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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