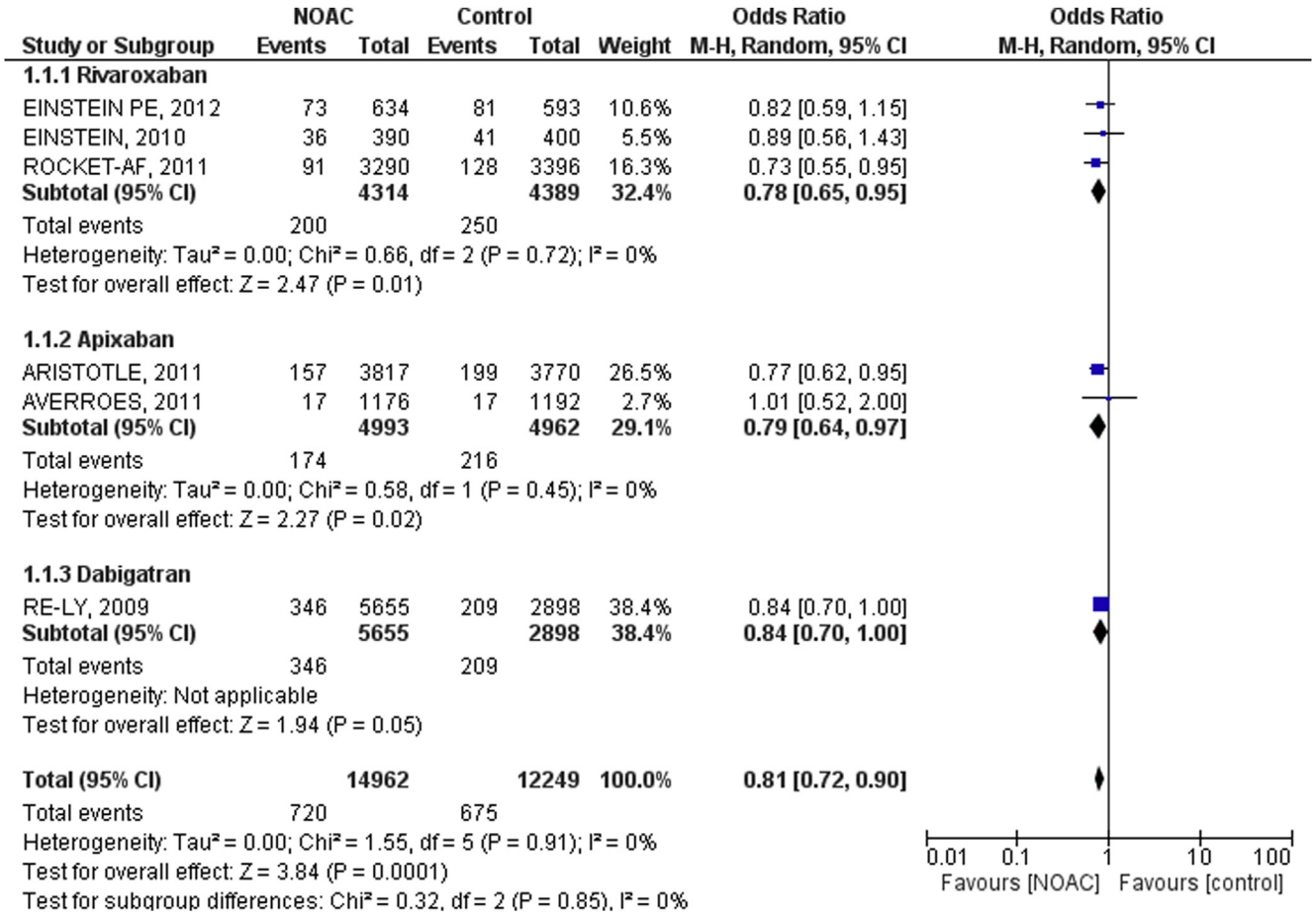

Figure 2. NOAC vs pharmacologically active agents for patients with mild renal insufficiency: major or clinically relevant bleeding. ARISTOTLE, Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; AVERROES, Apixaban Versus Acetylsalicylic Acid (ASA) to Prevent Strokes in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment; AVERROES, Apixaban Versus Acetylsalicylic Acid (ASA) to Prevent Strokes in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment; EINSTEIN, Oral Direct Factor Xa Inhibitor Rivaroxaban in Patients With Acute Symptomatic Deep Vein Thrombosis; EINSTEIN PE, Oral Direct Factor Xa Inhibitor Rivaroxaban in Patients With Acute Symptomatic Pulmonary Embolism; M-H, Mantel-Haenszel; NOAC, new oral anticoagulant; RE-LY, Randomized Evaluation of Long-term Anticoagulation Therapy; ROCKET-AF, Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonist for Prevention of Stroke and Embolism Trial in Atrial Fibrillation.

CI, 0.54-0.92; ARR, 0.95%; NNT, 105; Fig. 3). The NOACs were noninferior to conventional agents for prevention of VTE or VTE-related death (2.2% vs 2.3%; OR, 0.95; 95% CI, 0.41-2.17; Fig. 3). Rates of major or CRNM bleeding were lower with the NOACs than conventional anticoagulants in patients with AF (OR, 0.80; 95% CI, 0.71-0.90) but not in those with acute VTE (OR, 0.85; 95% CI, 0.64-1.11; Supplemental Fig. S1). Compared with warfarin, NOACs caused less major and CRNM bleeding (OR, 0.79; 95% CI, 0.70-0.90). Compared with LMWH or LMWH followed by VKA, the NOACs were associated with similar rates of bleeding (OR, 0.85; 95% CI, 0.64-1.11) (Supplemental Table S2). Bleeding was more frequent in patients with mild renal insufficiency treated with the NOACs compared with placebo, but the CI surrounding the relative risk is wide (OR, 3.57; 95% CI, 1.21-10.50).

NOACs in patients with moderate renal impairment

A total of 11,722 patients with moderate renal insufficiency were included; 6562 patients randomized to NOACs and 5160 patients in comparator groups. There was no difference between the rates of major or CRNM bleeding with NOACs compared with the conventional anticoagulants (6.8% vs 7.6%; OR, 0.82; 95% CI, 0.59-1.14; Fig. 4) when assessed using a random effects model, but an advantage to the NOACs reached statistical significance when assessed according to a fixed effects model (OR, 0.79; 95% CI, 0.68-0.92). Sensitivity analyses with 2 different doses of dabigatran (110 and 150 mg twice a day) showed similar results (Supplemental Table S3).

The risk of stroke or systemic embolism was significantly lower with NOACs than conventional agents in the random effects model (3.9% vs 5.3%; OR, 0.72; 95% CI, 0.57-0.92; ARR, 1.4%; NNT, 71; Fig. 5). Efficacy against VTE or VTE-related death for the NOACs and conventional drugs was comparable in patients with moderate renal dysfunction (3.0% vs 3.2%; OR, 0.97; 95% CI, 0.42-2.21). The risk of major or CRNM bleeding was no different during treatment with NOACs than with other anticoagulants in patients with AF (OR, 0.81; 95% CI,

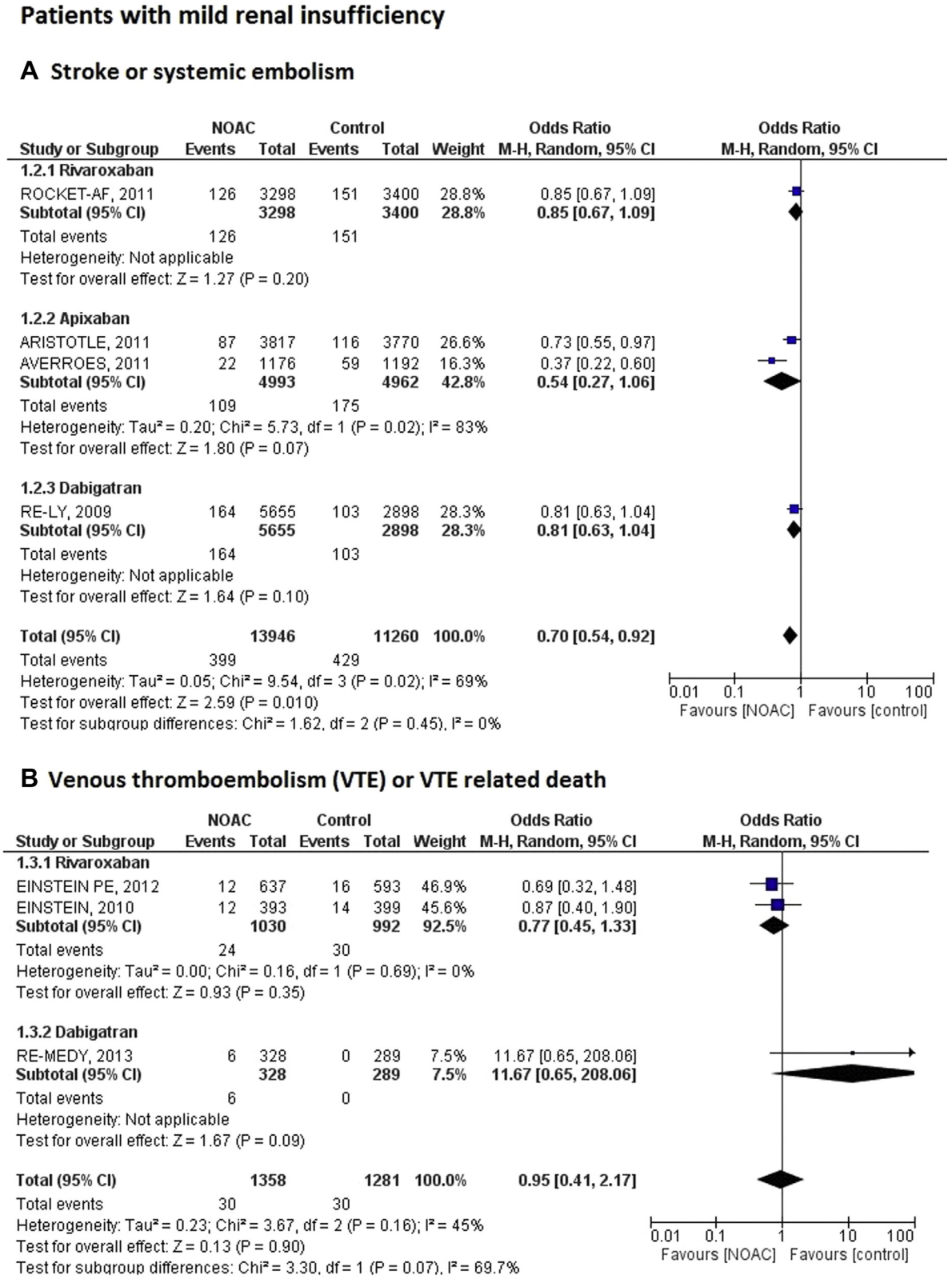

Figure 3. NOAC vs pharmacologically active agents for patients with mild renal insufficiency: (**A**) stroke or systemic embolism; (**B**) venous thromboembolism or venous thromboembolism-related death. ARISTOTLE, Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; AVERROES, Apixaban Versus Acetylsalicylic Acid (ASA) to Prevent Strokes in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment; EINSTEIN, Oral Direct Factor Xa Inhibitor Rivaroxaban in Patients With Acute Symptomatic Deep Vein Thrombosis; EINSTEIN PE, Oral Direct Factor Xa Inhibitor Rivaroxaban in Patients With Acute Symptomatic Pulmonary Embolism; M-H, Mantel-Haenszel; NOAC, new oral anticoagulant; RE-LY, Randomized Evaluation of Long-term Anticoagulation Therapy; ROCKET-AF, Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonist for Prevention of Stroke and Embolism Trial in Atrial Fibrillation.

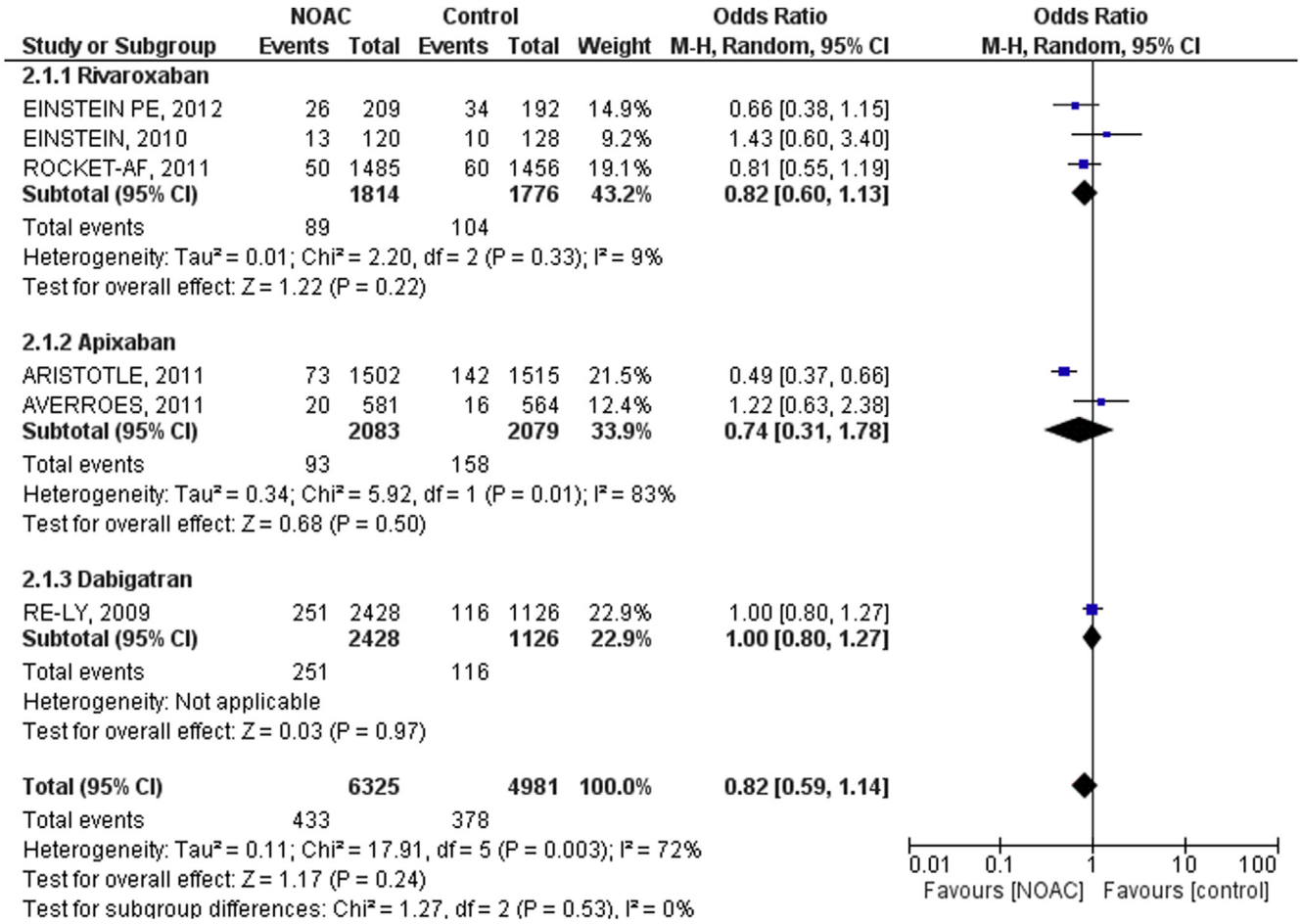

Figure 4. NOAC vs pharmacologically active agents for patients with moderate renal insufficiency: major or clinically relevant bleeding. ARISTOTLE, Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; AVERROES, Apixaban Versus Acetylsalicylic Acid (ASA) to Prevent Strokes in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment; EINSTEIN, Oral Direct Factor Xa Inhibitor Rivaroxaban in Patients With Acute Symptomatic Deep Vein Thrombosis; EINSTEIN PE, Oral Direct Factor Xa Inhibitor Rivaroxaban in Patients With Acute Symptomatic Pulmonary Embolism; M-H, Mantel-Haenszel; NOAC, new oral anticoagulant; RE-LY, Randomized Evaluation of Long-term Anticoagulation Therapy; ROCKET-AF, Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonist for Prevention of Stroke and Embolism Trial in Atrial Fibrillation.

0.54-1.21) and in those treated for acute VTE (OR, 0.90; 95% CI, 0.43-1.90; Supplemental Fig. S2). In patients with moderate renal insufficiency, the risk of major or CRNM bleeding did not differ significantly in patients assigned to 1 of the NOACs compared with warfarin (OR, 0.74; 95% CI, 0.47-1.16), LMWH or LMWH followed by VKA (OR, 0.90; 95% CI, 0.43-1.90), aspirin (OR, 1.22; 95% CI, 0.63-2.38), or placebo (OR, 1.79; 95% CI, 0.48-6.69; Supplemental Table S2).

Random effects vs fixed effects models

Estimates of treatment effect in the primary analysis for major or CRNM bleeding in patients with moderate renal insufficiency differed when a fixed-effects model was used. Results in the fixed effects model generally favoured the NOACs although trends suggesting benefit in the random effects model did not reach statistical significance. There was no evidence of small study effects (publication bias) using visual inspection of funnel plots or Egger test.

Discussion

Results of this meta-analysis suggest that the NOACs, given in recommended doses, are effective and safe compared with conventional anticoagulants, including VKAs and LMWH in patients with AF or VTE and moderate renal impairment. The risk of major or CRNM bleeding was lower with rivaroxaban, apixaban, and dabigatran in patients with mild renal insufficiency and comparable with that of conventional agents in those with moderate renal insufficiency. The NOACs were associated with significantly lower rates of stroke or systemic embolism compared with warfarin in patients with AF and mild or moderate renal insufficiency.

All 3 currently available NOACs are partially eliminated by renal clearance; dabigatran 80%, rivaroxaban 66%, and 33% unchanged, and apixaban 25%.[1,12] Previous studies showed an increase in the area under the plasma concentration curve and/or maximal plasma concentration for dabigatran, rivaroxaban, and apixaban in patients with impaired renal function.[12,28,29] Based on these data, modified dosing regimens were used for patients with renal insufficiency in most RCTs

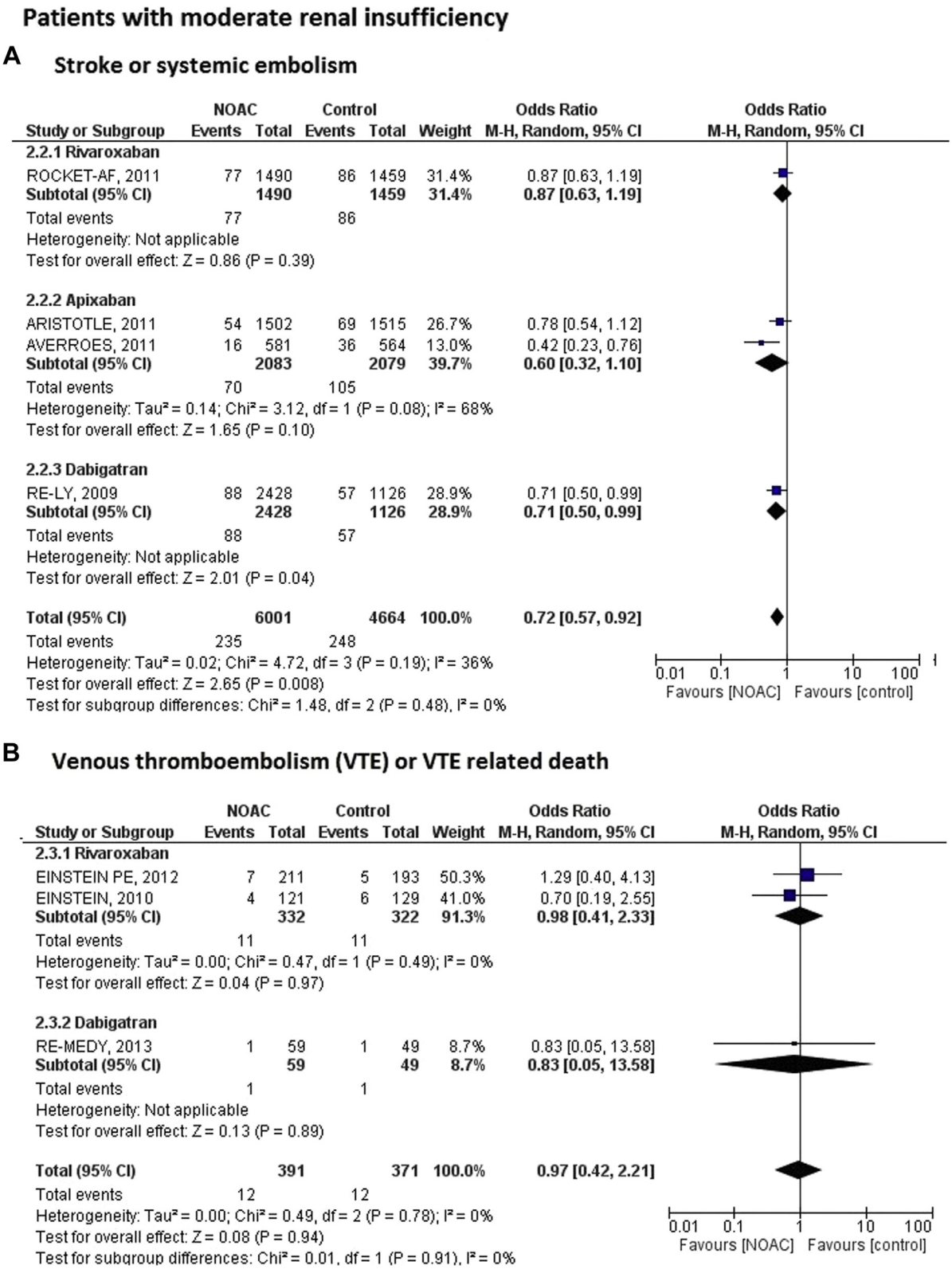

Figure 5. NOAC vs pharmacologically active agents for patients with moderate renal insufficiency: (**A**) stroke or systemic embolism; (**B**) venous thromboembolism or venous thromboembolism-related death. ARISTOTLE, Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; AVERROES, Apixaban Versus Acetylsalicylic Acid (ASA) to Prevent Strokes in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment; EINSTEIN, Oral Direct Factor Xa Inhibitor Rivaroxaban in Patients With Acute Symptomatic Deep Vein Thrombosis; EINSTEIN PE, Oral Direct Factor Xa Inhibitor Rivaroxaban in Patients With Acute Symptomatic Pulmonary Embolism; NOAC, new oral anticoagulant; RE-LY, Randomized Evaluation of Long-term Anticoagulation Therapy; ROCKET-AF, Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonist for Prevention of Stroke and Embolism Trial in Atrial Fibrillation.

evaluating the NOACs (Table 1). In the **R**ivaroxaban **O**nce Daily Oral Direct Factor Xa Inhibition **C**ompared With Vitamin **K** Antagonist for Prevention of Stroke and **E**mbolism **T**rial in **A**trial **F**ibrillation (ROCKET-AF) trial, a 15 mg daily dose of rivaroxaban was prescribed for patients with CrCl 30-49 mL/min, instead of the 20-mg daily dose recommended for patients with normal renal function.[15] In trials of apixaban, 2.5 mg twice daily was used for patients with serum creatinine $\geq$ 133 μmol/L who were older than 80 years or weighed $<$ 60 kg,[16,23] compared with the 5-mg twice per day dose used in patients without 2 or more of these features warranting dose reduction.

Results for major or CRNM bleeding in patients with moderate renal insufficiency reached statistical significance only in a fixed effects model. Fixed effect analyses are based on the assumption that a single fixed (common) effect underlies every included study. So, the basic assumption is that there is no (statistical) heterogeneity among the studies in the meta-analysis. A random effects meta-analysis is based on the assumption that individual studies estimated different treatment effects.[30] The point estimate of the treatment effect between fixed and random effects might differ because of publication or quality related bias. Differences in fixed and random effects analyses in this study might be related to study quality related bias, especially, reporting bias.

Several reports have suggested a greater risk of bleeding when NOACs are prescribed for patients with renal insufficiency,[13,14] based largely on observational data and case reports.

Our findings suggest that the NOACs might have a more acceptable efficacy and safety profile than the comparators used in these trials, when evaluated in patients with mild renal insufficiency. For patients with moderate renal insufficiency, these agents were equally safe as conventional agents (warfarin, LMWH). Although data from pharmacokinetic studies and limited clinical studies indicate that higher concentrations of NOACs accumulate in patients with renal impairment, raising the risk of bleeding, the novel agents might actually achieve safety and efficacy comparable with that demonstrated in the overall trial populations, which predominantly included patients with preserved renal function. One explanation for these findings is that the recommended doses of these agents were based on preclinical and pharmacokinetic data and modified to preserve safety and efficacy in the pivotal RCTs.

Although exploratory, the results of this meta-analysis have implications for clinical practice. Renal function should be routinely measured in all patients before starting NOAC therapy. In those with moderate renal impairment, the reduced doses of rivaroxaban and apixaban seem safe and effective compared with conventional therapy, and we found no evidence of excess bleeding. Safety data for dabigatran in patients with mild or moderate renal insufficiency are obtained only from the RE-LY trial; however, this trial reported outcomes data related to 12,107 patients with mild or moderate renal impairment. A low dose of dabigatran, 75 mg twice daily, has been approved in the United States for use in patients with CrCl 15-29 mL/min, based on pharmacokinetic modelling that demonstrated plasma concentrations of the drug comparable with those of the standard dose (150 mg twice per day) in patients with AF and normal renal function (CrCl $>$ 60 mL/min), but the safety and efficacy of this reduced dose regimen (75 mg twice daily) has not been independently confirmed. The recommended doses of NOACs are summarized in Supplemental Table S4.

No clinical efficacy and safety data are available for patients with severe (stage IV) renal insufficiency, and the NOACs should be avoided in these patients. Similarly, the efficacy and safety of NOACs for patients using renal replacement therapy (dialysis) has not been evaluated. Because of differences in protein binding, a higher proportion of dabigatran can be removed from the circulation by dialysis than rivaroxaban or apixaban. A fourth NOAC, edoxaban, has been evaluated in patients with AF and in those with VTE using a dose reduction strategy related to renal function.[31,32] A fifth, betrixaban, is less dependent than the others on renal excretion, has been evaluated only in a small phase II trial.[33]

Beyond the limitations inherent in all meta-analyses, the results provide encouraging insight regarding the safety of recommended doses of rivaroxaban, apixaban, and dabigatran in patients with renal insufficiency included in RCTs. The included trials differed with regard to protocol, criteria for mild and moderate renal insufficiency, definition of efficacy and safety outcomes, and baseline characteristics of randomized patients. For data reported as 'percent per year,' we calculated the number of events and sample size using mean and median follow-up data, which vary in some cases from the original trial statistics. Several of our conclusions are limited by wide CIs and a high degree of statistical heterogeneity, which could be reduced as data from additional NOAC agents become available.

The results of this analysis provide insight into the use of the NOACs in patients with mild or moderate renal impairment who have AF or VTE as indications for anticoagulant therapy. Rivaroxaban, apixaban, and dabigatran did not cause excess bleeding when administered in recommended doses; indeed, they were associated with less bleeding in patients with mild renal insufficiency and equal bleeding in patients with moderate renal insufficiency, compared with anticoagulants conventionally used in these populations.

Disclosures

Dr Halperin has received consulting fees from the following companies involved in the development and marketing of the NOACs: Bayer Healthcare, Boehringer Ingelheim, Daiichi-Sankyo, Johnson & Johnson, Ortho-McNeil-Janssen Pharmaceuticals, Pfizer, and Sanofi-Aventis. Dr Eyal Herzog is on the speaker bureau and a consultant for Pfizer, BMS, Daiichi Sankyo, and Astra Zeneca. The remaining authors have no conflicts of interest to disclose.

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Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Cardiology* at www.onlinecjc.ca and at http://dx.doi.org/10.1016/j.cjca.2014.04.015.