Peer Review File

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Review Comments:

The introduction part:

---The authors paid more attention to the residual risk of CVD patients in the introduction, talking about the secondary prevention. However, the topic of this review was the benefits of low-dose rivaroxaban in CAD patients. **Therefore, more content related to low-dose rivaroxaban or the reason why intensified antithrombotic therapy was needed in CAD patients should be mentioned in the introduction.**

Reply: The authors acknowledge the importance of raising the awareness on the management of residual risk in CVD patients. For this reason, we have complemented the Introduction text with the reference to **Figure 1** and to **Table 1**. The latter specifically addresses the approach of intensified antithrombotic therapy using low dose rivaroxaban.

The introduction part:

---In the first paragraph, please clarify what the “recommended medical therapy” was.

Reply: Revised as suggested by the reviewer.

You may now find the following sentence in the introduction:

In the secondary prevention subgroup (n=53,390), despite recommended medical therapy ***(including lipid-lowering agents and antithrombotic drugs, and antihypertensive and anti-diabetic drugs, whenever applicable)****, the observed annual rate of CV death, myocardial infarction (MI) or stroke was 4.6%.*

The second part:

---The second part of this review presented the evidence from clinical trials considering that oral anticoagulation provides vascular protection beyond antithrombotic activity on CAD or PAD patients.

---Please clarify what is the difference between vascular protection and antithrombotic activity in the secondary prevention of CAD?

Reply: To clarify the difference, the authors have added the following sentence in the last paragraph of the introduction:

"In this review, the term 'vascular protection' describes a comprehensive therapeutic strategy that prevents arterial ischemic events, such as myocardial infarction and ischemic stroke."

The second part:

---The introduction of the three clinical trials was interminable, which need to be condensed and simplified.

Reply: Revised as suggested by the reviewer.

You may now find a more concise introduction of the three clinical trials. Please note the text with highlighted changes followed by a simplified version (for easier reading) below.

- The ATLAS ACS 2 – TIMI 51 Trial: **updated from 242 to 130 words**.
- The COMPASS Trial: **updated from 239 to 152 words**.
- The VOYAGEUR PAD Trial: **updated from 207 to words 137**.

The ATLAS ACS 2 – TIMI 51 Trial

*The Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome–Thrombolysis in Myocardial Infarction 51 (ATLAS ACS 2 TIMI-51) trial was a double-blind ~~phase III~~ multicentre study enrolling ~~clinically~~ stable **ACS** patients ~~with a recent (≤7 days) ACS~~. To be eligible, those under 55 years of age had to have either DM or a previous MI ~~(in addition to the index event)~~. ~~Key exclusion criteria included previous intracranial haemorrhage, gastrointestinal bleeding in the preceding year, a platelet count <90,000/mm^3, a glomerular filtration rate (GFR) <30mL/min or a previous TIA or stroke on aspirin plus a thienopyridine~~. Patients were randomized ~~in a 1:1:1 fashion~~ to twice-daily ~~doses of either~~ 2.5mg or 5~~.0~~mg rivaroxaban or placebo. The primary efficacy endpoint was a composite of CV death, MI*

*or stroke. The primary safety endpoint was TIMI ~~(Thrombolysis in Myocardial Infarction)~~ major bleeding not related to coronary artery bypass grafting (CABG) **(23)**. ~~A total of~~ **Overall**, 15,526 patients were enrolled ~~with a~~ **(**mean age ~~of~~ 62 ~~± 9~~ years; ~~most patients were~~ **75%** male ~~(75%)~~, ~~with~~ **often with** ~~known~~ CV risk factors, ~~namely hypertension (67%), DM (32%) or dyslipidaemia (32%); previous MI was documented in a low proportion of cases (27%). ACS diagnosis was ST segment elevation MI (50%), non ST segment elevation MI (26%) or unstable angina (24%).~~ Patients were treated according to guidelines~~, receiving~~ **with** DAPT **(93%)** ~~(aspirin: 99%; thienopyridine – clopidogrel or ticlopidine: 93%)~~, statins (84%) and beta-blockers (66%) plus myocardial revascularization (60%).*

The ATLAS ACS 2 – TIMI 51 Trial

The Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome–Thrombolysis in Myocardial Infarction 51 (ATLAS ACS 2 TIMI-51) trial was a double-blind multicentre study enrolling stable ACS patients. To be eligible, those under 55 years of age had to have either DM or a previous MI. Patients were randomized to twice-daily 2.5mg or 5mg rivaroxaban or placebo. The primary efficacy endpoint was a composite of CV death, MI or stroke. The primary safety endpoint was TIMI major bleeding not related to coronary artery bypass grafting (CABG) **(23)**. Overall, 15,526 patients were enrolled (mean age 62 years; 75% male, often with CV risk factors). Patients were treated according to guidelines with DAPT (93%), statins (84%) and beta-blockers (66%) plus myocardial revascularization (60%).

The COMPASS trial

The Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trial was a double-blind ~~phase III~~ multicentre study that enrolled patients with stable atherosclerotic PAD, CAD or both. ~~To be eligible,~~ CAD patients younger than 65 years required ~~documentation of~~ atherosclerosis ~~involving~~ ***in*** *two vascular beds or two ~~additional~~* ***CV*** *risk factors ~~(current smoking, DM, CKD, HF or ischaemic stroke)~~. Key exclusion criteria included a formal indication for DAPT ~~or oral anticoagulation, stroke within 1 month or any haemorrhagic or lacunar stroke,~~* ***and*** *HF with left ventricular ejection fraction (LVEF) <30% or ~~New York Heart Association (~~NYHA~~)~~ III-IV ~~symptoms, and GFR <15 mL/min~~. Patients were randomized ~~in a 1:1:1 ratio~~ to aspirin ~~(~~100mg ~~once daily)~~, rivaroxaban ~~(~~5mg* ***bid*** *~~twice daily)~~, or rivaroxaban ~~(~~2.5mg* ***bid*** *~~twice daily)~~ plus aspirin ~~(~~100mg ~~once daily)~~. The primary efficacy endpoint was a composite of CV death, MI or stroke. The primary ~~composite~~ safety endpoint included fatal bleeding, symptomatic bleeding into a critical organ, bleeding into a surgical site requiring reoperation, and bleeding leading to hospitalization or acute care* ***(11)***. *Overall, 27,395 patients were enrolled~~, having a~~* ***(****mean age ~~of~~ 68 ~~± 8~~ years; ~~most patients were~~* ***78%*** *male ~~(78%)~~, ~~with a known history of~~* ***91% with*** *CAD (91~~%) or MI (62%); a lesser proportion had~~* ***and 27%*** *PAD ~~(27%), DM (38%), CKD (23%) and HF (22%~~). Patients were often* ***on*** *~~receiving~~ lipid-lowering agents (90%) ~~and Renin-Angiotensin-Aldosterone inhibitors (RAASi 71%). Mean systolic and diastolic BP was 136 and 78mmHg, respectively, and mean total cholesterol level was 162mg/dL~~* ***and had well controlled CV risk factors***.

The COMPASS trial

The Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trial was a double-blind multicentre study that enrolled patients with stable atherosclerotic PAD, CAD or both. CAD patients younger than 65 years required atherosclerosis in two vascular beds or two CV risk factors. Key exclusion criteria included a formal indication for DAPT and HF with left ventricular ejection fraction (LVEF) <30% or NYHA III-IV. Patients were randomized to aspirin 100mg, rivaroxaban 5mg bid, or rivaroxaban 2.5mg bid plus aspirin 100mg. The primary efficacy endpoint was a composite of CV death, MI or stroke. The primary safety endpoint included fatal bleeding, symptomatic bleeding into a critical organ, bleeding into a surgical site requiring reoperation, and bleeding leading to hospitalization or acute care **(11)**. Overall, 27,395 patients were enrolled (mean age 68 years; 78% male, 91% with CAD and 27% PAD). Patients were often on lipid-lowering agents (90%) and had well controlled CV risk factors.

The VOYAGER PAD trial

*"Recently, the results of the Vascular Outcomes Study of ASA Along with Rivaroxaban in Endovascular or Surgical Limb Revascularization for PAD (VOYAGER PAD) trial were published **(24)**. This was a double-blind ~~phase III~~ multicentre study that enrolled patients aged 50 years or older with moderate to severe symptomatic PAD ~~evidenced on imaging and hemodynamic assessments,~~ and a successful ~~(within 10 days)~~ peripheral revascularization ~~distal to the external iliac~~. Key exclusion criteria included planned long-term DAPT ~~(>6 months), full-dose anticoagulation, eGFR <15 mL/min/1,73m^2 and any intracranial haemorrhage or stroke~~. Patients were randomized to rivaroxaban 2.5mg ~~twice daily in addition~~ **bid added** to aspirin vs. ~~standard~~ aspirin alone. The primary*

efficacy outcome was a composite of acute limb ischaemic, major amputation for vascular causes, MI, ischaemic stroke or ***CV*** *death ~~from CV causes~~. Overall, 6,564* ***patients*** *were enrolled~~, with a~~* ***(****median age~~ of 67 (61-73) years~~; ~~most were~~* ***74%*** *male ~~(74%)~~****,*** *with a high burden of CV risk factors~~, namely hypertension (81%), hyperlipidaemia (60%) and DM (40%). Previous MI or known carotid artery disease was documented in a low proportion of cases (11% and 9%, respectively)~~.Patients were often on statins (80%) and ~~half were on~~ clopidogrel* ***(50%)*** *at ~~randomization~~* ***baseline****. Most ~~patients~~ (65%) were treated with an endovascular procedure, while the remainder ~~was~~* ***were*** *surgically treated.“*

The VOYAGER PAD trial

Recently, the results of the Vascular Outcomes Study of ASA Along with Rivaroxaban in Endovascular or Surgical Limb Revascularization for PAD (VOYAGER PAD) trial were published **(24)**. This was a double-blind multicentre study that enrolled patients aged 50 years or older with moderate to severe symptomatic PAD and a successful peripheral revascularization. Key exclusion criteria included planned long-term DAPT. Patients were randomized to rivaroxaban 2.5mg bid added to aspirin vs. aspirin alone. The primary efficacy outcome was a composite of acute limb ischaemic, major amputation for vascular causes, MI, ischaemic stroke or CV death. Overall, 6,564 patients were enrolled (median age 67 years; 74%, with a high burden of CV risk factors). Patients were often on statins (80%) and clopidogrel (50%) at baseline. Most (65%) were treated with an endovascular procedure, while the remainder were surgically treated.

The second part:

---Which results of the mentioned three clinical trials showed the vascular protection beyond antithrombotic activity of the low-dose rivaroxaban? If you consider the three trials as the evidence, you should point out the related key results, especially in the summary part.

The authors have clarified the meaning of the term ‘vascular protection’ as requested by the reviewer. A new sentence was added where one now reads the following: “(…) ***the term ‘vascular protection’ describes a comprehensive therapeutic strategy that prevents arterial ischemic events, such as myocardial infarction and ischemic stroke***.” Thus, it now becomes clear that the reduction of arterial ischaemic events observed in the three rivaroxaban trials qualifies as vascular protection benefits.

The third part:

---In the third part, the author discussed the mechanisms of factor Xa inhibitors in vascular protection.

---Too much was discussed about the coagulation system. Actually, as the author mentioned in the manuscript, the vascular protection effects were more related to PAR-mediated platelet activation and inflammation. Therefore, the discussion of the third part should be reorganized, emphasizing key points.

The authors believe that the close interactions and intertwining between the coagulation system, the endothelium and the inflammatory response are often under-recognized by clinicians. Understanding the mechanisms of these interactions and their impact on the pathogenesis of atherothrombotic cardiovascular disease has the potential to favourably influence both the recognition of patients at high risk of recurrent ischemic events and to improve physician adherence to guideline recommendations. For this reason, the authors have discussed the mechanisms of benefit in detail and illustrated these in **figure 3**.

The third part:

---The difference between warfarin and factor Xa inhibitors in vascular protection was discussed. Nevertheless, the difference among factor Xa inhibitors should also be discussed, as different results were observed in the clinical trials of dabigatran, apixaban and rivaroxaban considering the secondary prevention of CAD/PAD.

We agree that other factor Xa inhibitors should be mentioned. Indeed, we briefly discuss the phase II ESTEEM and RE-DEEM trials on dabigatran and ximelagatran, respectively, as well as the APPRAISE-2 trial on apixaban, focused on post-MI patients (we know of no trial of edoxaban in this population). Nevertheless, we added that the studies ESTEEM and RE-DEEM were phase II clinical trials. We have also clarified the language regarding the potential benefit of apixaban in a subgroup of patients in APPRAISE-2. We did not extensively review these trials given that the first two are older (year of publication 2003 and 2011, respectively), thus widely reviewed and discussed elsewhere, and a difference (by indirect comparison) with rivaroxaban would be ill-advised, as all of the above trials used standard doses (not lower doses) of the anticoagulants. The following may be read in the first paragraph of the section: "Oral Anticoagulation provides Vascular Protection beyond Antithrombotic Activity: evidence from Clinical Trials":

"(...) Furthermore, a benefit with anticoagulation in post-MI patients has been suggested in ***phase II*** *ESTEEM* ***(19)*** *and RE-DEEM* ***(20)*** *trials, with ximelagatran and dabigatran,* ***albeit hepatotoxicity and/or*** *bleeding limited their use,* ***respectively****. Similarly, the APPRAISE-2 trial* ***(21)*** *with apixaban was stopped early due to an increase in bleeding events,* ***having had a potential*** *benefit in the subgroup of patients without prior stroke* ***(22)****."*

The third part:

---When talking about the vascular protection, is it a dose-dependent effect?

Randomized data on the efficacy and safety of different doses of rivaroxaban derive from the ATLAS ACS-TIMI 46 and ATLAS ACS-TIMI 51 trials. The first is a phase II trial designed to select the most favourable dose and dosing regimen of rivaroxaban in acute coronary syndrome patients receiving aspirin with or without a thienopyridine for further assessment in a phase III study. On the basis of the graded increase in bleeding across doses of rivaroxaban (5 to 20 mg total daily dose) in conjunction with the efficacy noted at lower doses of the factor Xa inhibitor, 2.5 mg and 5 mg of rivaroxaban administered twice daily were selected for further assessment in the phase III ATLAS ACS 2-TIMI 51 trial. Although TIMI 46 was not designed to establish the efficacy of rivaroxaban, a dose dependent effect with respect to efficacy ('vascular protection') was not apparent. In the ATLAS ACS 2-TIMI 51, the 2.5 mg twice daily dose of rivaroxaban and the 5 mg twice daily dose showed similar reductions in the primary endpoint rate, but only the lower dose was associated with a reduction in all-cause mortality. Taken altogether, the data supports the use of a lower dose (2.5 mg twice daily) and do not suggest a dose-dependent effect.

The authors have added the following sentence to the second paragraph of the second part to better clarify the dosing regimen used for 'vascular protection':

"This dosing regimen was chosen on the basis of the ATLAS ACS-TIMI 46 results (25), which showed a graded increase in bleeding across total daily doses of 5 mg up to 20 mg, while efficacy was noted at the lowest dose."

The third part:

---Please explain why the vascular protection effects outweigh the anticoagulation effects considering the effects of low-dose rivaroxaban in CAD patients.

The authors have reviewed the manuscript and confirmed that nowhere have we stated that the vascular protection benefits outweigh the anticoagulation effects. As previously discussed, the authors believe that the close interactions between the coagulation system, the endothelium and the inflammatory response are often under-appreciated by clinicians. Due to this, the authors have written "***vascular protection beyond anticoagulation***" in several parts of the text to emphasize the fact that an oral anticoagulant can protect against atherosclerotic cardiovascular disease.