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April 5, 2019

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RE: Draft Scoping Document on Additive Therapies for Cardiovascular Disease: Effectiveness and Value

Dear Dr. Pearson,

On behalf of my colleagues at Amarin Pharma, Inc, thank you for the opportunity to submit comments in response to the Institute for Clinical and Economic Review's (ICER) draft scoping document on additive therapies for cardiovascular (CV) disease and we are pleased to offer the following suggestions for consideration.[1] While statin use and optimal medical management have reduced CV risk and improved patient outcomes over the last few decades, residual CV risk remains. This residual risk represents an important unmet medical need for patients and accounts for significant health care and economic burden.[2]

High-risk statin-treated patients with elevated triglycerides are increasing in number alongside the rise in obesity and diabetes.[3] Eicosapentaenoic acid (EPA) has demonstrated triglyceride-lowering and other potentially cardioprotective benefits. The recently completed REDUCE-IT outcomes trial was designed to assess the benefit of icosapent ethyl (an ethyl ester of EPA) in reducing CV risk in high-risk statin-treated patients with controlled low-density lipoprotein cholesterol (LDL-C) and triglyceride levels of 135 to 499 mg/dL.

We realize the economic analysis you will undertake will compare the incremental survival and quality-adjusted survival to the incremental cost of treatment with icosapent ethyl on top of optimized medical therapy including statins. The positive results demonstrated with icosapent ethyl in REDUCE-IT build upon the positive results demonstrated by ethyl-EPA in the JELIS study, albeit in a higher-risk population in REDUCE-IT.

Hypertriglyceridemia is an important factor in CV risk

Page 1: Background

- To ensure a more comprehensive understanding of CV risk in the context of the potential benefit of icosapent ethyl, consideration should be given to the fact that many studies across multiple lines of evidence (epidemiological, genetic, and clinical studies) link hypertriglyceridemia to increased CV risk.[5] This is further underscored by real-world evidence that demonstrates that hypertriglyceridemia increases not only CV risk but also direct medical costs and healthcare resource utilization.[6-10]

Icosapent ethyl mechanism of action goes beyond triglyceride-lowering effects

Page 2: Background

- Similar to various well-known therapies (eg, statins), the relative contributions of mechanisms responsible for the benefit of icosapent ethyl that was observed in REDUCE-IT are not fully known. The most comprehensive and compelling data from the broader peer-reviewed literature on EPA support mechanisms of prevention, stabilization, and regression of coronary plaque.[11,12] Individual pathways that contribute to this

effect and others may include beneficial changes to an atherogenic lipid profile, such as reduction in triglycerides, cholesterol, and apolipoproteins.[13,14] In addition, anti-inflammatory, antithrombotic, and membrane-stabilizing effects[15-18] likely each contribute to the overall plaque benefits.

- We'd also like to underscore that the observed icosapent ethyl benefit is unlikely to be explained entirely by triglyceride-lowering effects given that the benefit was independent of baseline (above/below 150 or 200 mg/dL) or achieved (above/below 150 mg/dL) triglyceride levels, and was observed across coronary, cerebral, fatal and nonfatal ischemic events, and revascularizations.[19,20] This is in agreement with JELIS in which a 19% reduction in coronary events was observed despite a relatively small decrease in triglyceride levels (~5%).[21]

ADA recently recommended icosapent ethyl for primary and secondary prevention

Page 2: Background

- On March 27th, 2019, the American Diabetes Association issued a critical update to the 2019 Standards of Medical Care in Diabetes.[4] Based on the findings of REDUCE-IT, the Standards of Care now include a Level A recommendation that icosapent ethyl be considered for primary and secondary prevention of CV risk in statin-treated patients with diabetes and atherosclerotic CV disease or other cardiac risk factors and controlled LDL-C but with elevated triglycerides of 135 to 499 mg/dL.[4]

Icosapent ethyl analytic framework should include the primary and secondary prevention populations together

Page 5: Analytic Framework — Populations

- The draft scoping document identifies the patient population to be used for the analysis of both icosapent ethyl and rivaroxaban as adults with established CV disease treated with optimal medical management. Indeed, patients in the pivotal COMPASS trial of rivaroxaban were required to have established atherosclerotic CV disease.[22] However, in addition to a secondary prevention cohort, REDUCE-IT also included a primary prevention cohort that represents almost 30% of the enrolled REDUCE-IT population.[19]
- The draft scoping document notes that input from clinical experts suggested that patients with established CV disease are more likely to be candidates for the additive therapies of interest in ICER's review. However, in REDUCE-IT, the benefit of icosapent ethyl was assessed and observed in the overall study population.[19] REDUCE-IT was not designed or powered to compare benefit in the primary versus secondary prevention subgroups.
- The primary versus secondary prevention subgroup analysis was exploratory, as were all REDUCE-IT subgroup analyses; the pre-specified p-value for statistical significance of <0.15 was only chosen to help identify potential trends, and not as a threshold for rejecting the null hypothesis. For the primary and key secondary endpoints, the p-values for interaction between the primary versus secondary prevention populations of 0.14 and 0.41, respectively, were greater than the conventional threshold for statistical significance of $p< 0.05$. Therefore, while there is an exploratory trend toward potential differences in benefit between the primary and secondary prevention cohorts in the primary expanded MACE endpoint (not in the key secondary hard MACE endpoint), this does not suggest a lack of benefit in either cohort. For this reason, we believe the ICER review and decision analytic model of icosapent ethyl should follow the REDUCE-IT prospective study design and include the full REDUCE-IT enrolled patient cohorts of primary and secondary prevention together. Keep in mind that all patients in the primary prevention cohort had diabetes and additional CV risk factors. This is also consistent with the ADA's recommendation for use of icosapent ethyl.

Icosapent ethyl review and analytic framework should be separate from rivaroxaban

Page 5: Analytic Framework — Populations

- Unlike COMPASS, which focused on patients with stable atherosclerotic CV disease and did not specifically require or record statin use or lipid levels, all patients in REDUCE-IT were required to be receiving statin therapy, to have established CV disease or diabetes plus other risk factors, and to have controlled LDL-C and triglyceride levels of 135 to 499 mg/dL. This should be taken into consideration in the ICER review and decision analytic model.

Page 6: Outcomes

- REDUCE-IT and COMPASS had differences in primary, secondary, tertiary, or exploratory endpoints and how they were handled statistically (ie, in terms of multiplicity adjustments).

Pages 4-6: Separating icosapent ethyl and rivaroxaban

- Because of the key differences in the designs, populations studied (including primary/secondary prevention), and outcome measures between REDUCE-IT and COMPASS outlined above, the decision analytic model should be handled separately for icosapent ethyl and rivaroxaban (and thus the two drugs should also be separated in Figure 1 accordingly).

The analytic framework is not a comparison of icosapent ethyl versus statin

Page 5: Comparator

- We'd like to affirm that the comparison to be made for icosapent ethyl is optimized medical therapy including statin + icosapent ethyl versus optimized medical therapy including statin alone. Figure 1 may benefit from clarification accordingly.
- Please also note that REDUCE-IT included predominantly moderate- to high-intensity statin therapy (over 93%) but the trial was not powered for subgroup analyses of statin intensity. Median baseline LDL-C in REDUCE-IT was well controlled at 75 mg/dL. However, there was a consistent benefit even among those patients in the lowest tertile of baseline LDL-C.

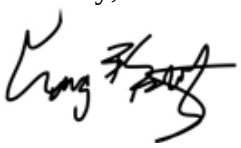
The REDUCE-IT time-to-event and the total event analyses should both be utilized

Page 8: Scope of Comparative Value Analyses

- Total event analyses from REDUCE-IT have recently been published in Bhatt et al, 2019.[20] These analyses are important because they allow direct inclusion in ICER's economic analysis of the total primary or key secondary composite endpoint events (or rates) from the two arms of REDUCE-IT over a median follow-up duration of 4.9 years.
- Incorporating actual observed events (or rates) from REDUCE-IT would support more accurate modeling as compared to only using a cohort simulation (via the Markov model) and applying assumed constant hazard ratios to annual event rates (and comparing two simulated cohorts: optimized medical therapy including statin + icosapent ethyl versus optimized medical therapy including statin alone). The total primary and key secondary composite endpoint events (which include first and all subsequent events) provide direct evidence for what would otherwise have to be simulated in the Markov model by creating in-trial post-event health states for patients who suffer a CV event.
- We propose that ICER use the REDUCE-IT total primary and key secondary composite endpoint events (or rates) during the in-trial follow-up time, and then use a Markov model (or other model, for example a Discrete Event Simulation model if ICER has enough data) to project for lifespan beyond the trial and to estimate life-time costs and outcomes (life-years, QALYs, etc.) for the two treatment arms.
- We note that William Weintraub, MD, of the MedStar Cardiovascular Research Network, is leading the development of an economic analysis that will include examination of total events in REDUCE-IT.

In conclusion, we propose that ICER's review and decision analytic model for icosapent ethyl be separated from that of rivaroxaban and include the following: (1) hypertriglyceridemia as an important CV risk factor, (2) both the primary and secondary prevention populations analyzed together, and (3) the recent total event analyses from REDUCE-IT. We welcome an opportunity to discuss the scope and methodology of the planned review with you in more detail.

Sincerely,



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April 5, 2019

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Dear Dr. Pearson:

AstraZeneca is aware that ICER is proposing a draft scope to review various agents utilized in patients with established cardiovascular disease (eCVD). One of the comparisons being considered is rivaroxaban (an anticoagulant) + aspirin (ASA) against dual antiplatelet therapy (DAPT). Ticagrelor is being considered in this comparison as a component of DAPT. We strongly believe that comparing ticagrelor + ASA to rivaroxaban + ASA is not appropriate and inconsistent with the approved indications for these products. Below we highlight the reasons for our viewpoint.

The Proposed Draft Scope:
The draft ICER scope includes patients with eCVD which includes many kinds of patients, with varying degrees of cardiovascular (CV) risk. Coronary artery disease (CAD), also known as coronary heart disease, is a subset of eCVD. Patients with CAD include those with acute coronary syndrome (ACS) (ST elevation myocardial infarction, non-ST elevation myocardial infarction, and unstable angina), and those with a history of myocardial infarction (MI). Also included in the group of CAD, are patients with stable CAD (who have either stable symptoms, or may have been rendered asymptomatic by having undergone a percutaneous coronary intervention and/or coronary artery bypass grafting surgery, and patients who might have obstructive disease and are asymptomatic). These patients are spread across a CV risk continuum, with a varying risk for future CV events. The management strategies for this group of patients are different depending on where the patient is in the risk continuum. Even the CV guidelines recommend different management strategies based on the patient type.[1,2,3]

Different Approved Indications
The approved indications for ticagrelor and rivaroxaban are different.[4,5] Ticagrelor is a reversibly binding $P2Y_{12}$ receptor inhibitor which is indicated in patients with ACS or prior MI based on the large registration trials, PLATO and PEGASUS respectively.[4,6,7] Rivaroxaban is a Factor Xa inhibitor indicated in patients with chronic CAD or peripheral artery disease (PAD) based on the COMPASS trial.[5,8] Rivaroxaban is not indicated for patients with an ACS.[5] As such we have purposely omitted comparing rivaroxaban to ticagrelor in the ACS setting.

Differences in Populations Studied and Study Designs of PEGASUS and COMPASS
As a proposed comparator to rivaroxaban, it is our assumption that ticagrelor will be evaluated in the prior MI population, below is our rationale how the pivotal trial PEGASUS differed from COMPASS. The major differences in the study populations are shown in the table below. These differences speak to critical risk modifiers that exist within the eCVD population and as such warrant different treatment approaches. Furthermore, the number of patients with these enriched risk modifiers and the character of the disease at the time of study enrollment (such as PAD and time from prior MI) can impact the overall result of the trial.

	PEGASUS[7]	COMPASS[8]
Design	Randomized, double-blind, placebo-controlled, parallel-group, event driven multinational study in 21,162 patients with a **history of MI 1-3 years prior to randomization and at least 1 additional CV risk factor**	Randomized, double-blind, placebo controlled, event-driven, multinational study in 27,395 patients with **stable CAD or PAD**
Objectives	• Evaluated whether long-term therapy with ticagrelor + low-dose ASA reduced the risk of CV death, MI, or stroke in patients with a history of MI and ≥1 additional risk factor compared to placebo + low-dose ASA • Examined 2 intensities of ticagrelor (90 mg BID or 60 mg BID) to optimize the balance of efficacy and bleeding	Determined whether the combination of rivaroxaban 2.5 mg BID + ASA 100 mg or rivaroxaban 5 mg BID alone reduced the risk of CV death, MI, or stroke in patients with stable CAD or PAD compared to ASA 100 mg alone
Inclusion of Patients with Prior MI (%)	100% had a prior MI	62% had a prior MI
Timing of MI Inclusion Criteria Prior to Randomization	MI 1-3 years prior	MI within the last 20 years
Time from Qualifying MI Prior to Randomization	Median of 1.7 years from qualifying MI	Mean of 7.1 years from their index MI
Patients with PAD	5.4% of patients had PAD	27.3% of patients had a history of PAD
Patients with Diabetes	32.2% of patients had diabetes	37.7% of patients had diabetes
Mean Age	65.3 ± 8.4	68.2 ± 7.9
Run-in Phase	None	30 days
Study duration	Median, 33 months	Mean, 23 months
Study treatments	• Ticagrelor 90 mg BID or • Ticagrelor 60 mg BID or • Placebo BID All patients received background therapy of ASA 75-150 mg daily	• Rivaroxaban 2.5 mg BID + ASA 100 mg QD or • Rivaroxaban 5 mg BID or • ASA 100 mg QD
Primary composite efficacy endpoint	CV death, MI, or stroke	CV death, MI, or stroke
Primary safety endpoint	TIMI major bleeding	Major bleeding (modified ISTH)

ISTH = International Society on Thrombosis and Haemostasis; TIMI = Thrombolysis In Myocardial Infarction.

Other Pertinent Trial Differences and Key Points

A very small percentage of the COMPASS population met the PEGASUS entry criteria of having had an MI 1-3 years prior to randomization.[7,9] The greater efficacy for rivaroxaban + ASA in COMPASS was in patients who had either not had a prior MI or were remote from an MI (>5 years).[9]

In COMPASS patients could have been enrolled with a history of PAD only.[8]

The COMPASS trial was terminated early, and only the primary composite efficacy endpoint was powered for an outcome.[8] All other analyses are exploratory with nominal p values, as no further hierarchical testing was performed.[8,10]

COMPASS was neither a head to head study against ticagrelor + ASA nor a switch study from ticagrelor + ASA to rivaroxaban + ASA.[8] There is no data available, in the public domain, on the prior exposure to $P2Y_{12}$ receptor inhibitors in COMPASS.

Experience from the National Institute for Health and Care Excellence (NICE): Final Appraisal Determination by NICE on Ticagrelor for Preventing Atherothrombotic Events After MI

Finally, we share an example from NICE in the UK, where a comparison of ticagrelor + ASA to clopidogrel + ASA was being considered in high risk patients with a prior MI.[11] The difficulties experienced in doing such a comparison, given the available data, are likely to be experienced in the current scope from ICER, and may lead to inappropriate conclusions. In the final analysis NICE decided to abandon the comparison, a decision recommended by their Evidence Review Group (ERG). NICE initially requested an indirect comparison of ticagrelor + ASA against clopidogrel + ASA, since no head to head data was available in the population being considered in the scope. However, the NICE committee ultimately agreed with the ERG and concluded that clopidogrel + ASA was not an appropriate comparator and that the most appropriate comparison for its decision-making was to compare ticagrelor + ASA with ASA alone. The ERG made the recommendation based on the same arguments outlined in this letter: major differences in the trial designs and the populations studied. Please find below a hyperlink to the NICE appraisal document:
https://www.nice.org.uk/guidance/ta420/documents/final-appraisal-determination-document

In conclusion, AstraZeneca strongly believes that based on the rationale provided, comparing ticagrelor to rivaroxaban in the current scope is inappropriate and will result in misleading conclusions. There are significant differences in the trial designs, populations and indications between ticagrelor and rivaroxaban, and these differences will confound a meaningful clinical value assessment.

Yours truly,

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XARELTO® (rivaroxaban)

ICER Cardiovascular Disease SCOPING DOCUMENT
Response to Request for Public Comments

The enclosed information has been supplied to you in response to your unsolicited request. Information contained in this response is not intended as an endorsement or promotion of any usage. For information on ongoing clinical trials for our products, please visit www.clinicaltrials.gov.

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SCOPE

Background:

- It is important to note that coronary artery disease (CAD) and peripheral arterial disease (PAD) are part of the same polyvascular disease process of arterial atherothrombosis (Bhatt 2010, Pareek 2018, Fox 2018). As such, any future modeling or analysis should focus on CAD and PAD as a single disease process. While there is often a long asymptomatic latency period, the symptomatic clinical consequences are severe, including stroke, heart attack, cardiovascular (CV) death, heart failure, limb threatening ischemia, and amputation. The phenotypic expression of systemic atherothrombosis share common major risk factors (Pareek 2018).
- The prevalence of polyvascular disease increases from 25% in CAD patients to 40% in cerebrovascular disease patients and to 61% in PAD patients (Cacoub 2009).
- Of note, as the number of affected arterial beds increase, there is a substantial increase in CV event rates (Suarez 2010).
- The landmark COMPASS study which included patients with stable CAD and/or PAD, demonstrated that the combination of rivaroxaban 2.5 mg twice daily (BID) plus aspirin vs. aspirin alone resulted in a significant relative risk reduction (RRR) of 24% in the primary composite outcome of CV death, stroke, or myocardial infarction (MI) (4.1% vs. 5.4%; hazard ratio (HR): 0.76; CI:0.66-0.86; p<0.001) (Eikelboom 2017). Additionally, the combination of rivaroxaban plus aspirin reduced all-cause mortality by 18% compared to aspirin alone (3.4% vs. 4.1%; HR 0.82; 95% CI:0.71-0.96) (Eikelboom 2017), a finding that was not seen in other contemporary antithrombotic trials (Bhagirath 2018). The net clinical benefit balanced the lower risk of CV death, stroke, or MI against the most serious bleeding events (i.e., fatal bleeding, symptomatic bleeding in a critical organ) and showed a positive net clinical benefit of the combination therapy compared to aspirin alone (4.7% vs 5.9%; HR: 0.80; 95% CI: 0.70-0.91) (Eikelboom 2017).

Comparators:

Dual antiplatelet therapy (DAPT) is not an appropriate comparator as proposed by ICER due to the following reasons:

- There are no trials where comparable populations were studied either through direct or indirect comparison.
- Several other products in combination with aspirin have been investigated in large trials for the management of patients with stable CAD and/or PAD, including clopidogrel (CHARISMA) (Bhatt 2006, Bhatt 2007) and ticagrelor (PEGASUS-TIMI 54) (Bonaca 2015, Bonaca 2016). However, with

both clopidogrel and ticagrelor only certain types of patients benefited in terms of reduction in MACE, and the magnitude of treatment effects differed by type of event prevented (Fox 2018). No significant decreases in all-cause mortality were noted in any of these studies and additionally, in the PEGASUS trial, there was an increased risk of bleeding in the ticagrelor plus aspirin group (Bhagirath 2018, Bonaca 2015).

- XARELTO® (rivaroxaban) in combination with low-dose aspirin is the only antithrombotic combination indicated to reduce the risk of major cardiovascular events (CV death, MI and stroke) for treatment of both chronic CAD and PAD. It is important to acknowledge the inclusion of reduction in CV death in the indication for rivaroxaban, whereas clopidogrel does not include CV death in their indication.
    - Rivaroxaban is indicated "in combination with aspirin, to reduce the risk of major cardiovascular events (CV death, MI and stroke) in patients with chronic CAD or PAD." (XARELTO PI)
- Clopidogrel is indicated to reduce the rate of MI and stroke in patients with established PAD, or with a history of recent MI or recent stroke. (Plavix PI). This is a narrower indication than that of rivaroxaban, which encompasses a broader population of chronic CAD, not just those with recent MI or stroke. Of note, the indication for reducing CV death was removed by the Food and Drug Administration (FDA) in the prescribing information for clopidogrel.
- Ticagrelor "is indicated to reduce the risk of CV death, MI and stroke in patients with acute coronary syndrome (ACS) or a history of MI" (Brilinta PI). This is a substantially narrower indication than that of rivaroxaban, which encompasses both chronic CAD and PAD. Additionally, ticagrelor is not indicted as a treatment for patients with PAD, as data from the EUCLID trial demonstrated no benefit with ticagrelor over clopidogrel in patients with symptomatic PAD (Hiatt 2017).
- While DAPT has been established in reducing ischemic events in patients with ACS, there is less convincing evidence with DAPT in patients with stable ischemic heart disease (SIHD). As per the 2012 American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) guidelines:
    - In patients with SIHD, the guidelines recommend treatment with aspirin as the only Level 1A recommendation for antithrombotic therapy (Fihn 2012).
    - Treatment with DAPT consisting of clopidogrel and aspirin is only a class IIb recommendation, considered reasonable in certain high-risk patients with SIHD (Fihn 2012). This is based on lower strength of evidence from a post hoc analysis of the CHARISMA trial. In the CHARISMA trial, the primary efficacy endpoint (composite of MI, stroke, or death from CV causes) was not reduced with clopidogrel plus aspirin compared to aspirin alone in the overall study population (Bhatt 2006, Fihn 2012). However, a post hoc analysis suggested that a subgroup of patients with documented prior MI, ischemic stroke, or symptomatic PAD had better outcomes with clopidogrel plus aspirin (Bhatt 2007, Fihn 2012).
    - In the 2016 AHA/ACC PAD Guidelines, DAPT is only a IIb B-R recommendation as "the effectiveness of dual antiplatelet therapy (aspirin and clopidogrel) to reduce the risk of cardiovascular ischemic events in patients with symptomatic PAD is not well established (Gerhard-Herman 2017).
- In the PEGASUS trial, which compared ticagrelor plus aspirin to aspirin alone, eligible patients had a spontaneous MI 1 to 3 years before enrollment (median 1.7 years from prior MI; Bonaca 2015), whereas COMPASS included patients that had an MI within the past 20 years (mean 7.1 years since last MI) (Bosch 2017, Eikelboom 2017).
    - In the PEGASUS trial, the primary composite end point of CV death, MI, or stroke was significantly reduced, while the rates of TIMI major bleeding were significantly higher with ticagrelor plus aspirin compared to aspirin alone (2.60% with 90mg and 2.30% with 60 mg vs. 1.06% with aspirin alone; $p<0.001$ for each dose vs. aspirin alone) (Bonaca 2015).
    - The rate of death from any cause did not differ significantly with either ticagrelor dose plus aspirin, as compared with aspirin alone (Bonaca 2015).
    - The benefit of ticagrelor depended on the time from last dose of ticagrelor, with HRs (95% CI) for ticagrelor (pooled doses) vs. aspirin of 0.73 (0.61–0.87), 0.86 (0.71–1.04), and 1.01 (0.80–1.27) for ≤30 days, >30-360 days, >360 days, respectively) (Bonaca 2016a).

- In a subgroup of PAD patients in PEGASUS, ticagrelor plus aspirin significantly reduced major adverse limb events (defined as the composite of acute limb ischemia and peripheral revascularization for ischemia) with the 90 mg dose but not with the 60 mg dose. (Of note, the 90 mg dose is only approved during the first year after an ACS event, whereas the 60 mg dose is the approved dose for patients after one year of an event). Additionally, no statistically significant benefit with ticagrelor plus aspirin was observed in the reduction of acute limb ischemia (ALI) (Bonaca 2016b).

Outcomes:

- The model should represent the following relevant outcomes: major adverse limb events (MALE), acute limb ischemia (ALI); chronic limb ischemia (CLI), amputations, and peripheral revascularizations (Anand 2018a,b). Of note, in COMPASS, there were 7,470 patients with PAD. Of those patients with PAD, approximately 65% of patients also had a history of CAD (Anand 2018a), demonstrating the high prevalence of polyvascular disease (i.e., patients that have ≥2 vascular beds affected). COMPASS is the only trial to show combined benefits in limb outcomes as well as MACE benefits as rivaroxaban plus aspirin demonstrated consistently favorable outcomes in reducing CV events and limb outcomes in patients with PAD (Anand 2018a). In the prespecified PAD subgroup of the COMPASS study, MALE was reduced by 46% (1% vs 2%; HR: 0.54; 95% CI: 0.35-0.84) with rivaroxaban 2.5 BID plus aspirin compared to aspirin alone (Anand 2018a).
- ICER should consider including multiple health utilities that correspond to different severities of stroke to appropriately reflect QALY and costs. Strokes are very diverse in nature specifically in degree of irreversible disability. The post-hoc analysis of the COMPASS trial showed that rivaroxaban plus aspirin not only reduced the number of strokes but also the occurrence of fatal and disabling strokes (modified Rankin Scale, 3-6) (Sharma 2019). Health utilities vary significantly for different stroke severities (Ali 2017).
- It is important to clarify how serious bleeding events are being defined. Of note, bleeding definitions varied across trials. In COMPASS, the primary safety outcome was a modification of the International Society on Thrombosis and Haemostasis (ISTH) including the composite of fatal bleeding, symptomatic bleeding in a critical organ, bleeding into a surgical site requiring reoperation, and bleeding that led to hospitalization (including presentation to an acute care facility without an overnight stay) (Eikelboom 2017). In PEGASUS, the primary safety end point was Thrombolysis in Myocardial Infarction (TIMI) major bleeding (Bonaca 2015). In CHARISMA, the primary safety end point was severe bleeding as defined by the GUSTO (Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries) criteria (Bhatt 2006).

Scope of Comparative Value Analysis:

- Based on market research and consultation with leading medical experts in the field, Janssen's focus for the next few years will be addressing an unmet medical need in high-risk CAD/PAD patients to have access to rivaroxaban 2.5mg, a patient population which should be considered in the development of a budget impact model.
- Additionally, ICER should consider available claims data for the rivaroxaban 2.5mg dose utilization (e.g. IQVIA data) which is the indicated dose for CAD/PAD to estimate or extrapolate uptake.
- Loss of patent protection for rivaroxaban 2.5 mg within the next 6 years should be taken into consideration in the cost effectiveness analysis.
- Given the US healthcare landscape, having had 8 years of competitive contracting, the reviewers should take into consideration the rebates (net price) in developing the model.

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