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Efficacy and safety of low dose rivaroxaban in patients with coronary heart disease: a systematic review and meta-analysis

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Abstract

The mortality effects and risk-benefit profile of low dose rivaroxaban (2.5 mg twice daily) in patients with coronary heart disease are not completely understood. Five randomized controlled trials (26,110 patients) were selected using PubMed and Cochrane library till April 2019. The background antiplatelet therapy was aspirin in 3 trials, P2Y12 inhibitor in 1 trial, and in 1 trial 65% patients received aspirin and 35% were on dual antiplatelet therapy (DAPT). The outcomes of interest were cardiovascular mortality, all-cause mortality, myocardial infarction (MI), stroke and major bleeding events. Random effects hazard ratios (HR) with 95% confidence intervals (CI) were calculated. Low dose rivaroxaban did not reduce the risk of cardiovascular mortality (HR 0.90, 95% CI 0.73–1.11, P = 0.34) or all-cause mortality (HR 0.91, 95% CI 0.74–1.12, P = 0.38) compared with control. However, low dose rivaroxaban was associated with reduction in MI (HR 0.85, 95% CI 0.73–0.99, P = 0.04), and stroke (HR 0.59, 95%CI 0.48–0.73, P < 0.001) at the expense of major bleeding (HR 1.64, 95% CI 1.39–1.94, P < 0.001) compared with control. These effects did not vary according to acute coronary syndrome or stable coronary heart disease (P-interaction > 0.05). The use of low dose rivaroxaban in patients with coronary heart disease predominantly receiving antiplatelet monotherapy did not reduce cardiovascular or all-cause

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Compliance with ethical standards

Ethical approval This article does not contain any studies with human participants performed by any of the authors. This article does not contain any studies with animals performed by any of the authors.

Informed consent None needed.

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mortality. The benefits of preventing MI and stroke were balanced by increased risk of major bleeding.

Keywords

Rivaroxaban; Mortality; Meta-analysis

Introduction

Despite the use of guideline directed optimal medical therapy, 12% of patients with stable coronary heart disease and 18% of patients with recent acute coronary syndrome experience recurrent major adverse cardiovascular events [1]. The risk of recurrent cardiovascular events may be related to persistent elevation of thrombin beyond the index event [2, 3] which leads to progression of cardiovascular disease by inducing inflammation, endothelial dysfunction and thrombosis [4]. In patients with coronary heart disease, vitamin K antagonists (VKAs) and direct oral anticoagulants (DOACs) have been explored as secondary prevention strategies and have shown cardiovascular benefits at the cost of higher bleeding events [5–8]. The European Society of Cardiology (ESC) recommends low dose rivaroxaban 2.5 mg twice daily for patients with Non-ST elevation myocardial infarction (NSTEMI) in addition to dual antiplatelet therapy (DAPT) if they have high ischemic burden and low bleeding risk (class II b) [9]. Based on the results of the COMPASS (Cardiovascular Outcomes for People Using Anticoagulation Strategies) trial [10–12] the US Food and Drug Administration (FDA) has recently approved rivaroxaban 2.5 mg twice daily for the prevention of recurrent adverse cardiovascular events in patients with stable coronary heart disease and peripheral arterial disease (PAD). However, the risk–benefit profile of low dose rivaroxaban when used with single antiplatelet therapy (aspirin or P2Y12 inhibitor monotherapy) in patients with coronary heart disease are not completely understood. Herein, we performed meta-analysis to fill this knowledge gap.

Methods

This trial level meta-analysis was conducted in accordance with the Cochrane Collaboration guidelines and PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) [13, 14].

Data sources and searches

Two independent researchers (M.U.K and S.V) conducted the literature search using PubMed and Cochrane library databases till April 2019. A search strategy included key search terms: “rivaroxaban”, “mortality”, “cardiovascular outcomes”, “myocardial infarction”, and “stroke” (Supplementary Table 1). The search filters were applied on “Human and clinical trials”. All citations were downloaded into Endnote X9.1 (Clarivate Analytics). Duplicate records were removed electronically and manually. Two authors (M.U.K and S.V) screened the remaining articles at the title and abstract level followed by full text screening based on the pre-determined selection criteria.

Study selection

The pre-defined inclusion criteria were: (1) randomized controlled trials of low dose rivaroxaban (2.5 mg twice daily), (2) trials must have participants with recent acute coronary syndrome or stable coronary heart disease, (3) trials must report mortality and cardiovascular outcomes of interest in adult patients (≥ 18 years), and (4) trials must have follow-up of ≥ 6 months to provide more reliable estimates. There were no restrictions on language and sample size.

Quality assessment and data extraction

Data was collected on a standard data collection form by two investigators (M.U.K and M.S.K), who adjudicated the data and resolved any disagreements related to data with the opinion of third investigator (S.U.K). Following information was abstracted: baseline characteristics of the trials and participants, background antiplatelet therapy, control groups, events and sample sizes, crude point estimates and follow-up duration. While the included trials reported different doses and combination of rivaroxaban at different follow-ups, we extracted data on low dose rivaroxaban from each trial at maximum follow-up duration. The data extraction was performed according to intention to treat principle. The risk of bias assessment was performed at trial level according to the Cochrane Risk of Bias Tool by M.U.K and M.S.K (Supplementary Table 2) [15].

Outcome measures

The outcomes of interest were cardiovascular mortality, all-cause mortality, myocardial infarction (MI), stroke, and major bleeding. The definition of major bleeding varied across the trials. Trials grouped under recent acute coronary syndrome category defined major bleeding as per TIMI (Thrombolysis in Myocardial Infarction) criteria, and those grouped under stable coronary heart disease category defined major bleeding as per ISTH (International Society of Thrombosis and Hemostasis) criteria. For all other endpoints, we used definitions as used in the original trials.

Estimates were pooled using generic invariance random effects model and calculated as hazard ratios (HR) with 95% confidence intervals (CI). Heterogeneity was evaluated using the Cochrane Q statistics with $I^2 > 75\%$ being consistent with a high degree of heterogeneity [16]. Publication bias was not assessed due to small number of studies (< 10). Subgroup analysis were performed according to acute coronary syndrome and stable coronary heart disease. For all-analyses, statistical significance was set at 5%. Meta-analyses were performed using the Comprehensive Meta-Analysis Software 3.0 (Biostat, Englewood, NJ).

Results

Of 235 records, 165 were screened after removal of duplicates, 114 articles were excluded at title and abstract level, 45 full text articles were removed based on a priori selection criteria, and one trial, PIONEER AF-PCI (Open-Label, Randomized, Controlled, Multicenter Study Exploring Two Treatment Strategies of Rivaroxaban and a Dose Adjusted Oral Vitamin K Antagonist [VKA] Treatment Strategy in Subjects with Atrial Fibrillation [AF] who Undergo Percutaneous Coronary Intervention [PCI]) was excluded because this study was

conducted in unique population who had AF and PCI, and the comparator groups had higher doses of rivaroxaban 15 mg once daily plus P2Y12 inhibitor or VKA once daily plus DAPT [17].

Ultimately, five randomized controlled trials (27,814 patients) met inclusion criteria [11, 12, 18–22] (Fig. 1). Data for recent acute coronary syndrome patients were abstracted from three trials: GEMINI-ACS-1 (Clinically Significant Bleeding with Low-Dose Rivaroxaban vs Aspirin, in Addition to P2Y12 Inhibition, in Acute Coronary Syndrome) [18] which compared low dose rivaroxaban 2.5 mg twice daily with aspirin receiving background P2Y12 inhibitor. Data from 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 MI 51) and ATLAS ACS- TIMI 46 (Rivaroxaban in Combination With Aspirin Alone or With Aspirin and a Thienopyridine in Patients With Acute Coronary Syndrome) were abstracted from report by Gibson et al., who pooled patients with acute coronary syndrome from both trials receiving aspirin monotherapy [20–22]. Two trials studied low dose rivaroxaban in patients with stable coronary heart disease: the COMPASS trial examined rivaroxaban 2.5 mg twice daily plus aspirin, rivaroxaban 5 mg twice and aspirin alone [11, 12], and the COMMANDER HF (A Study to Assess the Effectiveness and Safety of Rivaroxaban in Reducing the Risk of Death, MI, or Stroke in Participants with Heart Failure [HF] and Coronary Artery Disease Following an Episode of Decompensated HF) [19] assessed rivaroxaban 2.5 mg twice daily vs placebo in patients with chronic systolic HF, stable coronary heart disease and sinus rhythm receiving aspirin monotherapy or DAPT. Table 1 reports the characteristics of the included trials. Table-2 reports the Key outcomes of primary and secondary endpoints of included trials.

Low dose rivaroxaban did not reduce the risk of cardiovascular mortality (HR 0.90, 95% CI 0.73–1.11, P = 0.34; Fig. 2) or all-cause mortality (HR 0.91, 95% CI 0.74–1.12, P = 0.38; Fig. 3) compared with control. However, low dose rivaroxaban was associated with reduction in MI (HR 0.85, 95% CI 0.73–0.99, P = 0.04), and stroke (HR 0.59, 95%CI 0.48–0.73, P < 0.001) at the expense of major bleeding events (HR 1.64, 95% CI 1.39–1.94, P < 0.001) compared with control. While these benefits appear to be driven by results in stable coronary heart disease patients, subgroup interaction between acute coronary syndrome or stable coronary heart disease was not statistically significant (P-interaction > 0.05).

Discussion

These analyses showed that use of low dose rivaroxaban with predominantly single antiplatelet therapy was not associated with reducing cardiovascular or all-cause mortality in patients with coronary heart disease. Low dose rivaroxaban reduced MI and stroke at the expense of higher bleeding rates. The lack of mortality benefit shown by low dose rivaroxaban could be because the low event rates and limited follow up of trials, which makes it difficult for any therapy to demonstrate a significant survival benefit [23, 24]; or the low dose rivaroxaban 2.5 twice daily may simply does not confer the desired therapeutic benefits and higher doses should be tried in future trials. It is also possible that the combined beneficial effects of antithrombotic and antiplatelet therapies may have plateaued, and addition of further similar therapies will merely increase the bleeding risk without reducing

ischemic events. It is also noteworthy that 75% of the included trials used single antiplatelet therapy, with three trials using aspirin monotherapy [11, 12, 20–22], 1 trial using P2Y12 inhibitor [18], and in 1 trial ~ 35% patients were on DAPT [19]. Moreover, variation in PCI techniques including vascular access, complexity of coronary atherosclerosis, types and sizes of stents and procedural anticoagulation may have an impact on cardiovascular outcomes and could have confounded the results. Finally, the inherent risks of concurrent comorbidities could have influenced the mortality rates. For instance, the event rates for primary outcome in COMPASS were low (4.1% vs 5.4%) and majority of events were atherothrombotic (cardiovascular death, MI and stroke) vs higher event rates in COMMANDER-HF (25% vs 26.2%) where majority of deaths were caused by progression of HF rather than atherothrombotic events.

In this analysis the effects of low dose rivaroxaban appeared to be stronger in patients with stable coronary heart disease than recent acute coronary syndrome. The most likely explanations are that patients with recent acute coronary syndrome were assigned low dose rivaroxaban with single antiplatelet therapy, while only the COMMANDER-HF utilized 35% DAPT which can potentially bias the effect in favor of low dose rivaroxaban. In a meta-analysis of seven trials encompassing 31,574 patients with recent acute coronary syndrome, addition of a DOAC to single antiplatelet agent neither increased the risk of clinically significant bleeding nor reduced the major adverse cardiovascular events (MACE). Conversely, there was 14% risk reduction in MACE but more than twice the risk of bleeding with DOAC plus DAPT [8]. Second, the acute coronary syndrome data were somewhat influenced by phase II trials and only ATLAS ACS 2-TIMI 51 was phase III clinical trial [20]. The European Medicinal Agency approved the use of low dose rivaroxaban with DAPT in NSTEMI based on the findings of ATLAS ACS-2 TIMI 51 trial [9, 20]. However, this trial had issues related to incomplete follow-up, uncounted mortality and informative censoring, leading to decline in the drug approval by the FDA for acute coronary syndrome in 2012 [8]. Finally, since acute coronary syndrome is a higher risk condition compared with stable coronary heart disease [1], use of low dose rivaroxaban with single antiplatelet therapy might not provide enough therapeutic protection against recurrent MACE.

We compared our results with other meta-analyses. Khan and colleagues showed reduction in MACE by use of rivaroxaban at the expense of higher bleeding risk [8]. This meta-analysis did not investigate important cardiovascular endpoints such as mortality, MI or stroke and the analyses were not adjusted for different doses of DOACs [8]. More recently, Gibson and colleagues reported pooled data from the ATLAS ACS-2 TIMI-51 and COMMANDER-HF trial and showed all-cause mortality (HR 0.71, 95% CI 0.61–0.83) reduction with low dose rivaroxaban compared with placebo. There were higher rates of major bleeding with rivaroxaban vs. placebo (2.7 vs. 1.5 events per 100 patient years; $P < 0.01$) [25]. Since baseline risk varies substantially between both groups, we performed separate analyses to examine effects of low dose rivaroxaban in these distinct patient populations.

This meta-analysis has certain limitations. The baseline characteristics of the participants, concurrent medical therapy and follow up varied considerably among trials. The patient population had comorbidities with different inherent risks of mortality and cardiovascular

outcomes. Due to limited available data, effects of low dose rivaroxaban with background DAPT could not be examined. These findings might not be universally applicable to all candidates because some trials recruited patients with low bleeding risk, concurrent use of proton pump inhibitors was limited, and presentation of acute coronary syndrome was variable. A participant level analysis will be ideal in exploring the such differences.

In summary, the use of low dose rivaroxaban with antiplatelet monotherapy did not reduce cardiovascular or all-cause mortality in patients with recent acute coronary syndrome or stable coronary heart disease. The benefits of MI and stroke reduction were achieved at the cost of major bleeding risk. Antiplatelet therapy is the standard approach for the secondary prevention of cardiovascular disease [26, 27]. Additional use of oral anticoagulant on top of antiplatelet monotherapy calls for a trade-off between higher bleeding risk and prevention of recurrent MACE [8]. Therefore, use of low dose rivaroxaban should be carefully prescribed only to subjects having ischemic risk exceeding their bleeding propensity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- The US Food and Drug Administration (FDA) has recently approved rivaroxaban 2.5 mg twice daily for the prevention of recurrent adverse cardiovascular events in patients with stable coronary heart disease.
- There is still paucity of data related to effects of low dose rivaroxaban on mortality in patients with recent acute coronary syndrome and stable coronary heart disease.
- This meta-analysis shows that low dose rivaroxaban with antiplatelet monotherapy did not reduce cardiovascular or all-cause mortality in patients with recent acute coronary syndrome or stable coronary heart disease.
- The benefits of MI and stroke reduction were achieved at the cost of major bleeding risk.

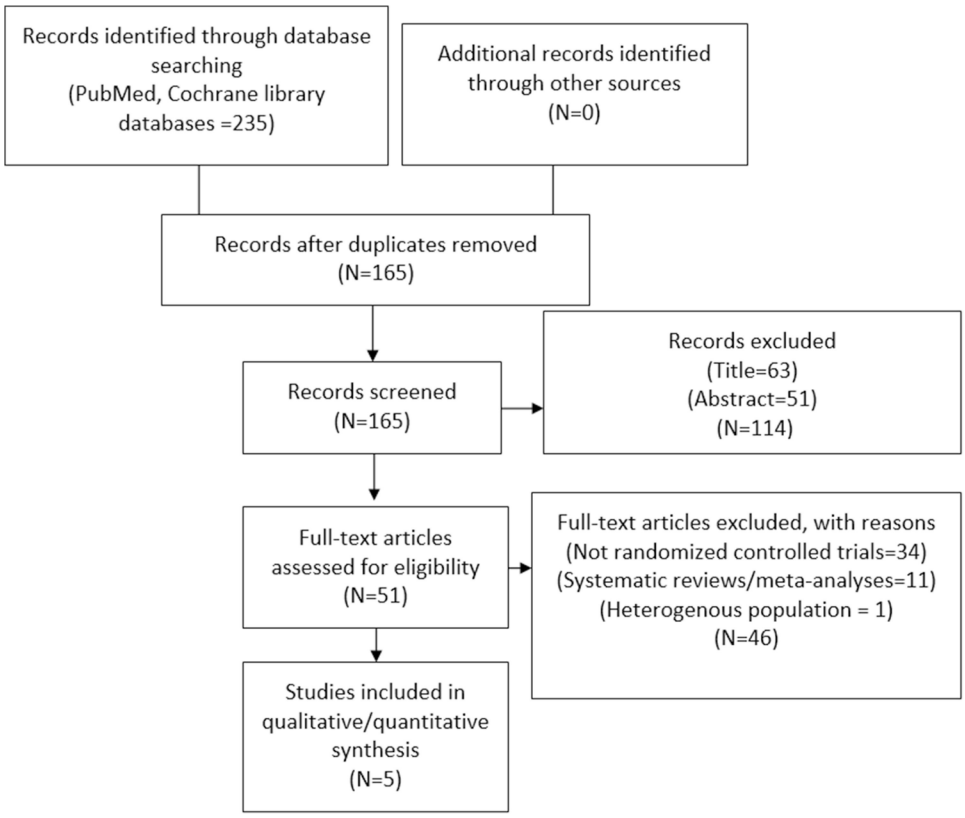

Fig. 1.

Study selection process. Study flow chart according to Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA)

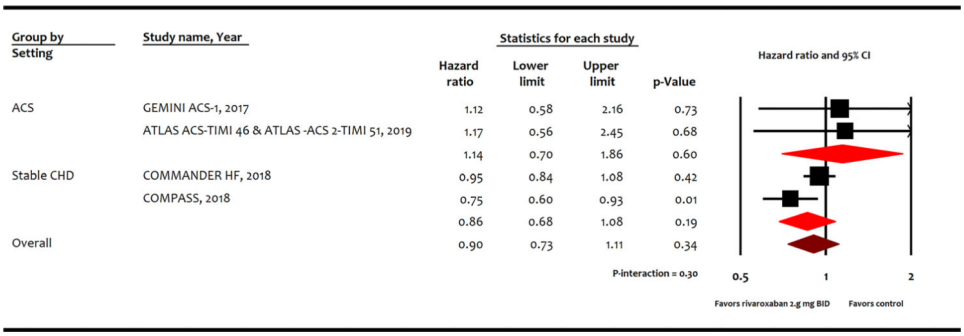

Fig. 2.

Meta-analysis for cardiovascular mortality. ATLAS ACS-TIMI 46, Rivaroxaban in Combination With Aspirin Alone or With Aspirin and a Thienopyridine in Patients With Acute Coronary Syndromes; ATLAS ACS2-TIMI 51, Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome-Thrombolysis in Myocardial Infarction 5; 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; GEMINI ACS-1, Clinically Significant Bleeding with Low-Dose Rivaroxaban versus Aspirin, in Addition to P2Y12 Inhibition, in Acute Coronary Syndromes

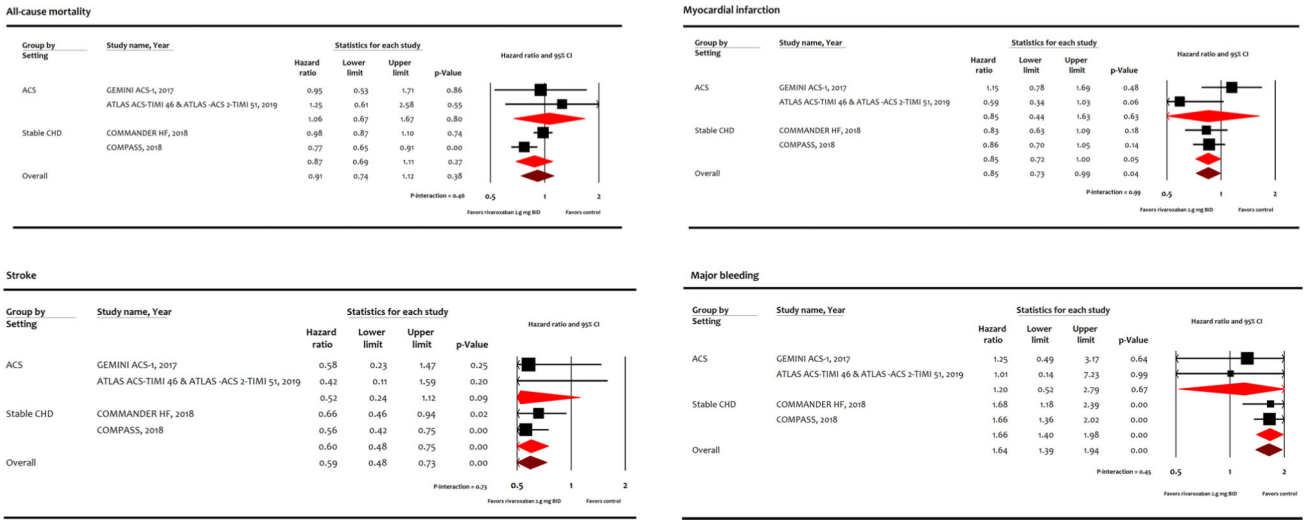

Fig. 3.

Meta-Analysis for secondary endpoints. ATLAS ACS- TIMI 46, Rivaroxaban in Combination With Aspirin Alone or With Aspirin and a Thienopyridine in Patients With Acute Coronary Syndromes; ATLAS ACS2-TIMI 51, Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome-Thrombolysis in Myocardial Infarction 5; 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; GEMINI ACS-1, Clinically Significant Bleeding with Low- Dose Rivaroxaban versus Aspirin, in Addition to P2Y12 Inhibition, in Acute Coronary Syndromes

Table 1

Baseline characteristics of the trials and participants

Study (year)	Age (years)	Females	Active drug (dose)	Control (dose)	Participants	Background antiplatelet therapy	Primary composite outcome	Bleeding criteria	Follow-up (months)
ATLAS ACS-TIMI 46 (2009) [20, 21]	60.3	294 (69%)	Rivaroxaban (2.5 or 5 mg BID)	Placebo	427	Aspirin (low dose)	Cardiovascular death, MI, or stroke (ischemic, hemorrhagic, or of uncertain cause	TIMI	6
ATLAS ACS2-TIMI 51 (2012) [19, 20]	61.6	573 (54%)	Rivaroxaban (2.5 or 5 mg BID)	Placebo	1050	Aspirin (low dose)	Cardiovascular death, MI, or stroke (ischemic, hemorrhagic, or of uncertain cause	TIMI	13
GEMINI ACS-1 (2017) [17]	62.0	762 (25%)	Rivaroxaban (2.5 mg BID)	Aspirin (100 mg)	3037	P2Y12 inhibitor (clopidogrel or ticagrelor)	cardiovascular death, MI, stroke, or definite stent thrombosis	TIMI	11
COMPASS (2018)	69	3382 (20%)	Rivaroxaban (2.5 mg BID)	Aspirin (100 mg)	16,574	Aspirin (100 mg)	Cardiovascular death, stroke, or MI	ISTH	23
COMMANDER HF (2018) [18]	66.4	1150 (23%)	Rivaroxaban (2.5 mg BID)	Placebo	5022	Aspirin/DAPT	Death from any cause, MI, or stroke	ISTH	21

ATLAS ACS- TIMI 46, Rivaroxaban in Combination With Aspirin Alone or With Aspirin and a Thienopyridine in Patients With Acute Coronary Syndromes; ATLAS ACS2-TIMI 51, Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome-Thrombolysis in Myocardial Infarction 5; 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; DAPT, Dual Antiplatelet Therapy, GEMINI ACS-1, Clinically Significant Bleeding with Low-Dose Rivaroxaban versus Aspirin, in Addition to P2Y12 Inhibition, in Acute Coronary Syndromes; ISTH, International Society of Thrombosis and Hemostasis; MI, Myocardial Infarction; TIMI, Thrombolysis in Myocardial Infarction

Table 2

Key outcomes of primary and secondary endpoints of included trials

	Primary composite[a]	All-cause mortality[b]	Myocardial infarction[b]	Stroke[b]	Major bleeding[c]
ATLAS ACS-TIMI 46 (2009) [20, 21] and ATLAS ACS2-TIMI 51 (2012) [19, 20]					
Active (%)	62 (11.4)	25 (5.6)	33 (7.3)	12 (1.9)	8 (1.5)
Control (%)	65 (16.3)	16 (3.2)	44 (11.7)	9 (2.6)	2 (0.3)
HR [95% CI]	0.69 [0.45–1.07]	1.25 (0.61–2.59)	0.59 [0.34–1.03]	0.42 [0.11–1.59]	1.01 [0.14–7.23]
P value	0.09	0.99	0.06	0.20	0.99
GEMINI ACS-1 (2017) [17]					
Active (%)	76 (5)	22 (1)	56 (4)	7 (< 1)	10 (1)
Control (%)	72 (5)	23 (1.5)	49 (3)	12 (1)	8 (1)
HR [95% CI]	1.06 [0.77–1.46]	0.95 [0.53–1.71]	1.15 [0.78–1.68]	0.58 [0.23–1.48]	1.25 [0.49–3.17]
P value	0.73	0.87	0.48	0.25	0.63
Compass (2018)					
Active (%)	347 (4)	262 (3)	195 (2)	74 (1)	263 (3)
Control (%)	460 (6)	339 (4)	98 (3.9)	130 (2)	158 (2)
HR [95% CI]	0.74 [0.65–0.86]	0.77 [0.65–0.90]	0.86 [0.70–1.05]	0.56 [0.42–0.75]	1.66 [1.37–2.03]
P value	< 0.01	0.001	0.15	< 0.01	< 0.01
Commander HF (2018) [18]					
Active (%)	626 (25)	546 (21.8)	98 (3.9)	51 (2)	82 (3.3)
Control (%)	658 (26.2)	556 (22.1)	118 (4.7)	76 (3)	50 (2)
HR [95% CI]	0.94 [0.84–1.05]	0.98 [0.87–1.10]	0.83 [0.63–1.08]	0.66 [0.47–0.95]	1.68 [1.18–2.39]
P-interaction	0.27	–	–	–	< 0.01

ATLAS ACS- TIMI 46, Rivaroxaban in Combination With Aspirin Alone or With Aspirin and a Thienopyridine in Patients With Acute Coronary Syndromes; ATLAS ACS2-TIMI 51, Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome-Thrombolysis in Myocardial Infarction 5; 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; GEMINI ACS-1, Clinically Significant Bleeding with Low-Dose Rivaroxaban versus Aspirin, in Addition to P2Y12 Inhibition, in Acute Coronary Syndromes; *HR* hazard ratio

[a] Primary efficacy outcome

[b] Secondary efficacy outcome

[c] Primary safety outcome