



Safety and Effectiveness of Rivaroxaban Versus Warfarin Across GFR Levels in Atrial Fibrillation: A Population-Based Study in Australia and Canada

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Rationale & Objective: The benefit–risk profile of rivaroxaban versus warfarin for atrial fibrillation (AF) in patients with chronic kidney disease is uncertain. We compared rivaroxaban with warfarin across the range of kidney function in adults with AF.

Study Design: Multicenter retrospective cohort.

Setting & Participants: Adults with AF and a measure of estimated glomerular filtration rate (eGFR); using administrative data from 5 jurisdictions across Australia and Canada (2011–2018). Kidney function was categorized as eGFR ≥ 60 , 45–59, 30–44, and <30 mL/min/1.73 m². Patients receiving dialysis and kidney transplant recipients were excluded.

Exposures: New dispensation of either rivaroxaban or warfarin.

Outcomes: Composite (1) effectiveness outcome (all-cause death, ischemic stroke, or transient ischemic attack) and (2) major bleeding events (intracranial, gastrointestinal, or other) at 1 year.

Analytical Approach: Cox proportional hazards models accounting for propensity score matching were performed independently in each jurisdiction and then pooled using random-effects meta-analysis.

Results: 55,568 patients (27,784 rivaroxaban–warfarin user matched pairs; mean age 74 years, 46% female, 33.5% with eGFR <60 mL/min/1.73 m²) experienced a total of 4,733 (8.5%) effectiveness and 1,144 (2.0%) bleeding events. Compared to warfarin, rivaroxaban was associated with greater or similar effectiveness across a broad range of kidney function (pooled HRs of 0.72 [95% CI, 0.66–0.78], 0.78 [95% CI, 0.58–1.06], 0.70 [95% CI, 0.57–0.87], and 0.78 [95% CI, 0.62–0.99] for eGFR ≥ 60 , 45–59, 30–44, and <30 mL/min/1.73 m², respectively). Rivaroxaban was also associated with similar risk of major bleeding across all eGFR categories (pooled HRs of 0.75 [95% CI, 0.56–1.00], 1.01 [95% CI, 0.79–1.30], 0.87 [95% CI, 0.66–1.15], and 0.63 [95% CI, 0.37–1.09], respectively).

Limitations: Unmeasured treatment selection bias and residual confounding.

Conclusions: In adults with AF, rivaroxaban compared with warfarin was associated with lower or similar risk of all-cause death, ischemic stroke and transient ischemic attack and similar risk of bleeding across a broad range of kidney function.

Visual Abstract included

Complete author and article information provided before references.

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Chronic kidney disease (CKD) and atrial fibrillation (AF) are common interrelated major public health concerns. Both conditions are strong risk factors for stroke or systemic embolism, congestive heart failure, myocardial infarction, and all-cause death.^{1–4} Direct oral anticoagu-

Although rivaroxaban is approved for patients with greatly reduced kidney function (to the lowest limit of CrCl 15 mL/min),⁷ this is based on limited pharmacokinetic data without comprehensive assessment of cardiovascular thrombotic events and bleeding outcomes, comparing rivaroxaban with warfarin, in high-risk patients with AF and CrCl <30 mL/min.⁸ It remains uncertain whether the clinical benefit of rivaroxaban seen in patients with AF and mild-moderate CKD⁹ extends to those with advanced CKD who have been excluded from most randomized trials. Several population-based studies have compared rivaroxaban with warfarin, focused on assessing the risks of stroke and bleeding, but have demonstrated conflicting findings: with both higher⁵ and lower^{10,11} risk of bleeding reported along with variability in the risk of ischemic stroke.^{5,10,12–15} They have also had a number of limitations including single-center design,

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lants (DOACs) are now a mainstay of anticoagulant therapy for the prevention of cardiovascular thrombotic events. Rivaroxaban is commonly prescribed for people with AF and early-stage CKD.⁵ This is supported by CKD subgroup data from randomized trials indicating superior benefit–risk profiles compared to vitamin K antagonists in this group.⁶ Whether similarly favorable benefit–risk profiles exist for rivaroxaban across the spectrum of CKD remains uncertain.

PLAIN-LANGUAGE SUMMARY

This real-world study involved a large cohort of 55,568 adults with atrial fibrillation from 5 jurisdictions across Australia and Canada. It showed that the favorable safety (bleeding) and effectiveness (stroke or death) profile of rivaroxaban compared with warfarin was consistent across different levels of kidney function. This study adds important safety data on the use of rivaroxaban in patients with reduced kidney function, including those with estimated glomerular filtration rate <30 mL/min/ 1.73 m² in whom the risks and benefits of rivaroxaban use is most uncertain. Overall, the study supports the use of rivaroxaban as a safe and effective alternative to warfarin for atrial fibrillation across differing levels of kidney function.

lack of organ-specific bleeding data, and limited sample sizes for the high-risk eGFR <30 mL/min/ 1.73 m² subgroup where clinical data is most lacking,^{5,10,12-15} limiting the generalizability of their findings across the range of kidney function.

We conducted a large, multicenter cohort study of adults with AF to comprehensively assess the effectiveness (risk of all-cause death, ischemic stroke, or transient ischemic attack [TIA]), and safety (risk of hospitalization for major bleeding: either intracranial, upper or lower gastrointestinal, or other) of rivaroxaban compared with warfarin across the range of kidney function.

METHODS**Study Design and Source Population**

We conducted a retrospective, propensity score-matched parallel cohort study using a common protocol for health care data from 5 jurisdictions across Australia and Canada. In Australia, we used linked data from the EXamining ouTcomeS in chronic Disease in the 45 and Up [EXTEND45] Study,¹⁶ a population-based cohort study assembled on the Sax Institute's 45 and Up Study,¹⁷ with participants randomly sampled from the Services Australia Medicare enrollment database, which provides near complete coverage of the population. In Canada, we used administrative and registry health care data from the provinces of Alberta, British Columbia, Manitoba, and Ontario (see Table S1 for details). The study design, source population, and analytical methods have been described previously.¹⁸

Cohort Definition

The study cohort included adults with at least one outpatient serum creatinine measurement within 1 year before the cohort entry date who were newly dispensed either rivaroxaban or warfarin between January 1, 2011 and the end date of the available data in each jurisdiction (latest end

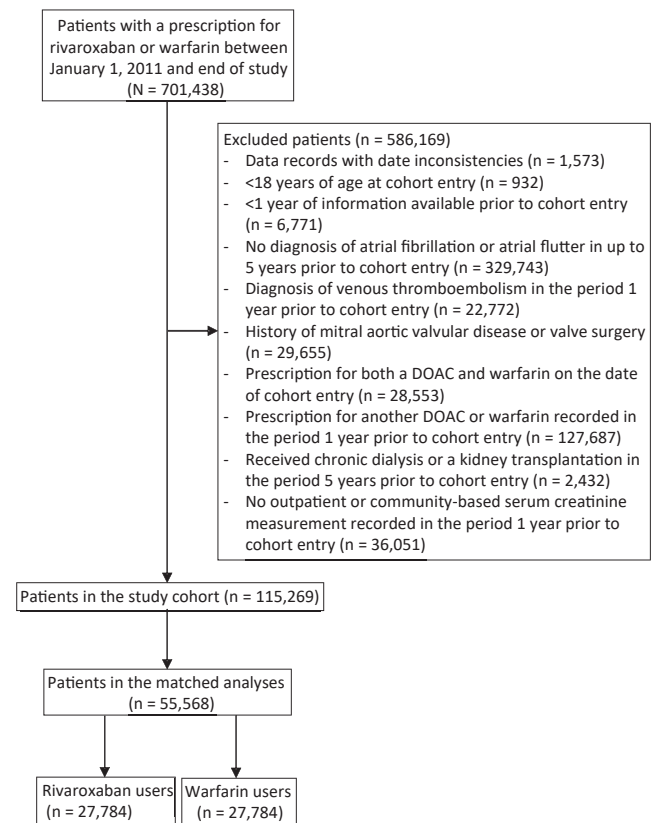


Figure 1. Identification of study cohort. DOAC, direct oral anticoagulant.

date: December 31, 2018). Cohort entry (ie, index date) was defined as the date of the first dispensed rivaroxaban or warfarin prescription during the study period. Patients were eligible for inclusion if they had a diagnosis of AF or atrial flutter (International Classification of Diseases [ICD], Ninth Revision code 427.31/2; Tenth Revision code I48^{19,20}) in up to 5 years before and including the date of cohort entry. We excluded patients who had (1) less than 1 year of information in the database before cohort entry; (2) a diagnosis of venous thromboembolism within 1 year before cohort entry; (3) a history of mitral aortic valvular disease or valve surgery in the period 5 years before cohort entry; (4) a prescription for another DOAC (dabigatran or apixaban) or warfarin within 1 year before cohort entry; or (5) both a DOAC and warfarin dispensed on the date of their first prescription (Fig 1). We excluded patients who had received maintenance dialysis or kidney transplantation in the 5-year period before the cohort entry date.

New rivaroxaban and warfarin users were matched at the time of the first dispensed prescription. Matching was based on propensity scores (the propensity to receive rivaroxaban) calculated at the time of cohort entry (detailed below). In the primary intention-to-treat analysis, exposure to either rivaroxaban or warfarin was considered a time-fixed variable throughout the study follow-up.

Assessment of Kidney Function

We estimated baseline glomerular filtration rate (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.²¹ Participants were grouped into the following eGFR categories: ≥ 60 , 45–59, 30–44, and < 30 mL/min/1.73 m².

Covariates

Demographic characteristics and comorbid conditions were assessed using health care data files of the participating sites. Comorbid conditions were defined by ICD-9 and ICD-10 diagnosis codes based on data available for the 365 days preceding cohort entry (Table S2). Comorbid conditions included diabetes, hypertension, congestive heart failure, cerebrovascular disease (including TIA and stroke [ischemic or hemorrhagic]), and history of bleeding requiring hospitalization. We assessed baseline use of prescription antiplatelet agents, nonsteroidal anti-inflammatory drugs, and proton pump inhibitors, defined as ≥ 1 dispensed prescription of these agents within 90 days before cohort entry. For descriptive purposes, we calculated the CHA₂DS₂-VASc²² score, a risk score that estimates the risk of stroke in patients with AF, and a modified HAS-BLED²³ score, a risk score that estimates the risk of major bleeding in patients with AF.

Outcomes

We assessed the 1-year composite outcomes of (1) all-cause death, first hospitalization for ischemic stroke, or TIA (hereafter referred to as the effectiveness outcome); and (2) first hospitalization for major bleeding, defined as intracranial, upper or lower gastrointestinal, or other bleeding (identified using validated ICD-9 and ICD-10 codes^{24,25}; Table S2). Individual components of the effectiveness and bleeding outcomes were also assessed separately. Participants were followed from their date of cohort entry until the earliest of the following events: date of the outcome, death, end of the 1-year follow-up period, or study end (December 31, 2018).

Statistical Analyses

A multivariable logistic regression model that included demographic information, year of cohort entry, comorbid conditions, and prescription medication use (listed above) was developed to estimate the conditional probability of being prescribed rivaroxaban within each eGFR category. We used 1-to-1 matching without replacement and a caliper width of 0.2 of the standard deviation of the logit of the propensity score.²⁶ Matching was conducted within each eGFR category to ensure similar distribution of measured baseline covariates between rivaroxaban and warfarin users by eGFR category. Balance in baseline covariates between rivaroxaban and warfarin users before and after matching was determined using the standardized difference. Meaningful imbalance was defined as an absolute standardized difference $> 10\%$.²⁷

Poisson regression was used to summarize study outcome event rates (expressed as per 100 person-years) by oral anticoagulant type (rivaroxaban or warfarin use) and eGFR category. Rates of the effectiveness and safety outcomes were used to estimate the absolute risk difference of study outcomes between rivaroxaban users and warfarin users by eGFR category. Cox proportional hazards models (accounting for clustering within matched pairs using robust sandwich estimator of variance and adjusted for baseline eGFR category) were constructed to estimate the association between rivaroxaban/warfarin use and outcomes within 1 year from the date of cohort entry by eGFR category. Within each eGFR category, warfarin users were considered as the reference category in estimating the hazard ratios (HRs) and their corresponding 95% confidence intervals (CIs) for each of the study outcomes. Separate models were constructed for the effectiveness and bleeding outcomes (overall and individually). Analyses were performed independently in each jurisdiction according to a common protocol using SAS, version 9.4 (SAS Institute Inc). A two-sided P value < 0.05 was considered statistically significant.

Meta-analysis

Summary estimates of HRs and corresponding 95% CIs were obtained within each eGFR category by pooling site-level data using the DerSimonian and Laird random-effects model. The percentage of variability across sites attributable to heterogeneity beyond chance were estimated using the I² statistic²⁸ where values of $\leq 25\%$, > 25 to 75% , and $> 75\%$ corresponded to low, moderate, and high levels of heterogeneity, respectively. Meta-regression assessed for modification of the comparative effectiveness and safety of rivaroxaban versus warfarin by eGFR category. Meta-analysis was performed with Stata software, version 16.1 (Stata Corp).

Sensitivity Analyses

Additional prespecified sensitivity analyses were performed: (1) all analyses were repeated using an as-treated approach (in which patients were censored on oral anticoagulant treatment switches or discontinuation); (2) adjusted Cox models for baseline eGFR as well as variables observed to be meaningfully imbalanced when covariate balance was assessed in each eGFR category (Table S3); (3) tested ascertainment of study outcome events using both hospital and emergency department data (in jurisdictions where emergency department data were available); and (4) we assessed the comparative effectiveness of rivaroxaban and warfarin initiation by eGFR category on the outcome of myocardial infarction (both as part of the composite outcome and individually).

Ethics Approval

In New South Wales, Australia, ethical approval for the EXTEND45 Study was obtained from the New South

Wales Population and Health Services Research Ethics Committee (HREC/13/CIPHS/69). The 45 and Up Study received ethics approval from the University of NSW Human Research Ethics Committee. In the Canadian provinces of Alberta, British Columbia, and Manitoba, the study was approved by the institutional review boards of the University of Calgary (REB18-0471_REN2), University of British Columbia Providence Health Care Research Institute (H18-02319), and University of Manitoba (HS22072), respectively. In Ontario, Canada, the use of administrative health data was authorized under section 45 of Ontario's Personal Health Information Protection Act, which does not require review by a Research Ethics Board.

RESULTS

Patient Characteristics

We identified 115,269 eligible adults with a diagnosis of AF and a new prescription for rivaroxaban ($n=63,108$) or warfarin ($n=52,161$) who had at least 1 outpatient baseline serum creatinine measurement (Fig 1). There were differences in baseline characteristics between the rivaroxaban and warfarin groups of the unmatched cohort. Rivaroxaban users, compared with warfarin users, had higher mean eGFR, and comorbid conditions such as diabetes and cerebrovascular disease were less prevalent (Table 1). Patterns in rivaroxaban and warfarin prescribing during the study period (2011-2019) are shown in Fig S1.

A total of 55,568 patients (27,784 rivaroxaban-warfarin user matched pairs) were included in the propensity score-matched analyses (EXTEND45 = 530; Alberta = 10,774; British Columbia = 110; Manitoba = 3,004; Ontario = 41,150). Overall, balance was achieved across all covariates after matching (Table 1). The mean age of the matched cohort was 74 years, 33.5% ($n=18,618$) had eGFR <60 mL/min/1.73 m² (2.4% [$n=1,348$] had eGFR <30 mL/min/1.73 m², with the majority 2.2% [$n=1,200$] having eGFR 15-29 mL/min/1.73 m²). Of the matched cohort, 51,508 (92.7%) had CHA₂DS₂-VAsC scores ≥ 2 , and 17,368 (31.3%) had HAS-BLED scores ≥ 3 . Median number of days (range across the 5 jurisdictions from which data was pooled) from last AF/atrial flutter diagnosis to cohort entry date was 12 (3-274) days (Table S4).

Effectiveness Outcome

A total of 4,733 patients experienced the effectiveness outcome (8.5%) over the 1-year follow-up period. The number of ischemic stroke or TIA events was 577 (1.0%), and there were 4,287 deaths (7.7%). Compared to warfarin, rivaroxaban initiation was associated with similar or greater effectiveness (HRs of 0.72 [95% CI, 0.66-0.78], 0.78 [95% CI, 0.58-1.06], 0.70 [95% CI, 0.57-0.87], and 0.78 [95% CI, 0.62-0.99]), across the strata of kidney function, for eGFR ≥ 60 , 45-59, 30-44, and <30 mL/min/1.73 m², respectively (Fig 2). There was no evidence of

heterogeneity across jurisdictions within eGFR groups, except for eGFR 45-59 mL/min/1.73 m² ($I^2 = 55.2\%$; P for heterogeneity = 0.06). Meta-regression showed that the association was consistent across eGFR categories and across all jurisdictions ($P = 0.75$). Compared with warfarin, rivaroxaban initiation was associated with similar or lower risk of all-cause death (HRs of 0.70 [95% CI, 0.65-0.77], 0.78 [95% CI, 0.57-1.07], 0.71 [95% CI, 0.63-0.82], and 0.76 [95% CI, 0.59-0.97]), across the strata of kidney function, for eGFR ≥ 60 , 45-59, 30-44, and <30 mL/min/1.73 m², respectively (Table S5). Further, compared with warfarin, rivaroxaban initiation was associated with similar risk of ischemic stroke or TIA (HRs of 0.80 [95% CI, 0.54-1.19], 0.75 [95% CI, 0.53-1.04], 0.71 [95% CI, 0.23-2.20] and 0.99 [95% CI, 0.45-2.17]), across the strata of kidney function, for eGFR ≥ 60 , 45-59, 30-44, and <30 mL/min/1.73 m², respectively (Table S5).

Major Bleeding Outcomes

A total of 1,144 (2.0%) experienced a major bleeding event. The numbers of intracranial, upper or lower gastrointestinal, and other bleeding events were 138 (0.2%), 731 (1.3%), and 267 (0.5%), respectively. Overall, incidence rates of the major bleeding outcomes increased with progressively lower eGFR in both rivaroxaban and warfarin users (Table S6).

Rivaroxaban was associated with similar risk of major bleeding across all categories of eGFR (HRs for eGFR categories ≥ 60 , 45-59, 30-44, and <30 mL/min/1.73 m²: 0.75 [95% CI, 0.56-1.00], 1.01 [95% CI, 0.79-1.30], 0.87 [95% CI, 0.66-1.15], and 0.63 [95% CI, 0.37-1.09], respectively; Fig 3). There was no evidence of heterogeneity across jurisdictions within eGFR groups, except for eGFR ≥ 60 mL/min/1.73 m² for major bleeding ($I^2 = 45.4\%$). Meta-regression showed that the comparative safety of rivaroxaban versus warfarin was consistent across eGFR categories and the 5 jurisdictions ($P = 0.76$). Similar results were observed when components of the major bleeding outcome were assessed individually (Table S5).

Patterns of Reduced Rivaroxaban Dosing According to eGFR Category

Forty-six percent of rivaroxaban users were prescribed a reduced dose. Among rivaroxaban users with eGFR ≥ 60 , 45-59, 30-44, and <30 mL/min/1.73 m², the proportion of patients prescribed reduced doses were 36%, 53%, 77%, and 86%, respectively (Fig S2).

Sensitivity Analysis

Results generally remained unchanged (Fig 4) in all sensitivity analyses including (1) as-treated analysis; (2) models adjusted for covariates identified as imbalanced when covariate balance was evaluated according to eGFR category; (3) analyses using both hospitalization and emergency department data to assess the occurrence of study outcome events in jurisdictions where data were

Table 1. Baseline Characteristics of Patients With Atrial Fibrillation, by Rivaroxaban and Warfarin Use, Before and After Propensity Score Matching

	Unmatched Cohort		Standardized Difference ^a	Matched Cohort		Standardized Difference ^a
	Rivaroxaban	Warfarin		Rivaroxaban	Warfarin	
Number of patients	63,108	52,161		27,784	27,784	
Age (y); mean (SD) ^a	74.1 (9.4)	75.5 (10.2)	0.180	74.2 (9.8)	74.5 (10.3)	0.030
Female	29,578 (46.9%)	24,094 (46.2%)	0.041	12,711 (45.7%)	12,773 (46.0%)	0.015
eGFR (mL/min/1.73 m ²); mean (SD) ^a	70.8 (17.5)	62.7 (22.2)	0.399	68.5 (19.1)	68.0 (19.5)	0.031
≥60	45,809 (72.6%)	29,668 (56.9%)		18,475 (66.5%)	18,475 (66.5%)	
45-59	12,060 (19.1%)	10,111 (19.4%)		5,498 (19.8%)	5,498 (19.8%)	
30-44	4,554 (7.2%)	7,344 (14.1%)		3,137 (11.3%)	3,137 (11.3%)	
<30	685 (1.1%)	5,038 (9.7%)		674 (2.4%)	674 (2.4%)	
Diabetes	19,489 (30.9%)	17,797 (34.1%)	0.157	8,980 (32.3%)	8,971 (32.3%)	0.015
Hypertension	46,673 (74.0%)	40,029 (76.7%)	0.135	20,513 (73.8%)	20,751 (74.7%)	0.020
Myocardial infarction	4,543 (7.2%)	7,538 (14.5%)	0.196	2,885 (10.4%)	3,052 (11.0%)	0.021
Congestive heart failure	13,005 (20.6%)	18,960 (36.3%)	0.353	7,928 (28.5%)	7,986 (28.7%)	0.021
Cerebrovascular disease	8,882 (14.1%)	11,004 (21.1%)	0.194	5,025 (18.1%)	5,056 (18.2%)	0.018
Peripheral vascular disease	1,433 (2.3%)	3,114 (6.0%)	0.130	1,069 (3.8%)	1,178 (4.2%)	0.021
Chronic obstructive pulmonary disease	5,774 (9.1%)	8,759 (16.8%)	0.110	3,683 (13.3%)	3,816 (13.7%)	0.010
Liver disease	2,675 (4.2%)	2,182 (4.2%)	0.014	1,208 (4.3%)	1,185 (4.3%)	0.010
Cancer	18,848 (30.0%)	15,077 (28.9%)	0.018	7,881 (28.4%)	7,899 (28.4%)	0.005
Prior major bleeding requiring hospital admission ^b	729 (1.2%)	949 (1.8%)	0.056	378 (1.4%)	378 (1.4%)	0.010
Prescription drug use						
Antiplatelet agents	4,079 (6.5%)	4,866 (9.3%)	0.108	2,116 (7.6%)	2,119 (7.6%)	0.018
Nonsteroidal anti-inflammatory drugs	11,627 (18.4%)	8,296 (15.9%)	0.018	4,514 (16.2%)	4,506 (16.2%)	0.006
Proton pump inhibitors	15,809 (25.1%)	15,009 (28.8%)	0.050	7,163 (25.8%)	7,283 (26.2%)	0.011
CHA ₂ DS ₂ -VASc score						
0-1	5,068 (8.0%)	2,979 (5.7%)	0.131	2,261 (8.1%)	1,799 (6.5%)	0.039
≥2	58,040 (92.0%)	49,182 (94.3%)	0.122	25,523 (91.9%)	25,985 (93.5%)	0.024
Modified HAS-BLED score						
0-2	18,778 (29.8%)	18,993 (36.4%)	0.112	19,094 (68.7%)	19,106 (68.8%)	0.023
≥3	44,330 (70.2%)	33,168 (63.6%)	0.127	8,690 (31.3%)	8,678 (31.2%)	0.015

Note: Data are presented as the number of patients and the corresponding percentage of the cohort unless otherwise indicated. Cells of tables with patient counts <5 were suppressed by participating centers due to privacy restrictions. The sum of count data may thus differ slightly from the presented total. CHA₂DS₂-VASc and modified HAS-BLED scores estimate the risk of stroke and bleeding, respectively, in patients with atrial fibrillation. Abbreviations: eGFR, estimated glomerular filtration rate; SD, standard deviation.

^asample size weighted mean or standardized difference.

^bbleeding defined as first hospitalization for intracranial, gastrointestinal, or other bleeding.

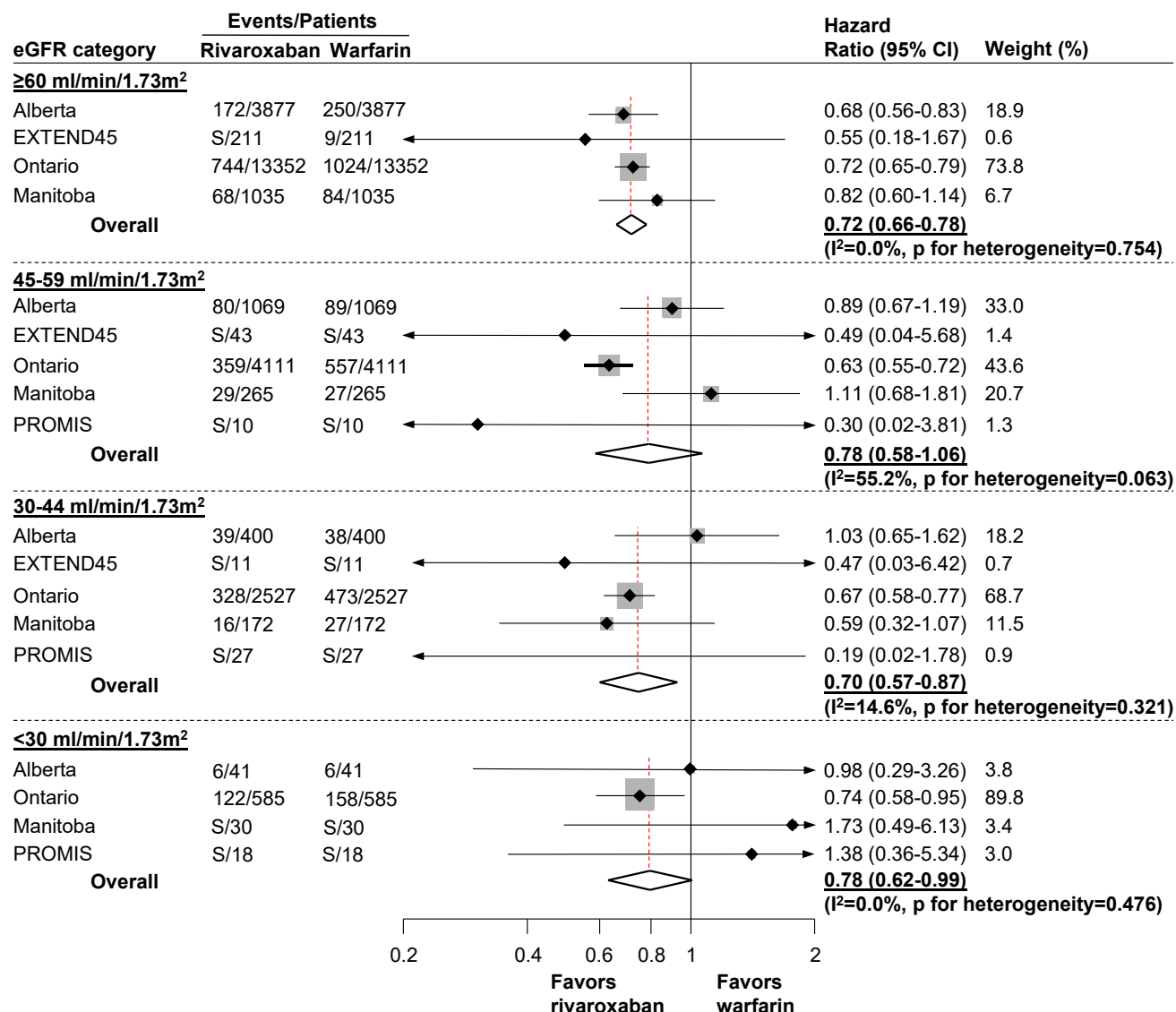


Figure 2. Hazard ratios (95% CIs) for the effectiveness outcome^a by eGFR category; within each eGFR category, warfarin initiation was considered as the reference category in estimating the hazard ratios and their 95% CI.

Meta-regression showed that the association between rivaroxaban initiation (compared with warfarin initiation) and the effectiveness outcome was not modified by eGFR category ($P = 0.75$).

^aDefined as the composite of all-cause death, ischemic stroke, or transient ischemic attack.

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; EXTEND45, Examining Outcomes in Chronic Disease in the 45 and Up Study (the data source used in the state of New South Wales, Australia. In EXTEND45, there were no rivaroxaban–warfarin matched pairs included for eGFR <30 mL/min/1.73 m²); PROMIS, Patient Records and Outcome Management Information System (data source used in the province of British Columbia, Canada; PROMIS is an integrated registry and clinical information system for chronic kidney disease [eGFR <60 mL/min/1.73 m²] and therefore was excluded from eGFR category ≥60 mL/min/1.73m²); S, number of outcome events were <5 and cells were suppressed to meet privacy restrictions.

available; and (4) the outcome of nonfatal myocardial infarction (individually and as part of the effectiveness outcome) by eGFR category.

DISCUSSION

In this large multicenter study of adults with AF, rivaroxaban versus warfarin was associated with similar or better effectiveness and similar safety across a broad range

of kidney function. Findings were consistent across the jurisdictions and a series of sensitivity analyses. Despite its limitations as an observational study, it has important clinical implications given the lack of trials including patients with AF and CKD, especially advanced CKD.

DOAC therapy is a key component of the prevention of thromboembolic events in people with AF and is widely used in this patient population. However, these agents are prescribed less frequently in patients with reduced kidney

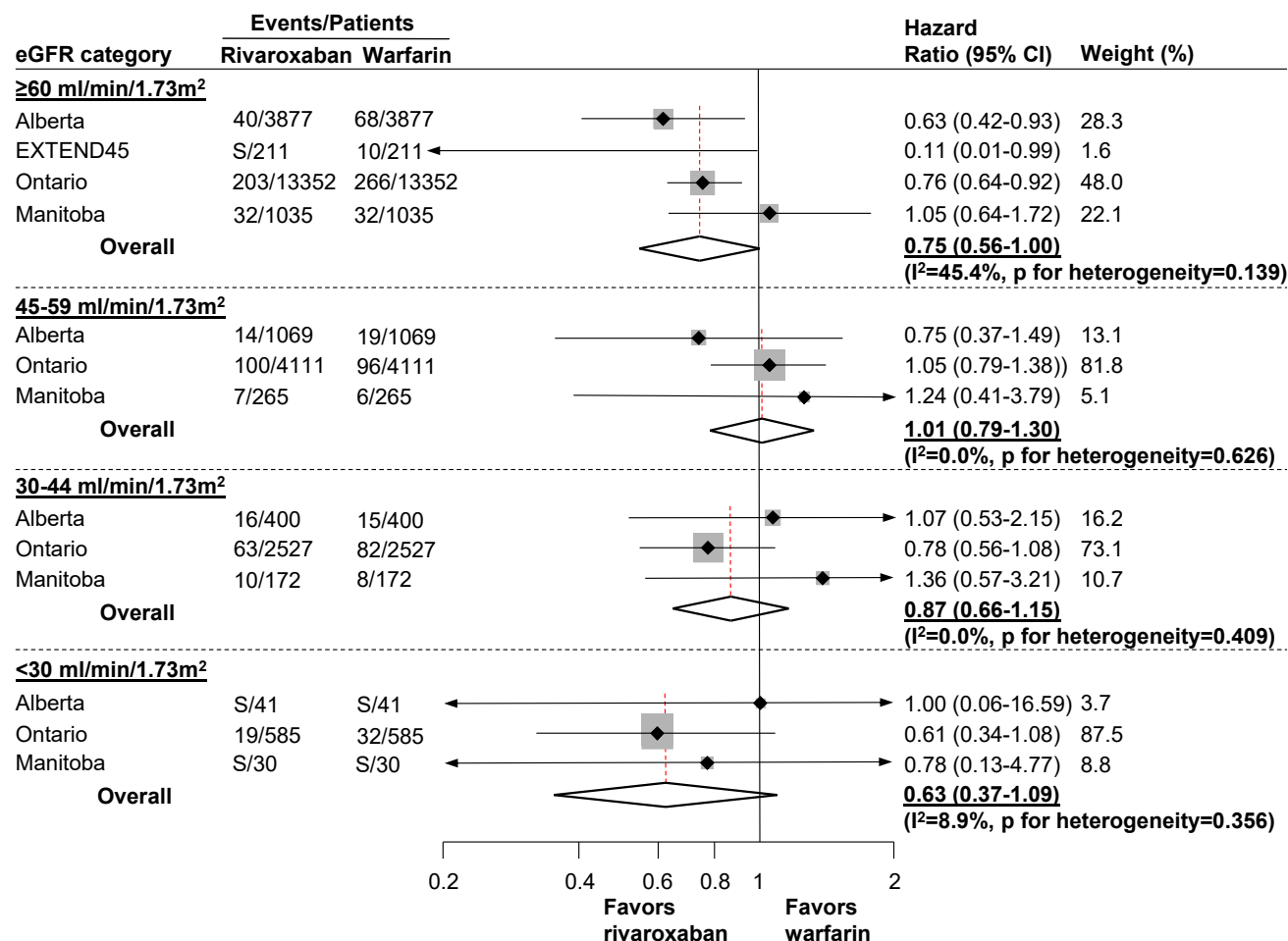


Figure 3. Hazard ratios (95% CIs) for the major bleeding outcome^a by eGFR category; within each eGFR category, warfarin initiation was considered as the reference category in estimating the hazard ratios and their 95% CIs.

Meta-regression showed that the association between rivaroxaban initiation (compared with warfarin initiation) and the safety outcome was not modified by eGFR category ($P = 0.76$).

^aDefined as the first hospitalization for major bleeding (intracranial, upper or lower gastrointestinal, or other bleeding).

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; EXTEND45, Examining Outcomes in Chronic Disease in the 45 and Up Study (data source used in the state of New South Wales, Australia; due to 0 cells [ie, no outcome events] recorded for eGFR categories 45-59 mL/min/1.73 m² and eGFR 30-44 mL/min/1.73 m², data from EXTEND45 were excluded from these eGFR categories; there were no rivaroxaban-warfarin matched pairs included for eGFR <30 mL/min/1.73 m²); PROMIS, Patient Records and Outcome Management Information System (the data source used in the province of British Columbia, Canada; PROMIS is an integrated registry and clinical information system for chronic kidney disease [eGFR <60 mL/min/1.73 m²] and therefore was excluded from eGFR category ≥60 mL/min/1.73 m² group); S, number of outcome events were <5 and cells were suppressed to meet privacy restrictions.

function than those with normal kidney function,²⁹ attributable to uncertainty regarding the risk of bleeding in individuals with reduced kidney function. Our results have important implications in this regard. First, our findings on the favorable benefit-risk profile of rivaroxaban in patients with AF and moderately reduced kidney function support its ongoing use in this patient group. This was initially demonstrated in the ROCKET-AF and J-ROCKET-AF trials, which included patients with CrCl 30 to 50 mL/min.^{9,30,31} Our study substantially adds to this studied population, including over 8,600 rivaroxaban users with eGFR 30-59 mL/min/1.73 m². Second, our study adds important safety data. It

raises no obvious concerns regarding the comparative safety of rivaroxaban versus warfarin across a broad range of kidney function, showing a similar risk of organ-specific major bleeding, including gastrointestinal bleeding.

There remains insufficient evidence to establish benefits or harms of DOACs or warfarin in patients with advanced CKD, who have been largely excluded from randomized trials.⁶ These patients may be preferentially prescribed warfarin over DOACs due to reduced drug elimination of DOACs at lower creatinine clearances, lack of widely accessible reversal agents, and lack of an assay to reliably measure the anticoagulant effect of any DOAC in CKD.⁹

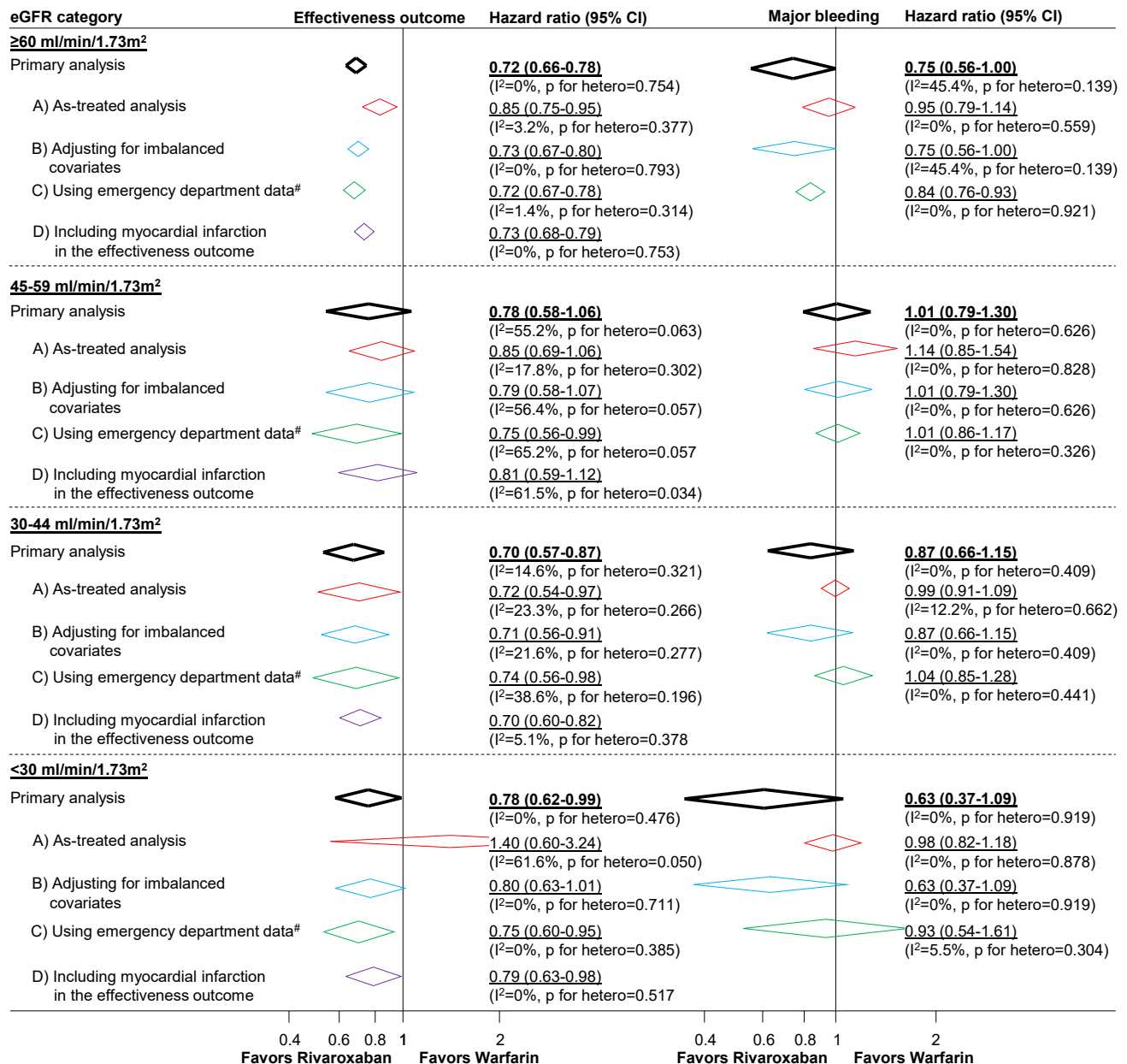


Figure 4. Sensitivity analyses assessing the comparative effectiveness and safety of rivaroxaban and warfarin according to eGFR category.^a (A) As-treated analysis in which patients were censored on oral anticoagulant treatment switches or discontinuation; (B) Analysis adjusted for baseline eGFR category and variables observed to be meaningfully imbalanced when covariate balance was assessed in each eGFR category; (C) Analysis in which the occurrence of study outcome events were identified using both hospital and emergency department data (in participating sites where emergency department data were available) and (D) Analysis in which the comparative effectiveness outcome additionally included myocardial infarction.

^aThe percentage of variability across sites attributable to heterogeneity beyond chance were estimated using the *I*² statistic where values of ≤25%, >25% to 75%, and >75% correspond to low, moderate, and high levels of heterogeneity, respectively.

This study contributes important data suggesting no safety signal or lack of effectiveness for rivaroxaban compared to warfarin in over 1,300 participants with eGFR <30 mL/min/1.73 m², providing some reassurance for its use as an alternative to warfarin.

Our findings are also largely consistent with previous cohort studies examining the influence of kidney function on ischemic stroke and major bleeding in patients with AF

treated with rivaroxaban or warfarin, with a few exceptions.¹²⁻¹⁴ A major study by Shin et al⁵ demonstrated that patients with AF and eGFR <60 mL/min/1.73 m² derived similar benefits from DOACs for prevention of ischemic stroke compared with warfarin but surprisingly had a higher risk of bleeding. In comparison, our study suggests that rivaroxaban is at least a safe alternative to warfarin in patients with moderately reduced kidney function.

The strengths of our study include assessment of the effectiveness and safety of rivaroxaban in patients with AF across a broad range of kidney function in a large binational cohort. In addition, our study involved a large and diverse patient population, including individuals typically excluded from randomized trials, with around a third of the matched cohort at high cardiovascular risk, with diabetes, congestive heart failure, and/or eGFR <60 mL/min/1.73 m². Previous cohort studies have focused on stroke and bleeding outcomes without attention to other cardiovascular thrombotic events including nonfatal myocardial infarction in a high-risk population with reduced kidney function. When comparing rivaroxaban with warfarin, we have demonstrated no clear difference in the risk of myocardial infarction in patients with AF across all categories of eGFR. We acknowledge the sensitivity analysis including myocardial infarction could have been strengthened by more comprehensive data on antiplatelet use. However, our linked data was not able to capture concurrent use of aspirin, an over-the-counter medication in the included jurisdictions.

Our study also has limitations. Data on appropriate dosing of rivaroxaban in patients with reduced kidney function and time in the therapeutic range of warfarinized patients were not available. We assessed bleeding events requiring hospitalization (due to differences in data availability across jurisdictions), which may have underestimated the full extent of bleeding rates in the study, although our findings were consistent when including emergency department data where available. Considered together, these may reflect the lower major bleeding rate (2.0%) in the matched cohorts compared to previous cohorts and trials. However, our study provides real-world evidence for the prescription of oral anticoagulants in patients with moderately reduced kidney function where international normalized ratios can be labile.^{12,30} Although patients with eGFR <30 mL/min/1.73 m² were included, patients with poor kidney function (eGFR <15 mL/min/1.73 m²) were still underrepresented in our cohort, which limited our ability to further assess the safety and effectiveness of rivaroxaban compared with warfarin in this patient group. Hence, the possibility of excess bleeding risk with rivaroxaban in this high-risk population cannot be excluded. We assessed study outcomes within 1 year from rivaroxaban or warfarin initiation, and therefore, the risk–benefit ratio of rivaroxaban in patients with AF and CKD over longer periods was not studied. Finally, as an observational study, the potential for unmeasured residual confounding remains.

In this large cohort of adults with AF, rivaroxaban compared with warfarin was associated with greater or similar effectiveness and similar safety across a broad range of kidney function. Our results suggest rivaroxaban may have a favorable benefit–risk ratio in patients with AF independent of kidney function, including those with advanced nondialysis CKD.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Figure S1: Patterns in rivaroxaban and warfarin prescribing during the study period (2011–2019).

Figure S2: Rivaroxaban dosing patterns in the study cohort according to eGFR category.

Table S1: Data Sources Used in the Study Across the Participating Centers

Table S2: ICD-9-CM and ICD-10-CA Diagnosis Codes for the Identification of Atrial Fibrillation, Covariates, and Study Outcomes

Table S3: Baseline Characteristics of Patients With Atrial Fibrillation by eGFR Category, Before and After Propensity Score Matching

Table S4: Distribution of Time Between AF/Atrial Flutter Diagnosis and First Prescription for Rivaroxaban or Warfarin (Cohort Entry Date)

Table S5: Pooled Hazard Ratios (95% Confidence Intervals) for the Individual Components of the Effectiveness and Major Bleeding Outcomes by eGFR Category

Table S6: Incidence Rates (95% CIs) of the Effectiveness and Major Bleeding Outcomes by Rivaroxaban and Warfarin Use and eGFR Category

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New South Wales (NSW), Australia: Data from the EXTEND45 study (a population-based cohort study assembled on the Sax Institute's 45 and Up Study,¹⁷ a large prospective study of a cohort of NSW residents aged ≥ 45 years originally recruited between 2005 and 2009) were used. Of the 267,357 participants originally recruited to the 45 and Up Study, patient data on 530 participants were included in the current study. This research was completed using data collected through the 45 and Up Study (www.saxinstitute.org.au). The 45 and Up Study is managed by the Sax Institute in collaboration with major partner Cancer Council NSW; and partners: the Heart Foundation; NSW Ministry of Health; NSW Department of Communities and Justice; and Australian Red Cross Lifeblood. We thank the many thousands of people participating in the 45 and Up Study. Record linkage of the 45 and Up Study baseline questionnaire responses with corresponding information from the NSW Admitted Patient Data Collection, the Registry of Births, Deaths and Marriages, and community laboratory testing services was performed by the NSW Centre for Health Record Linkage (CHeReL) covering the period 2005-2014. CHeReL uses a probabilistic procedure to link records, in which records with an uncertain probability of being true matches are checked by hand. Its current estimated false

positive rate is 0.5% (CHeReL; <https://www.cherel.org.au>). The Medicare Benefits Schedule (MBS; recorded claims for subsidized medical and diagnostic services in Australia) and Pharmaceutical Benefits Scheme (PBS; recorded claims for subsidized pharmaceutical products in Australia) data were provided to the Sax Institute by Services Australia. Record linkage of the 45 and Up Study data to the MBS and PBS data was facilitated by the Sax Institute using a unique identifier provided by Services Australia and based on deterministic matching. All linked data available in the EXTEND45 study were accessed through the Secure Unified Research Environment (SURE).

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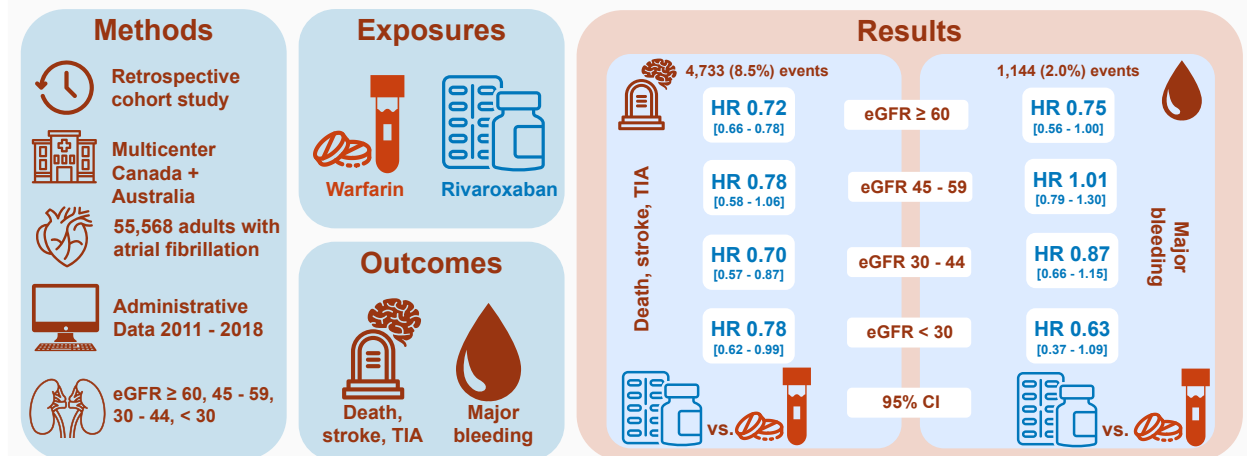
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What is the safety and effectiveness of rivaroxaban vs warfarin in adults with atrial fibrillation and CKD?

Kidney
Medicine



Conclusion: In adults with AF, rivaroxaban as compared to warfarin, was associated with lower or similar risk of all-cause death, ischemic stroke and transient ischemic attack and similar risk of bleeding across a broad range of kidney function.

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