Additive Therapies for Cardiovascular Disease: Effectiveness and Value

Research Protocol

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Institute for Clinical and Economic Review

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Background, Objectives, and Research Questions

Background

The term cardiovascular disease (CVD) defines a complex, burdensome, and highly prevalent set of conditions. Three of the major types of CVD, coronary artery disease (CAD), peripheral artery disease (PAD), and cerebrovascular disease, result from atherosclerosis, a chronic degenerative process involving increasing buildup of plaque formed by fat- and cholesterol-based deposits. Over time, these deposits result in arterial narrowing and wall hardening, which in turn can result in angina, claudication, myocardial infarction, or stroke, among other problems. In total, CVD is estimated to affect one-half of adults in the United States (US), and is the leading cause of death, with approximately 850,000 deaths annually.[1] CVD also imposes a substantial financial burden, with annual direct and indirect costs estimated to total $1.1 trillion.[1]

The management of patients with CVD has commonly consisted of behavior modification (i.e., diet, weight reduction, physical activity, smoking cessation) to interrupt atherosclerotic processes, as well as risk factor management, including blood pressure control, treatment with lipid-lowering agents, antiplatelet therapy, and when necessary, surgical, or percutaneous revascularization. Although low-dose acetylsalicylic acid (aspirin, or ASA) and statins have become cornerstone therapies with proven benefit for patients with established CVD, this population remains at high residual risk for cardiovascular events. In addition, those without documented CVD but with established risk factors such as diabetes and comorbid hypertension or hypercholesterolemia are also at elevated risk for major cardiovascular events. For these patients, there is clinical interest in exploring other types of medical management in addition to the strategies described above.

The cardioprotective effects of two such agents, rivaroxaban (Xarelto®, Janssen Pharmaceutica) and icosapent ethyl (Vascepa®, Amarin Pharma) were recently investigated as add-on therapy in patients with established CVD, and in the case of icosapent ethyl, patients without evidence of CVD but with diabetes and at least one additional risk factor. Rivaroxaban is a direct inhibitor of factor Xa in the blood coagulation pathway. It was first approved for the prevention of deep vein thrombosis in patients undergoing major orthopedic surgery, is commonly used in the management of atrial fibrillation and venous thromboembolic disease, and received an indication for the prevention of major cardiovascular events in patients with CAD or PAD in the fall of 2018. It is the latest in a line of antithrombotic regimens that have been tested as alternatives or additions to aspirin, including vitamin K antagonists, antiplatelet therapies, and thrombin receptor antagonists.[2]

Icosapent ethyl is a purified ethyl ester of the omega-3 fatty acid known as eicosapentaenoic acid (EPA), which was initially approved in 2012 as an adjunct to diet to treat severe hypertriglyceridemia (triglyceride levels ≥500 mg/dL). After a randomized trial showed lower CVD event risk in patients treated with icosapent ethyl,[3] the manufacturer filed for an expanded

indication in March of 2019. Icosapent ethyl's mechanism of action in cardioprotection is not fully known; while hypertriglyceridemia increases the risk of ischemic events, reduction in these levels with icosapent ethyl may only partially explain the treatment effects observed in the trial. Other mechanisms, such as antithrombotic effects and stabilization and regression of coronary plaque have also been hypothesized.[3]

Objectives

The scope of this project was previously available for public comment and has been revised upon further discussions and input from stakeholders. In accordance with the revised scope, this project will assess both the comparative clinical effectiveness and economic impacts of rivaroxaban and icosapent ethyl for the treatment of CVD. The assessment aims to systematically evaluate the existing evidence, taking uncertainty into account. To that aim, the assessment is informed by two research components: a systematic review of the existing evidence and an economic evaluation. This document presents the protocol for the systematic review of existing evidence (i.e., the clinical review). See the model analysis plan for details on the proposed methodology and model structure that will be used for the economic evaluation (expected date of publication June 6, 2019).

Research Questions

To inform our review of the clinical evidence, we have developed the following research questions with input from clinical experts, patients, and patient groups:

- In patients with established CVD, what is the comparative efficacy, safety, and effectiveness of rivaroxaban + ASA versus optimal medical management including ASA without an additional antiplatelet agent in terms of cardiovascular mortality, myocardial infarction, stroke, and other key outcomes?
- In patients with established CVD, what is the comparative efficacy, safety, and effectiveness of rivaroxaban + ASA versus optimal medical management including ASA as a part of dual antiplatelet therapy (DAPT) in terms of cardiovascular mortality, myocardial infarction, stroke, and other key outcomes?
- In patients with established CVD or without known CVD but at high risk for cardiovascular events, what is the comparative efficacy, safety, and effectiveness of icosapent ethyl versus optimal medical management including statin therapy in terms of cardiovascular mortality, myocardial infarction, stroke, and other key outcomes?

PICOTS Criteria

In line with the above research questions, the following specific criteria have been defined utilizing PICOTS (Population, Interventions, Comparisons, Outcomes, Timing, Setting and Study Design) elements.

Population

The population of focus for the review is adults with established CVD who are currently treated with optimal medical management. For the assessment of icosapent ethyl, we will also review evidence for patients without known CVD but at high risk for cardiovascular (CV) events.

Data permitting, we also plan to examine evidence for key subgroups suggested by clinical experts, including (but not necessarily limited to) the following:

1. Diagnosis of diabetes mellitus
2. Diagnosis of CAD alone versus CAD and concomitant PAD (rivaroxaban only)
3. Levels of high-sensitivity C-reactive protein (hsCRP) at baseline (i.e., ≤2 mg/l or >2 mg/l) as well as changes in hsCRP from baseline to follow-up
4. Subgroups defined by level of CV risk at baseline
5. Renal dysfunction

Interventions

The list of interventions was developed with input from patient organizations, clinicians, manufacturers, and payers on which drugs to include. The full list of interventions is as follows:

1. Rivaroxaban + ASA
    - Patients are assumed to also be receiving optimal medical management, including ASA
2. Icosapent ethyl
    - Patients are assumed to also be receiving optimal medical management including statins

Comparators

Comparators were defined to reflect the input of clinicians and other stakeholders on treatment strategies that would be considered relevant alternatives for the overall population of interest or a prominent subset, as well as the comparators as defined in major clinical studies of icosapent ethyl and rivaroxaban.

1. Rivaroxaban comparators:
    - optimal medical management including ASA without an additional antiplatelet agent

- optimal medical management including ASA as part of dual antiplatelet therapy (DAPT) with an oral $P2Y_{12}$ inhibitor (e.g., clopidogrel)

2. Icosapent ethyl comparator:
    - Optimal medical management including statin therapy

Outcomes

The outcomes of interest are described in Table 1 below.

Table 1. Outcomes and Harms

Outcomes	Key Harms
All-cause mortality	Treatment-emergent adverse events (TEAEs)
Cardiovascular mortality	Discontinuation due to TEAEs
Myocardial infarction	Serious TEAEs
Stroke	Major bleeding events
Coronary revascularization	
Unstable angina	
Heart failure	
Venous thromboembolism	
Health-related quality of life	
Cardiovascular hospitalization	
Major adverse limb events (MALE)	

Timing

Evidence on intervention effectiveness will be derived from studies of at least one year's duration and evidence on harms from studies of at least three month's duration.

Setting

All relevant settings will be considered, with a focus on outpatient management in the United States.

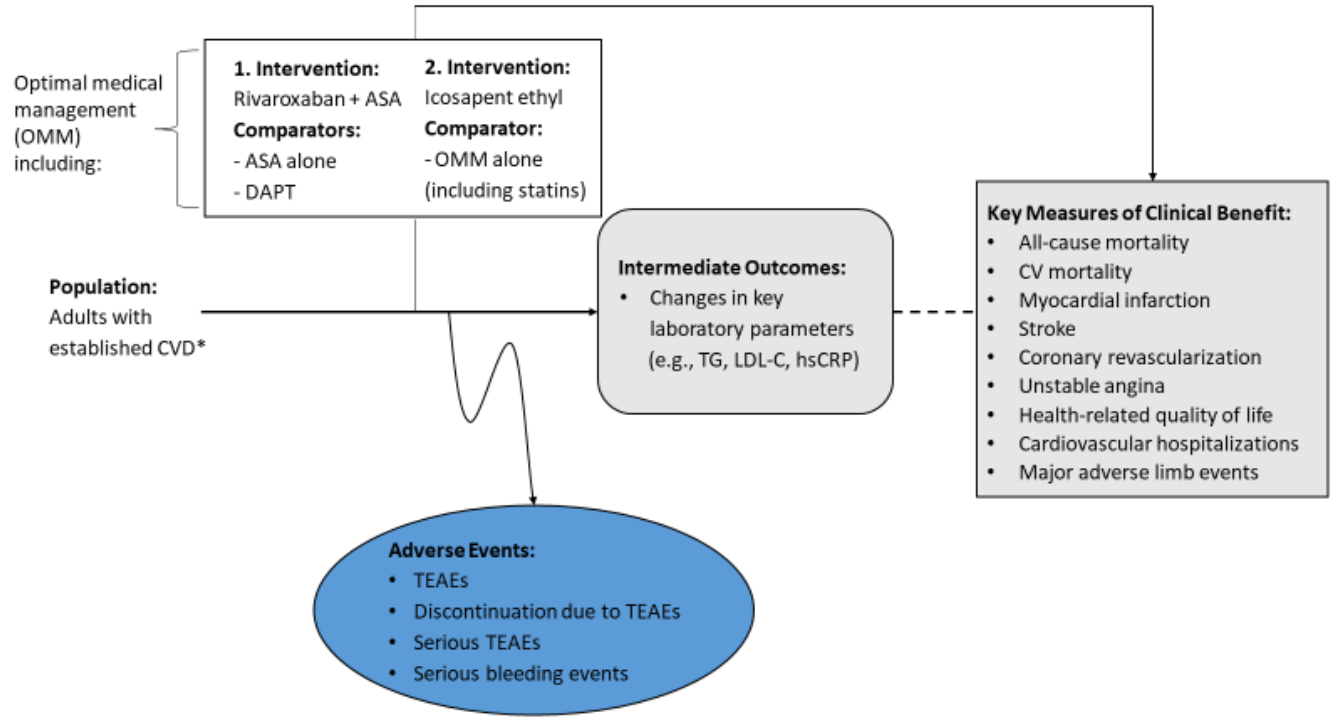
Study Design

Randomized controlled trials, non-randomized controlled trials, and observational studies with any sample size will be included.

Analytic Framework

The proposed analytic framework for this project is depicted in Figure 1.

Figure 1. Analytic Framework: Rivaroxaban and Icosapent Ethyl for CVD



ASA: acetylsalicylic acid, CV: cardiovascular, CVD: cardiovascular disease, DAPT: dual antiplatelet therapy, hsCRP: high-sensitivity C-reactive protein, LDL-C: low-density lipoprotein cholesterol, OMM: optimal medical management, TEAE: treatment-emergent adverse event, TG: triglyceride
*For the assessment of icosapent ethyl, we will also review evidence for patients without known CVD but at high risk for CV events.

The diagram begins with the population of interest on the left. Actions, such as treatment, are depicted with solid arrows which link the population to outcomes. For example, a treatment may be associated with specific clinical or health outcomes. Outcomes are listed in the shaded boxes: those within the rounded boxes are intermediate outcomes (e.g., change in blood pressure), and those within the squared-off boxes are key measures of clinical benefit (e.g., health-related quality of life). The key measures of clinical benefit are linked to intermediate outcomes via a dashed line, as the relationship between these two types of outcomes may not always be validated. Curved arrows lead to the adverse events of an action (typically treatment), which are listed within the blue ellipsis.[4]

Evidence Review Methods

Search Methods and Data Sources

Procedures for the systematic literature review assessing the evidence on rivaroxaban and icosapent ethyl for CVD will follow established best methods.[5,6] The review will be conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[7] The PRISMA guidelines include a list of 27 checklist items, which are described further in Appendix A.

We will search MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials for relevant studies. Each search will be limited to English language studies of human subjects and will exclude articles indexed as guidelines, letters, editorials, narrative reviews, case reports, or news items. We will include abstracts from conference proceedings identified from the systematic literature search. All search strategies will be generated utilizing the Population, Intervention, Comparator, and Study Design elements described above. The proposed search strategies include a combination of indexing terms (MeSH terms in MEDLINE and EMTREE terms in EMBASE), as well as free-text terms, and are presented in Tables 2-3.

To supplement the database searches, we will perform a manual check of the reference lists of included trials and reviews and invite key stakeholders to share references germane to the scope of this project. We will also supplement our review of published studies with data from conference proceedings, regulatory documents, information submitted by manufacturers, and other grey literature when the evidence meets ICER standards (for more information, see http://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/grey-literature-policy/).

Table 2. Search Strategy of MEDLINE and Cochrane Central Register of Controlled Trials (via Ovid)

1	((cardiovascular or heart or coronary or atherosclero$ or isch?emic or peripheral or arter$ or cerebrovascular) adj2 (diseas$ or disorder$ or syndrome$ or atherosclero$)).ti,ab.
2	('icosapent ethyl' or vascepa or amr101).ti,ab.
3	exp rivaroxaban/ or (rivaroxaban or Xarelto).ti,ab.
4	2 or 3
5	1 and 4
6	(animals not (humans and animals)).sh.
7	5 not 6
8	(addresses or autobiography or bibliography or biography or case reports or classical article or clinical conference or clinical trial, phase i or comment or congresses or consensus development conference or consensus development conference, nih or dataset or dictionary or directory or duplicate publication or editorial or equivalence trial or "expression of concern" or guideline or historical article or interactive tutorial or interview or introductory journal article or lectures or legal cases or legislation or letter or news or newspaper article or overall or patient education handout or periodical index or personal narratives or portraits or practice guideline or "published erratum review" or "scientific integrity review" or technical report or twin study or validation studies or video-audio media or webcasts).pt.
9	7 not 8
10	limit 9 to english language

Table 3. Search Strategy of EMBASE

#1	((cardiovascular OR heart OR coronary OR atherosclero* OR isch*emic OR peripheral OR arter* OR cerebrovascular) NEAR/2 (diseas* OR disorder* OR syndrome* OR atherosclero*)):ti,ab
#2	'icosapentaenoic acid ethyl ester'/exp OR 'icosapent ethyl':ti,ab OR vascepa:ti,ab OR amr101:ti,ab
#3	'rivaroxaban'/exp OR rivaroxaban:ti,ab OR xarelto:ti,ab
#4	#2 OR #3
#5	#1 AND #4
#6	('animal'/exp OR 'nonhuman'/exp OR 'animal experiment'/exp) NOT 'human'/exp
#7	#5 NOT #6
#8	#7 AND ('case report'/de OR 'in vitro study'/de OR 'chapter'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'review'/it)
#9	#7 NOT #8
#10	#9 NOT [medline]/lim
#11	#10 AND [english]/lim

Eligibility Criteria

We will exclude studies that do not meet the PICOTS criteria defined above. We will only include studies of rivaroxaban that evaluate the FDA-indicated dose for patients with CAD or PAD (i.e., 2.5 mg twice daily in combination with ASA 75-100 mg once daily). Studies of rivaroxaban conducted in patients with acute coronary syndrome or other indications for which rivaroxaban is indicated (e.g., nonvalvular atrial fibrillation) will be excluded; however, we will consider reviewing safety data from these studies if they evaluate rivaroxaban 2.5 mg twice daily in combination with ASA. Likewise, we will consider safety findings from studies of the impact of icosapent ethyl on lipid levels only if the 4 g daily dose was used.

Selection of Eligible Studies

Subsequent to the literature search and removal of duplicate citations using both online and local software tools, study selection will be accomplished through two levels of screening, at the abstract and full-text levels. Two reviewers will independently screen the titles and abstracts of all publications identified using DistillerSR (Evidence Partners, Ottawa, Canada); a third reviewer will work with the initial two reviewers to resolve any issues of disagreement through consensus. No study will be excluded at abstract-level screening due to insufficient information. For example, an abstract that does not report an outcome of interest in the abstract would be accepted for further review in full text.

Citations accepted during abstract-level screening will be retrieved in full text for review. Reasons for exclusion will be categorized according to the PICOTS elements during both title/abstract and full-text review.

Data Extraction Strategy

Data will be extracted into evidence tables. The basic design and elements of the extraction forms will follow those used for other ICER reports. Elements include a description of patient populations, sample size, duration of follow-up, study design features, interventions (agent, dosage, frequency, schedules), concomitant therapy allowed and used (agent, dosage, frequency, schedules), outcome assessments, results, and quality assessment for each study.

The data extraction will be performed in the following steps:

1. One reviewer will extract information from the full articles, and a second reviewer will validate the extracted data.
2. Extracted data will be reviewed for logic, and a random proportion of data will be validated by a third investigator for additional quality assurance.

Quality Assessment Criteria

We will use criteria published by the US Preventive Services Task Force (USPSTF) to assess the quality of clinical trials and cohort studies, using the categories “good,” “fair,” or “poor.”[8]

Good: Meets all criteria: Comparable groups are assembled initially and maintained throughout the study; reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention paid to confounders in analysis. In addition, intention to treat analysis is used for RCTs.

Fair: Any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains whether

some (although not major) differences occurred with follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all-important outcomes are considered; and some but not all potential confounders are addressed. Intention to treat analysis is done for RCTs.

Poor: Any of the following fatal flaws exists; groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. For RCTs, intention to treat or modified intention to treat (e.g., randomized and received at least one dose of study drug) analysis is lacking.

Publication Bias Assessment

Given the emerging nature of the evidence base for these newer treatments, we will scan the ClinicalTrials.gov site to identify studies completed more than two years ago. Search terms will include rivaroxaban, Xarelto, icosapent ethyl, Vascepa, and AMR101. We will select studies which would have met our inclusion criteria, and for which no findings have been published. We will provide qualitative analysis of the objectives and methods of these studies to ascertain whether there may be a biased representation of study results in the published literature.

Evidence Synthesis

The purpose of the evidence synthesis is to estimate the clinical effectiveness of the interventions being compared. The analysis will be based on the data from all relevant studies identified from the systematic review. This section contains two components: 1) a summary of the evidence base and 2) a synthesis of outcome results.

Summary of Evidence Base

The studies will be summarized in the text and in evidence tables of the Evidence Report. This summary is key to understanding the evidence base pertaining to the topic. An evidence table shell is presented in Appendix B. Relevant data include those listed in the data extraction section. Any key differences between the studies in terms of the study design, patient characteristics, interventions (including dosing and frequency), outcomes (including definitions and methods of assessments), and study quality will be noted in the text of the report.

Synthesis of Results

The results of the studies will be synthesized for each outcome and described narratively in the report. Analyses to be conducted will reflect the nature and quality of the evidence base. Key considerations for interpreting the results will be specified and described in the Evidence Report.

Analyses are expected to be descriptive in nature only, as differences in entry criteria, patient populations, outcome assessments, and other factors are likely to preclude formal pairwise meta-analyses as well as indirect or mixed treatment comparisons of rivaroxaban + ASA versus optimal medical management and DAPT, respectively, and icosapent ethyl versus optimal medical management plus statins. Nevertheless, if studies (or available subgroup data) are sufficiently similar in terms of patient populations, outcomes assessed, interventions, and comparators, we will conduct random effect pairwise meta-analyses and network meta-analyses where feasible. A pairwise meta-analysis quantitatively synthesizes results from multiple studies that assessed the same intervention and comparator.[9] A network meta-analysis extends pairwise meta-analyses by simultaneously combining both the direct estimates (i.e., estimates obtained from head-to-head comparisons) and indirect estimates (i.e., estimates obtained from common comparator[s]).[10,11] The specific approach for any (network) meta-analysis will depend on the available evidence and will be detailed in the report.

References

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Appendix A. PRISMA Checklist

The checklist below is drawn from Moher et al. 2009.[7] Additional explanation of each item can be found in Liberati et al. 2009.[12]

Section/Topic	#	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see Item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers).	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	

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Appendix B. Data Extraction Summary Table Shells

Table A. Study Quality Metrics

Study	Comparable Groups	Adequate Randomization	Patient Blinding	Physician Blinding	Outcome Adjudication Blinding	Non-Differential Follow-Up	ITT Analysis	Handling of Missing Data	Overall Quality

ITT: intent-to-treat

Table B. Study Design

Study	Study Design	N	Total Follow-Up (Units)	Primary Outcome and Key Secondary Outcomes	Inclusion Criteria	Exclusion Criteria

Table C. Baseline Characteristics

Study	Arm	N	Age	BMI	BP	Laboratory Parameters	Documented Vascular Disease	Prior CV Events	Comorbidities	Concomitant Medications	Other CV Risk Factors

BMI: body mass index, BP: blood pressure, CV: cardiovascular

Table D. Outcomes

Study	Arm	N	Follow-Up	CV Death, no. (%)	HR (95% CI)	MI, no. (%)	HR (95% CI)	Stroke, no. (%)	HR (95% CI)	All-Cause Death, no. (%)	HR (95% CI)	Composite MACE Outcome(s) no.(%)	HR (95% CI)	Other Outcomes	HR (95% CI)

CI: confidence interval, CV: cardiovascular, HR: hazard ratio, MACE: major adverse cardiovascular events; MI: myocardial infarction

Table E. Safety

Study	Arm	N	Follow-Up	Any AE, no. (%)	Any SAE, no. (%)	Discontinuation due to AE, no. (%)	Major Bleeding, no. (%)	Minor Bleeding, no. (%)	Fatal Bleeding, no. (%)	AEs Occurring ≥5%, no. (%)

AE: adverse event, SAE: serious adverse event