Efficacy of Rivaroxaban (Xarelto) ± Aspirin in the Prevention of Major Adverse Cardiovascular Events

Christina Chen, MMS (c)
Faculty Advisor: Renee Langstaff, MSPAS, PA-C
Department of Medical Science

Abstract

Coronary artery disease (CAD) is the leading cause of death in both sexes, accounting for a third of all deaths in developed countries. One of the mainstays in treatment in both CAD and peripheral arterial disease (PAD) is the prevention of thrombus formation using antiplatelets, with aspirin as the drug of choice. Currently, rivaroxaban, a direct factor Xa inhibitor, is being studied in patients with CAD and PAD. This review addresses the efficacy of rivaroxaban, with or without aspirin, in the prevention of major adverse cardiovascular events, in adults with CAD and PAD, compared to standard of care, aspirin.

Introduction

- CAD and PAD are most commonly the result of atherosclerosis.
- Many patients with CAD also have PAD.
- CAD may present with: asymptomatic ”silent” ischemia; acute coronary syndrome (ACS) such as myocardial infarction (MI); sudden cardiac death; ischemic stroke.
- PAD may present as ”silent” ischemia; claudication; pain at rest, skin atrophy, hair loss, cyanosis, ulcers, gangrene leading to limb loss.
- First line treatment for CAD & PAD when not requiring stent/surgery: Aspirin 75-100 mg once daily
- It is hypothesized that the selective inhibition of factor Xa could be highly effective in preventing the formation of thrombi, as factor Xa is positioned at the start of the coagulation pathway.
- This review analyzes the use of rivaroxaban ± aspirin vs. aspirin alone in the prevention of major adverse cardiovascular events (MACEs) and its comparative bleeding risks in adults with CAD and PAD.
- MACEs include cardiovascular death, MI, stroke, and were measured as the primary efficacy outcomes in five of the seven studies.
- Other variables measured were: major adverse limb events (MALE), VTE, heart failure, hospitalization, whether or not CABG was needed.
- Bleeding risk was measured by fatal and non-fatal bleeding events.

Methods

- A literature search was conducted through PubMed and Google Scholar in November 2018.
- Search terms: “Rivaroxaban” OR “Xarelto” AND “coronary artery disease” AND “peripheral vascular disease.”
- Seven articles were selected based on relevance to the clinical question, publication date after 2013, study design, sample population of adults, and outcome measurements.

Results

Four studies (Anand et al., Connolly et al., Eikelboom et al., Gibson et al.) showed statistically significant evidence that rivaroxaban 2.5 mg BID + aspirin 100 mg once daily reduces the risk of MACEs. These four studies also found that the results of rivaroxaban alone at 5 mg BID were not statistically significant. One study (Hart et al.) found that rivaroxaban at a high dose of 15 mg once daily was not effective at reducing MACEs but increased the risk of both fatal and non-fatal bleeding. Another study (Weitz et al.) compared rivaroxaban 10 mg once daily to 20 mg once daily and found that both reduced VTE without increased bleeding. However, both higher doses did not reduce MACEs. One study (Mega et al.) did not include aspirin but showed that rivaroxaban 2.5 mg BID was effective at reducing MACEs. Only one study (Anand et al.) showed statistically significant evidence that rivaroxaban 2.5 mg reduces the risk of MALEs.

RCT	Study Population	Population Demographic	Duration	Treatment Regimen & Comparator	Primary Efficacy Outcomes	Clinical Benefit	Bleeding Risk
Anand et al. (2017)	CAD; PAD; PAD of lower extremities	2,109 F 5,361 M N=7,470	21 months	1. Rivaroxaban 2.5 mg BID + Aspirin 100 mg QD 2. Rivaroxaban 5 mg BID Comparator: Aspirin 100 mg QD	CV death, MI, stroke, MALE	1. S 2. NS	1. NS 2. NS
Connolly et al. (2017)	CAD	5,032 F 19,792 M N=24,824	23 months	1. Rivaroxaban 2.5 mg BID + Aspirin 100 mg QD 2. Rivaroxaban 5 mg BID Comparator: Aspirin 100 mg QD	CV death, MI, stroke	1. S 2. NS	1. NS 2. NS
Eikelboom et al. (2017)	CAD; PAD	6,020 F 21,375 M N=27,395	23 months	1. Rivaroxaban 2.5 mg BID + Aspirin 100 mg QD 2. Rivaroxaban 5 mg BID Comparator: Aspirin 100 mg QD	CV death, MI, stroke, hospitalization	1. S 2. NS	1. NS 2. NS
Gibson et al. (2018)	ACS	N/A N=9,435	13.3 months	1. Rivaroxaban 2.5 mg BID + Aspirin 100 mg QD 2. Rivaroxaban 5 mg BID + Aspirin 100 mg QD Comparator: Aspirin 100 mg QD	CV death, MI, stroke	1. S 2. S	1. NS 2. NS
Hart et al. (2018)	History of embolic stroke	2,777 F 4,436 M N=7,213	11 months	1. Rivaroxaban 15 mg once a day; Comparator: Aspirin 100 mg QD	Recurrent stroke, systemic embolism, CV death, MI	1. NS	1. S
Mega et al. (2012)	ACS	3,936 F 11,600 M N=15,526	13.1 months	1. Rivaroxaban 2.5 mg BID + Aspirin 2. Rivaroxaban 5 mg BID Comparator: Placebo	CV death, MI, stroke	1. S 2. S	1. NS 2. S
Weitz et al. (2017)	VTE	1,531 F 1,865 M N=3,396	12 months	1. Rivaroxaban 20 mg once a day 2. Rivaroxaban 10 mg once a day Comparator: Aspirin 100 mg QD	Recurrent VTE	1. S 2. S	1. NS 2. NS

Key: RCT = Randomized Control Trial; CAD = Coronary Artery Disease; PAD = Peripheral Artery Disease; F = female; M = male; BID = twice a day; QD = once a day; CV = Cardiovascular; MI = Myocardial Infarction; MALE = Major Adverse Limb Event; ACS = Acute Coronary Syndrome; N/A = Information Not Available; VTE = Venous Thromboembolism; S = Statistically Significant ($P \leq 0.05$); NS = Not Statistically Significant ($P \leq 0.05$)

Discussion

All seven studies were found to have adequate blinding, statistical power, treatment timelines, and follow-up, without concerns for bias. Outcome measures varied slightly, but all compared the risk of bleeding vs. benefit of preventing thrombotic events.

Significant positive results were found in the four studies using rivaroxaban 2.5 mg BID + aspirin, as well as in the one study using high dose rivaroxaban in the prevention of VTE.

However, it is important to note that these studies excluded very high-risk patients, such as those with an already high bleeding risk, severe heart failure, or end-stage renal disease.

Conclusion

The study results are **positive**:

[Low dose] rivaroxaban 2.5 mg BID + aspirin 100 mg once daily offers net clinical benefits in prevention of MACEs in *low- to medium-risk* patients with CAD and PAD, without significant bleeding risk.

[High dose] rivaroxaban 10mg once a day reduces risk of VTE without significant bleeding risk.

These positive outcomes are leading to **FDA approval**:

- 2017: 10 mg dosing approved to reduce risk of VTE
- 2018: 2.5 mg “vascular dosing” approved to reduce risk of major cardiovascular events in patients with chronic CAD or PAD
- 2019: 10 mg dosing approved to prevent blood clots in acutely ill medical patients.

Major caveat = cost. New oral anticoagulants (NOACs) such as rivaroxaban are $$$ and can be cost-prohibitive for patients even with insurance coverage (e.g., high copay). At this time, overall cost savings and cost-effectiveness analyses are not available.

<u>Bottom line</u>: Clinicians must choose which medical therapy is most appropriate for their patients, both medically and financially.