



Efficacy and safety of Xa inhibitors in patients with heart failure and coronary or peripheral artery disease: a systematic review and meta-analysis of randomized controlled trials

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Background: To evaluate the efficacy and safety of Xa inhibitors in patients with heart failure (HF) and coronary artery disease (CAD) or peripheral artery disease (PAD).

Methods: A systematic electronic literature search was performed using the PubMed, Web of Science, EMBASE, and Cochrane Library databases from inception to June 26, 2019. A total of four randomized controlled trials involving 14,694 patients were included in this meta-analysis.

Results: The meta-analysis showed that there was no statistical difference between the Xa inhibitor and control group regarding the primary efficacy outcome [rivaroxaban 2.5 mg group: relative risk (RR) 0.82, 95% CI: 0.66–1.01, P=0.06; rivaroxaban 5 mg group: RR 0.86, 95% CI: 0.73–1.02, P=0.08]. The risk of the primary safety outcome was significantly increased among patients who received Xa inhibitors compared with the control group (rivaroxaban 2.5 mg group: RR 1.55, 95% CI: 1.21–1.98, P=0.0006; rivaroxaban 5 mg group: RR 1.66, 95% CI: 1.30–2.12, P<0.0001). There was no significant difference in the risk of cardiovascular death between the Xa inhibitor and control group (rivaroxaban 2.5 mg group: RR 0.79, 95% CI: 0.54–1.14, P=0.21; rivaroxaban 5 mg group: RR 0.89, 95% CI: 0.73–1.08, P=0.24). The risk of myocardial infarction (MI) in the rivaroxaban 5 mg group was significantly lower than that of the control group (RR 0.83, 95% CI: 0.69–0.99, P=0.04). However, the risk of MI in the rivaroxaban 2.5 mg group was similar to that of the control group (RR 0.85, 95% CI: 0.71–1.01, P=0.07).

Discussion: Xa inhibitors were associated with a higher risk of major adverse cardiovascular events and bleeding among HF and CAD or PAD patients. Therefore, Xa inhibitors should be used cautiously in patients with HF and CAD or PAD.

Keywords: Xa inhibitor; heart failure (HF); coronary artery disease (CAD); peripheral artery disease (PAD); meta-analysis

Submitted May 27, 2021. Accepted for publication Jul 14, 2021.

doi: 10.21037/apm-21-1645

View this article at: <https://dx.doi.org/10.21037/apm-21-1645>

Introduction

Heart failure (HF) is an important cause of human morbidity and mortality and is considered an epidemic disease worldwide, affecting approximately 1% to 3% of

the adult population (1). Because of the abnormality of the clotting cascade and blood flow in patients with HF, thrombotic complications (including ischemic stroke, peripheral arterial embolism, and pulmonary embolism,

etc.) are common among HF patients (2). HF and coronary artery disease (CAD) usually coexist in clinical practice. Coronary arteries with thrombosis are more prone to myocardial infarction (MI) or sudden death (3). Therefore, oral anticoagulants (OACs) are essential in the management of HF with atrial fibrillation (AF) (4).

Recently, prospective evidence from four randomized controlled trials, the WASH (5), WATCH (6), HELAS (7), and WARCEF (8) trials, for vitamin K antagonist (VKA) efficacy in patients with HF and sinus rhythm has become available. These four trials showed that there was no significant difference in benefit events other than ischemic stroke between the VKA group and the other groups. Furthermore, patients in the VKA group may have higher rates of major hemorrhages (9). Therefore, the clinical application of OACs remains controversial among patients with HF and CAD or PAD. Fortunately, Xa inhibitors are a new type of OAC that is being used widely clinically, because it significantly improves compliance and decreases bleed complications. Therefore, Xa inhibitors are promising OACs for the treatment of patients with HF and CAD or PAD.

Most previous studies focused on patients with HF complicated with AF. And the application value of OACs in AF was relatively clear. Patients with HF combined with CAD and PAD are high-risk groups for cardio-cerebrovascular adverse events. However, there is limited information about the efficacy and safety of Xa inhibitors among patients with HF combined with CAD or PAD. Therefore, we conducted this meta-analysis to evaluate the efficacy and safety of Xa inhibitors in patients with HF combined with CAD or PAD. We present the following article in accordance with the PRISMA reporting checklist (available at <https://dx.doi.org/10.21037/apm-21-1645>).

Methods

Search strategy and study selection

Two independent reviewers (YQC and XF) conducted a comprehensive literature search using a search strategy combining MeSH terms and free word searches in the PubMed, Web of Science, EMBASE, and Cochrane Library databases from inception to June 26, 2019. We identified randomized clinical trials (RCTs) that evaluated the efficacy and safety of Xa inhibitors in patients with HF and CAD or PAD. The search terms used were (CAD OR PAD) AND HF AND Xa inhibitors [details summarized

in the [Supplementary file \(Appendix 1\)](#)]. After excluding duplicated records, titles and abstracts were screened, and then entire articles were assessed based on inclusion and exclusion criteria. Data were extracted following the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines (10).

Inclusion and exclusion criteria

The inclusion criteria were as follows: (I) design: original articles of RCTs; (II) population: patients with HF and CAD or PAD; (III) interventions: oral Xa inhibitors with or without antiplatelet agents. The exclusion criteria were: (I) no data about efficacy and safety of patients, and (II) written in a language other than English.

Data extraction

Two reviewers (YQC and XF) independently extracted data from included studies. Disagreements were resolved through discussion with a third investigator (CLQ). The information extracted for each study included the lead author, publication year, participant characteristics, study design, sample size, and outcomes.

Study quality assessment

Assessment for risk of bias was independently conducted by two authors (LFZ and YS). The Cochrane Collaboration Risk of Bias Tool was used to assess the risk of bias in RCTs (11), including random sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting, and other sources of bias. Publication bias was not assessed, as the total number of included studies was less than 10.

Efficacy and safety outcomes

The primary efficacy outcome was the composite endpoint of death from any cause, MI and stroke, or the composite endpoint of death from any cardiovascular (CV) causes, MI and stroke (APPRAISE-2 trial used ischemic stroke) (12). The primary safety outcome was major bleeding defined by the International Society on Thrombosis and Hemostasis (ISTH) or major bleeding according to the Thrombolysis in Myocardial Infarction (TIMI) definition. The secondary endpoints included mortality, risk of MI, risk of stroke, etc.

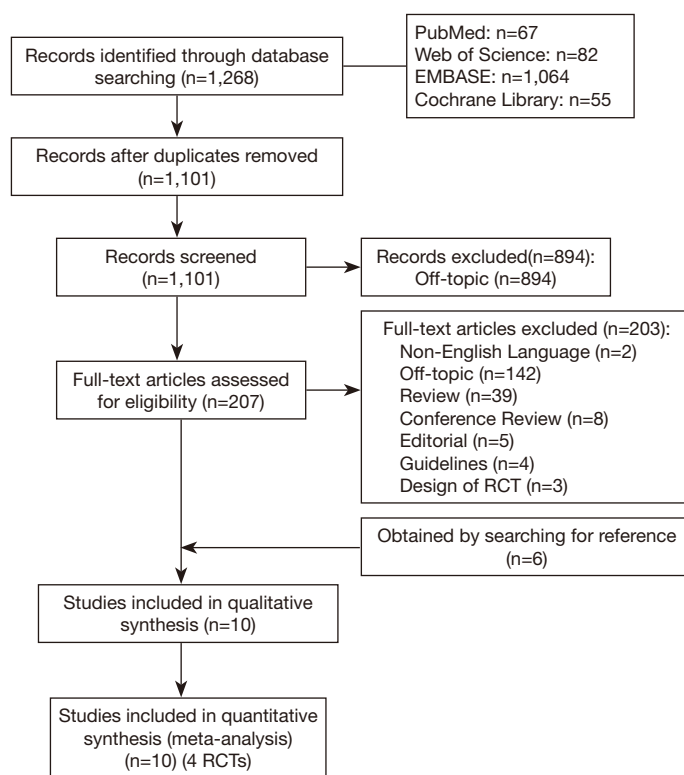


Figure 1 Flow diagram of study identification and selection process. RCT, randomized controlled trial.

Statistical analysis

The Review Manager 5.3 software (RevMan 5.3) was used to perform the analysis. Dichotomous outcomes were presented as a risk ratio (RR) and 95% confidence intervals (CIs). Studies were tested for heterogeneity using the I^2 statistic, and an I^2 value of greater than 50% suggested substantial heterogeneity. Fixed-effects models were used to pool data with insignificant heterogeneity and random-effects models for data with significant heterogeneity. A sensitivity analysis was performed by excluding one trial at a time to test the influence of a single study on the overall pooled estimate. Subgroup analysis was performed for patients with and without acute coronary syndrome (ACS). The significance level was set at a P value of 0.05.

Results

Study identification and selection

The electronic literature search strategy yielded 1,268 records, of which 167 were excluded as duplicates, and 894 were considered off-topic after an initial screen of title and

abstract, as they did not explicitly address Xa inhibitor use in patients with HF and CAD or PAD. Another 203 articles were excluded after a full-text review. Based on the inclusion and exclusion criteria, 4 eligible articles (12-15) were included, and another 6 articles (16-21) were obtained by searching through reference lists. The final sample comprised 4 RCTs, the APPRAISE-2 (12), ATLAS ACS 2-TIMI 51 (17), COMPASS (19), and COMMANDER HF (15) trials, involving 14,694 participants for inclusion in the quantitative analysis. The details of the study identification and selection process are shown in *Figure 1*. Since the APPRAISE-2 trial only provided the event rate per 100 patient-years of the apixaban and placebo groups in patients with prior HF, we calculated the data for each group based on the events in the total group, assuming the same follow-up time for each group.

Characterization of patients

Of the total of 14,694 participants included in this meta-analysis, 8,589 were in the Xa inhibitors group (with or without antiplatelet agents) and 6,105 patients in the

Table 1 Basic information of RCTs and baseline characteristics of patients

Information items	APPRAISE-2	ATLAS ACS 2-TIMI 51	COMPASS	COMMANDER HF
Design, year	RCT, 2011	RCT, 2012	RCT, 2017	RCT, 2018
Trial participants (n)	7,392	15,526	27,395	5,022
Xa inhibitors group	Apixaban 5 mg twice daily	Rivaroxaban 2.5 mg twice daily or Rivaroxaban 5 mg twice daily	Rivaroxaban 2.5 mg twice daily + aspirin 100 mg once daily or rivaroxaban 5 mg twice daily + aspirin-matched placebo once daily	Rivaroxaban 2.5 mg twice daily
Control group	Placebo twice daily	Placebo twice daily	Rivaroxaban-matched placebo twice daily + aspirin 100 mg once daily	Placebo twice daily
Patient population	ACS + HF	ACS + HF	CAD or PAD + HF	CAD + HF
Number of patients of groups (n)	Apixaban, 1,023; Placebo, 1,053	Rivaroxaban 2.5 mg, 562; Rivaroxaban 5 mg, 574; Placebo, 558	Rivaroxaban + aspirin, 1,963; Rivaroxaban alone, 1,960; Aspirin alone, 1,979	Rivaroxaban, 2,507; Placebo, 2,515
Age of patients, yr (mean ± SD)	67 [58–73] (median, 25th–75th percentiles)	Rivaroxaban 2.5 mg, 63.7±10.1; Rivaroxaban 5 mg, 63.2±9.3; Placebo, 63.9±10.0	65.5±9.0	Rivaroxaban, 66.5±10.1; Placebo, 66.3±10.3
Female sex, No. (%)	754 (36.3)	Rivaroxaban 2.5 mg, 188 (33.5); Rivaroxaban 5 mg, 199 (34.7); Placebo, 185 (33.2)	1,367 (23.2)	Rivaroxaban, 551 (22.0); Placebo, 599 (23.8)
Atrial fibrillation, No. (%)	216 (10.4)	Rivaroxaban 2.5 mg, 11(2.0); Rivaroxaban 5 mg, 14(2.4); Placebo, 16(2.9)	Not recorded at randomization; 1.4% developed during the trial	Excluded
Follow up (months)	8	13	23	21
Primary efficacy outcome	Composite of cardiovascular death, myocardial infarction, or ischemic stroke	Composite of cardiovascular death, myocardial infarction, or stroke	Composite of cardiovascular death, myocardial infarction, or stroke	Composite of death from any cause, myocardial infarction, or stroke
Primary safety outcome	Major bleeding defined by TIMI	Major bleeding defined by TIMI (not related to CABG)	Major bleeding defined by ISTH and fatal bleeding	Fatal bleeding or bleeding into a critical space with a potential for causing permanent disability

RCT, randomized controlled trial; APPRAISE-2, The Apixaban for Prevention of Acute Ischemic Events 2; ATLAS ACS 2-TIMI 51, Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome-Thrombolysis in Myocardial Infarction 51; COMPASS, Cardiovascular Outcomes for People Using Anticoagulation Strategies; COMMANDER HF, A Study to Assess the Effectiveness and Safety of Rivaroxaban in Reducing the Risk of Death, Myocardial Infarction, or Stroke in Participants with Heart Failure and Coronary Artery Disease Following an Episode of Decompensated Heart Failure; ACS, acute coronary syndrome; HF, heart failure; CAD, coronary artery disease; PAD, peripheral artery disease; SD, standard deviation; TIMI, thrombolysis in myocardial infarction; CABG, coronary artery bypass graft; ISTH, International Society on Thrombosis and Hemostasis.

control group (placebo or aspirin alone). The mean follow-up duration ranged from 8 months to 23 months. The baseline characteristics of patients are listed in *Table 1*.

Participants in the APPRAISE-2 and COMMANDER

HF trials were randomly divided into the Xa inhibitor and control group, but the Xa inhibitor groups in the ATLAS ACS 2-TIMI 51 and COMPASS trials comprised two different treatment regimens. We used groups with the

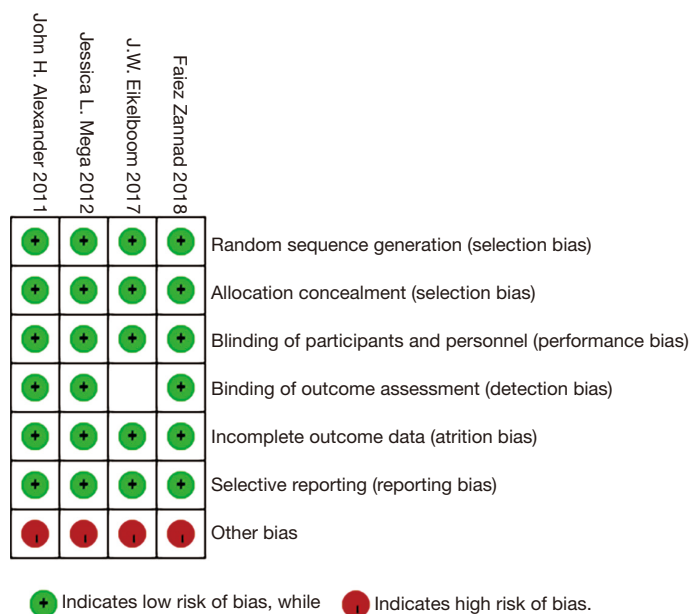


Figure 2 Risk of bias summary. Faiez Zannad 2018 corresponds to COMMANDER HF (A Study to Assess the Effectiveness and Safety of Rivaroxaban in Reducing the Risk of Death, Myocardial Infarction, or Stroke in Participants with Heart Failure and Coronary Artery Disease Following an Episode of Decompensated Heart Failure) trial. J.W. Eikelboom 2017 corresponds to COMPASS (Cardiovascular Outcomes for People Using Anticoagulation Strategies) trial. Jessica L. Mega 2012 corresponds to ATLAS ACS 2-TIMI 51 (Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome–Thrombolysis in Myocardial Infarction 51) trial. John H. Alexander 2011 corresponds to APPRAISE-2 (The Apixaban for Prevention of Acute Ischemic Events 2) trial. The correspondence relations are same to following figures.

same dose of Xa inhibitor as a parallel comparison and compared them separately with the control group. The APPRAISE-2 and ATLAS ACS 2-TIMI 51 trials enrolled patients with ACS, but no such patients were included for the COMPASS and COMMANDER HF trials. Therefore, we performed a subgroup analysis for patients with ACS.

Risks of bias summary

In this study, the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions were implemented (22). The results of the assessment showed that all of the four trials had a low risk of bias. The risk of bias assessment details is shown in *Figure 2*.

Primary efficacy outcome

Except for the COMMANDER HF trial, which used the composite endpoint of death from any cause, MI, or stroke as the primary efficacy outcome, the other three trials defined the composite endpoint as death from CV events,

MI, or stroke. (In the APPRAISE-2 trial, it was an ischemic stroke, and intracranial bleeding accounted for 0.3% and 0.1% in the apixaban and placebo group, respectively). CV death accounted for about 84.3% (929/1,102) of deaths from any cause in the COMMANDER HF trial. There was no significant difference between the Xa inhibitor and control group regarding the primary efficacy outcome (rivaroxaban 2.5 mg group: RR 0.82, 95% CI: 0.66–1.01, $P=0.06$, $I^2=77\%$, P for heterogeneity 0.004, *Figure 3A*; rivaroxaban 5 mg group: RR 0.86, 95% CI: 0.73–1.02, $P=0.08$, $I^2=62\%$, P for heterogeneity 0.05, *Figure 3B*).

Primary safety outcome

The primary safety outcome was defined as major bleeding according to the TIMI criteria in the APPRAISE-2 and ATLAS ACS 2-TIMI 51 trials. Data of major bleeding according to the ISTH criteria was reported in the COMPASS and COMMANDER HF trials. The risk of the primary safety outcome was significantly increased among patients receiving Xa inhibitors when compared with the

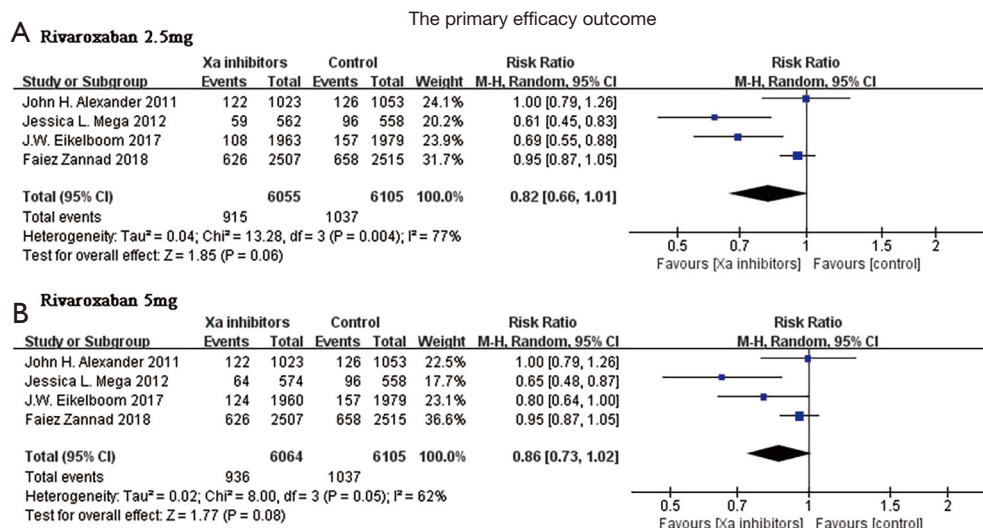


Figure 3 Meta-analysis for the primary efficacy outcome. (A) Includes the rivaroxaban 2.5 mg group in the ATLAS ACS 2-TIMI 51 trial and rivaroxaban 2.5 mg plus aspirin 100 mg group in the COMPASS trial; (B) includes the rivaroxaban 5 mg group in the ATLAS ACS 2-TIMI 51 trial and the rivaroxaban 5 mg group in the COMPASS trial. ATLAS ACS 2-TIMI 51, Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome-Thrombolysis in Myocardial Infarction 51. COMPASS, Cardiovascular Outcomes for People Using Anticoagulation Strategies.

control group (rivaroxaban 2.5 mg group: RR 1.55, 95% CI: 1.21–1.98, $P=0.0006$, $I^2=0\%$, P for heterogeneity 0.66, *Figure 4A*; rivaroxaban 5 mg group: RR 1.66, 95% CI: 1.30–2.12, $P<0.0001$, $I^2=0\%$, P for heterogeneity 0.97, *Figure 4B*).

Cardiovascular death

Only the APPRAISE-2, ATLAS ACS 2-TIMI 51 and COMMANDER HF trials provided data about CV death. There was no statistically significant difference in the CV death rate between patients in the Xa inhibitor and control groups (rivaroxaban 2.5 mg group: RR 0.79, 95% CI: 0.54–1.14, $P=0.21$, $I^2=77\%$, P for heterogeneity 0.01, *Figure 5A*; rivaroxaban 5 mg group: RR 0.89, 95% CI: 0.73–1.08, $P=0.24$, $I^2=37\%$, P for heterogeneity 0.21, *Figure 5B*).

Myocardial infarction

Data on the incidence of MI among patients with HF and CAD or PAD was not reported in the COMPASS trial. The risk of MI in patients who received 2.5 mg rivaroxaban was not significantly different from that of the control group (RR 0.85, 95% CI: 0.71–1.01, $P=0.07$, $I^2=0\%$, P for heterogeneity 0.53, *Figure 6A*). While patients who received 5 mg rivaroxaban had a lower risk of MI (RR 0.83, 95%

CI: 0.69–0.99, $P=0.04$, $I^2=22\%$, P for heterogeneity 0.28, *Figure 6B*) when compared with the control group.

Stroke

There was a similar risk of stroke in the Xa inhibitor and the control group for both the 2.5 mg rivaroxaban dosage (RR 0.68, 95% CI: 0.26–1.80, $P=0.44$) and the 5 mg rivaroxaban dosage (RR 1.13, 95% CI: 0.49–2.62, $P=0.78$) in the ATLAS ACS 2-TIMI 51 trial. Rivaroxaban with aspirin reduced the RR of stroke by 52% (RR 0.48, 95% CI: 0.28–0.83) in patients with HF in the COMPASS trial. In the COMMANDER HF trial, a significant reduction in the risk of stroke was also found in the rivaroxaban group (RR 0.66, 95% CI: 0.47–0.95). The risk of stroke was not significantly different in the rivaroxaban group compared to the control group in the APPRAISE-2 trial.

Sensitivity analysis

There was significant heterogeneity concerning comparisons with the primary efficacy outcome. Regarding the comparisons with the rivaroxaban 2.5 mg groups, although heterogeneity decreased significantly ($I^2=15\%$, P for heterogeneity 0.31) after excluding the ATLAS ACS

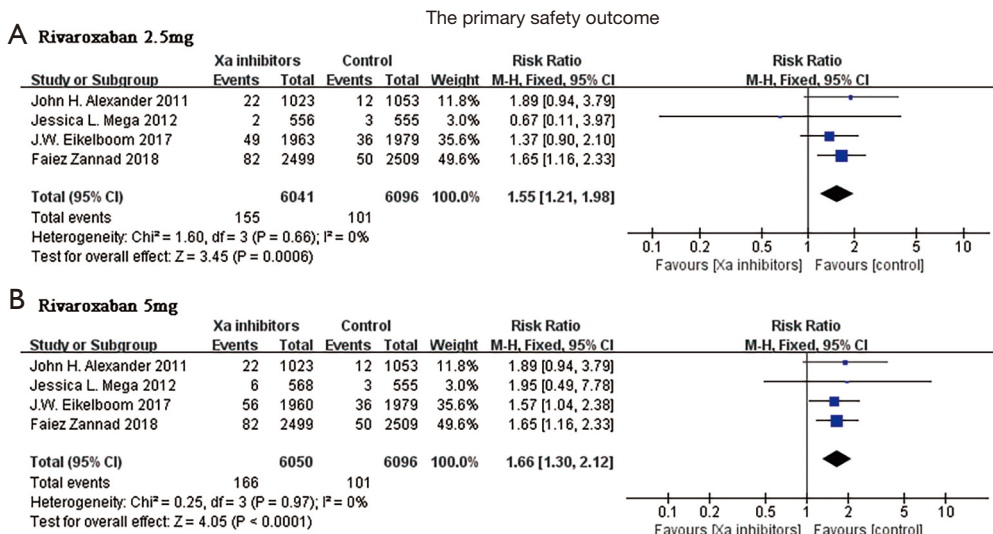


Figure 4 Meta-analysis for the primary safety outcome. (A) Includes the rivaroxaban 2.5 mg group in the ATLAS ACS 2-TIMI 51 trial and rivaroxaban 2.5 mg plus aspirin 100 mg group in the COMPASS trial; (B) includes the rivaroxaban 5 mg group in the ATLAS ACS 2-TIMI 51 trial and the rivaroxaban 5 mg group in the COMPASS trial. ATLAS ACS 2-TIMI 51, Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome-Thrombolysis in Myocardial Infarction 51. COMPASS, Cardiovascular Outcomes for People Using Anticoagulation Strategies.

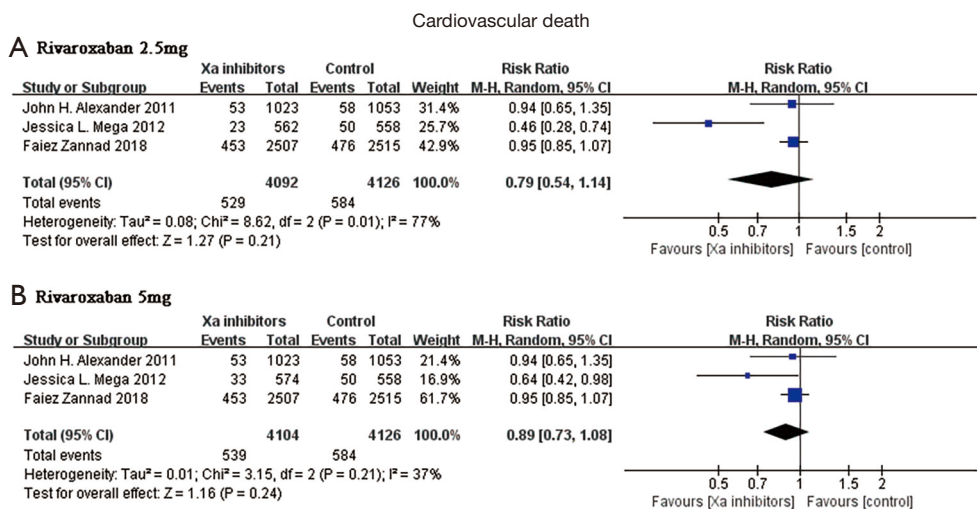


Figure 5 Meta-analysis for cardiovascular death. (A) includes the rivaroxaban 2.5 mg group in the ATLAS ACS 2-TIMI 51 trial; (B) includes the rivaroxaban 5 mg group in the ATLAS ACS 2-TIMI 51 trial. ATLAS ACS 2-TIMI 51, Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome-Thrombolysis in Myocardial Infarction 51.

2-TIMI 51 trial, the results did not change (RR 0.93, 95% CI: 0.84–1.03, P=0.16). It did not make a difference to heterogeneity if the other three trials were excluded one at a time. Based on these results, we concluded that

the ATLAS ACS 2-TIMI 51 trial was the source of heterogeneity. Regarding the sensitivity analysis involving the rivaroxaban 5 mg groups, there was no significant change in heterogeneity.

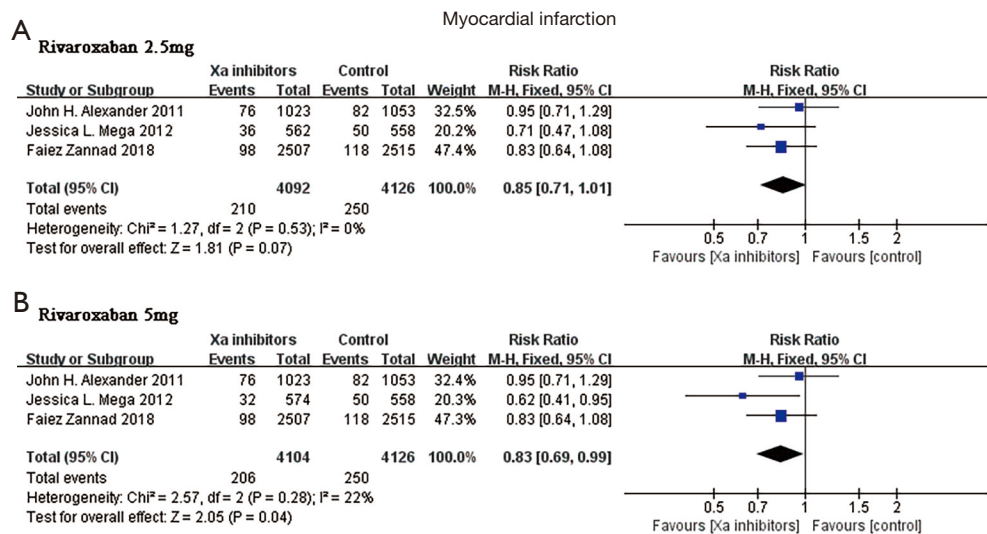


Figure 6 Meta-analysis for myocardial infarction. (A) includes the rivaroxaban 2.5 mg group in the ATLAS ACS 2-TIMI 51 trial; (B) includes the rivaroxaban 5 mg group in the ATLAS ACS 2-TIMI 51 trial. ATLAS ACS 2-TIMI 51, Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome-Thrombolysis in Myocardial Infarction 51.

It was also found that there was apparent heterogeneity concerning comparisons of the CV death rates involving the rivaroxaban 2.5 mg groups. When excluding the ATLAS ACS 2-TIMI 51 trial, heterogeneity decreased markedly ($I^2=0\%$, P for heterogeneity 0.94). However, there was still no significant difference between groups (RR 0.95, 95% CI: 0.85–1.06, P=0.40).

Subgroup analysis

Patients with ACS were eligible for the APPRAISE-2 and ATLAS ACS 2-TIMI 51 trials. However, the COMPASS trial only enrolled patients who had stable CV disease. The COMMANDER HF trial excluded patients who had acute MI. Therefore, we performed a subgroup analysis of patients with and without ACS. The results of the subgroup analysis were consistent with the combined group analysis for the primary efficacy outcome: for the rivaroxaban 2.5 mg groups (non-ACS: RR 0.83, 95% CI: 0.61–1.13, P=0.24, $I^2=84\%$, P for heterogeneity 0.01; ACS: RR 0.79, 95% CI: 0.49–1.27, P=0.33, $I^2=84\%$, P for heterogeneity 0.01, Figure 7A); and the rivaroxaban 5 mg groups (Non-ACS: RR 0.90, 95% CI: 0.76–1.06, P=0.21, $I^2=52\%$, P for heterogeneity 0.15; ACS: RR 0.81, 95% CI: 0.53–1.24, P=0.33, $I^2=80\%$, P for heterogeneity 0.02, Figure 7B). While for the primary safety outcome: rivaroxaban 2.5 mg groups did not increase significantly (RR 1.64, 95% CI: 0.86–3.11, P=0.13, $I^2=12\%$,

P for heterogeneity 0.29, Figure 7C) when compared with the control group. However, the results were different in that the safety in the ACS subgroup for the rivaroxaban 5 mg groups (non-ACS: RR 1.61, 95% CI: 1.24–2.11, P=0.0004, $I^2=0\%$, P for heterogeneity 0.86; ACS: RR 1.90, 95% CI: 1.02–3.54, P=0.04, $I^2=0\%$, P for heterogeneity 0.96, Figure 7D).

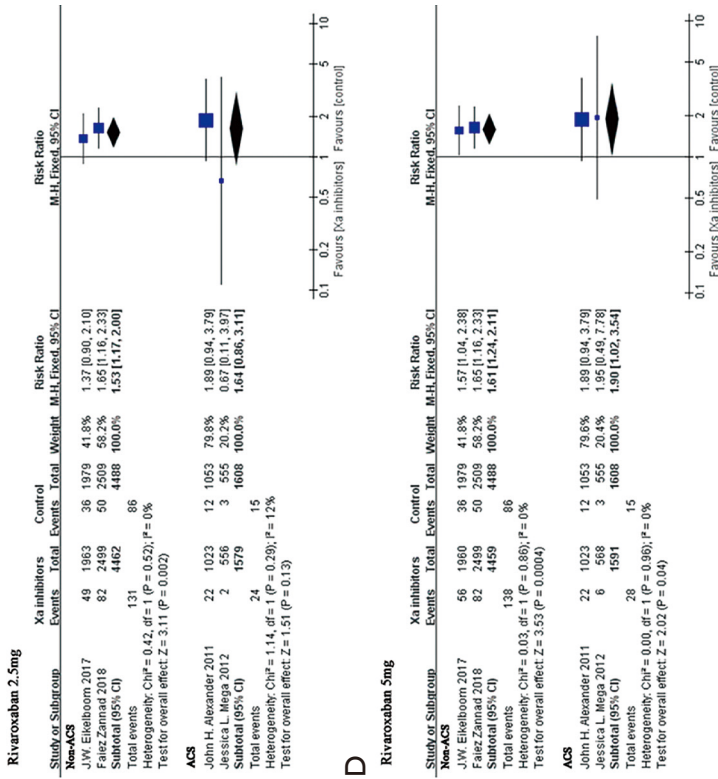
In the COMPASS trial, compared with aspirin alone, rivaroxaban with aspirin could significantly reduce the composite endpoints of cardiovascular death, MI and stroke (HR 0.67, 95% CI: 0.52–0.87); and did not significantly increase bleeding event (HR 1.43, 95% CI: 0.93–2.19).

Discussion

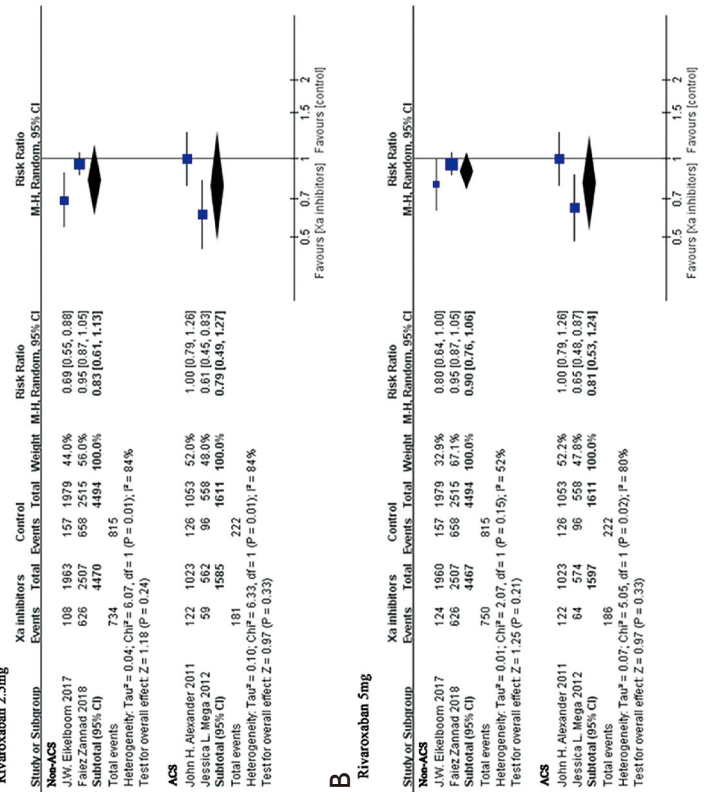
HF was associated with a prothrombotic or hypercoagulable state, which increases the risk of stroke and venous thromboembolism (23). Patients with dyskinesia in the left ventricle after MI were more likely to form mural thrombi and had an increased risk of subsequent peripheral thromboembolism and stroke (24). For patients with chronic atherosclerotic disease, coexisting HF could also lead to a higher incidence of major adverse cardiovascular events and mortality (25). Therefore, antithrombotic therapy was valuable among patients with HF and CAD or PAD.

However, current guidelines in Europe and the United States recommend antithrombotic therapy only for HF

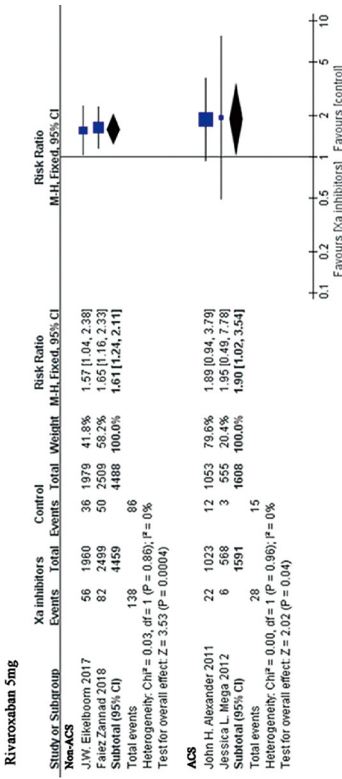
C Subgroup analysis of the primary safety outcome



A Subgroup analysis of the primary efficacy outcome



D Subgroup analysis of the primary safety outcome



B Subgroup analysis of the primary efficacy outcome

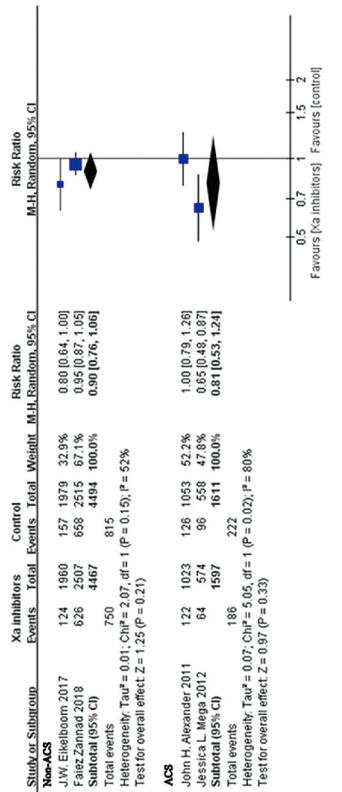


Figure 7 Meta-analysis for subgroup analysis. (A,C) include the rivaroxaban 2.5 mg group in the ATLAS ACS 2-TIMI 51 trial and the rivaroxaban 2.5 mg plus aspirin 100 mg group in the COMPASS trial; (B,D) include the rivaroxaban 5 mg group in the ATLAS ACS 2-TIMI 51 trial and the rivaroxaban 5 mg group in the COMPASS trial. ATLAS ACS 2-TIMI 51, Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome-Thrombolysis in Myocardial Infarction 51. COMPASS, Cardiovascular Outcomes for People Using Anticoagulation Strategies.

patients with a high risk of thromboembolism, such as left ventricular thrombosis or AF (26,27). Previously, VKA was common in antithrombotic therapy. However, due to the slow onset of action, the narrow therapeutic concentration window, and interactions with multiple drugs and diet, VKA has many drawbacks in anticoagulation therapy (3). Furthermore, VKA does not perform well in patients with HF (28).

Rivaroxaban and apixaban are novel types of OACs and are direct-acting medications for activated factor Xa, which is an integral component of the coagulation cascade. Factor Xa is the key protein that limits the propagation of thrombin generation. Thus Xa inhibitors play an important role in anticoagulation (29). A meta-analysis that included AF patients with HF showed that single- or high-dose Non-vitamin-K-dependent oral anti-coagulants (NOAC) regimens had a better efficacy and safety profile when compared with warfarin (30). Our study showed that Xa inhibitors reduced the primary efficacy outcome and CV death rate, while there were no statistically significant differences compared with the control groups.

A Rivaroxaban Once Daily Oral Direct Factor Xa Inhibitor Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF) study performed by Halperin *et al.* (31) showed that compared with warfarin, rivaroxaban could reduce the incidence of stroke and other systemic circulatory embolism in patients with AF, and bleeding events and other adverse events were comparable to warfarin. Furthermore, rivaroxaban could significantly reduce the incidence of intracranial hemorrhage and fatal hemorrhage. Not limited to AF, rivaroxaban is a better choice for the treatment of left ventricular thrombosis, with a better efficacy/safety ratio than warfarin (32). In addition, for the treatment of coronary or peripheral artery disease, low-dose rivaroxaban in combination with aspirin had a higher health cost effectiveness than aspirin alone (33).

Furthermore, our meta-analysis found that Xa inhibitors were associated with a higher risk of bleeding. This meta-analysis showed that the rivaroxaban 5 mg group significantly decreased the incidence of MI; this outcome may be related to the fact that the 5 mg rivaroxaban group had a lower risk of MI in the ATLAS ACS 2-TIMI 51 trial. In the subgroup analysis, there was no difference in the risk of bleeding for the rivaroxaban 2.5 mg group and the apixaban group of ACS patients when compared to the control group. Therefore, rivaroxaban 2.5 mg twice daily

or apixaban 5 mg twice daily should be recommended for patients with ACS and HF at high risk of bleeding, while rivaroxaban 5 mg twice daily should be recommended for patients at high risk of MI. Besides, for patients with non-ACS and HF at high risk of stroke, rivaroxaban 2.5 mg twice daily (with or without aspirin 100 mg once daily) could be an option.

According to the sensitivity analysis of the primary efficacy outcome and CV death rate, there was no statistical difference in the results before and after the analysis, which means that the conclusions are relatively stable.

In summary, the use of Xa inhibitors (alone or with aspirin) was associated with a higher risk of bleeding events when compared to placebo or aspirin alone, except for apixaban 5 mg twice daily and rivaroxaban 2.5 mg twice daily in patients with ACS. However, Xa inhibitors did not significantly reduce the risk of MACE. As for patients with ACS and HF at high risk of bleeding, rivaroxaban 2.5 mg twice daily or apixaban 5 mg twice daily may be an option. However, for patients at high risk of MI, rivaroxaban 5 mg twice daily could be recommended. Besides, for patients without ACS and HF at high risk of stroke, the use of rivaroxaban 2.5 mg twice daily (with or without aspirin 100 mg once daily) could be an option. Therefore, Xa inhibitors should be used with caution in patients with HF and CAD or PAD according to the risk of MACE and bleeding.

There were several limitations to this study. Firstly, the definition of HF was inconsistent across the four trials included in this meta-analysis; trials involved patients with HF with varying degrees of severity. Secondly, rivaroxaban was chosen in all studies except for apixaban in the APPRAISE-2 trial regarding the types of Xa inhibitors. Thirdly, the clinical follow-up time was different among the four trials included. Fourthly, the kinds of antiplatelet drugs were also different in the trials. Fifthly, although the APPRAISE-2 trial only provided data on the event rate per 100 patient-years, the deviation was not large enough to affect the statistical difference shown in the result. Sixthly, although 14,694 participants were included in this meta-analysis, the number of included RCTs was small. Lastly, language restrictions might have resulted in the exclusion of eligible trials.

Xa inhibitors were associated with a higher risk of MACE and bleeding among HF and CAD or PAD patients. Therefore, Xa inhibitors should be used cautiously in patients with HF and CAD or PAD.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at <https://dx.doi.org/10.21037/apm-21-1645>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://dx.doi.org/10.21037/apm-21-1645>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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- (English Language Editors: B. Meiser and J. Chapnick)

Cite this article as: Chen Y, Feng X, Qi C, Zhou L, Sun Y, Gu Z, Li X. Efficacy and safety of Xa inhibitors in patients with heart failure and coronary or peripheral artery disease: a systematic review and meta-analysis of randomized controlled trials. *Ann Palliat Med* 2021;10(7):8082-8093. doi: 10.21037/apm-21-1645

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(CAD (“coronary artery disease” or “coronary artery diseases” or “coronary disease” or “acute coronary syndrome” or “acute coronary syndromes” or “coronary arteriosclerosis” or “coronary arterioscleroses” or “myocardial ischemia” or “myocardial ischemias” or “ischemic heart disease” or “ischemic heart diseases” or “myocardial infarction” or “myocardial infarctions” or “cardiovascular stroke” or “cardiovascular strokes” or “heart attack” or “heart attackss” or “myocardial infarct” or “myocardial infarcts”) OR PAD (“peripheral arterial disease” or “peripheral arterial diseases” or “peripheral angiopathy” or “peripheral angiopathies”)) AND HF (“heart failure” or “heart decompensation” or “myocardial failure” or “congestive heart failure”) AND Xa inhibitors (“factor Xa inhibitors” or “direct factor Xa inhibitors” or “Xa inhibitor” or “Xa inhibitors” or “rivaroxaban” or “xarelto” or “bay 59 7939” or “edoxaban” or “edoxaban tosylate” or “DU-176” or “DU-176b” or “apixaban” or “BMS 562247”)

Registration number in PROSPERO

CRD42019139777