
Additive Therapies for Cardiovascular Disease: Effectiveness and Value

Public Meeting – September 26, 2019



INSTITUTE FOR CLINICAL
AND ECONOMIC REVIEW

WIFI

Network: TritonNet

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Password: TransformLives2019!

Why are we here today?

- “Everyone in my family is afraid I will have another heart attack. I do everything I can to manage my disease, but I always feel like I’m waiting for the worst to happen. Because I know it can at any time.”
 - *Patient with cardiovascular disease*

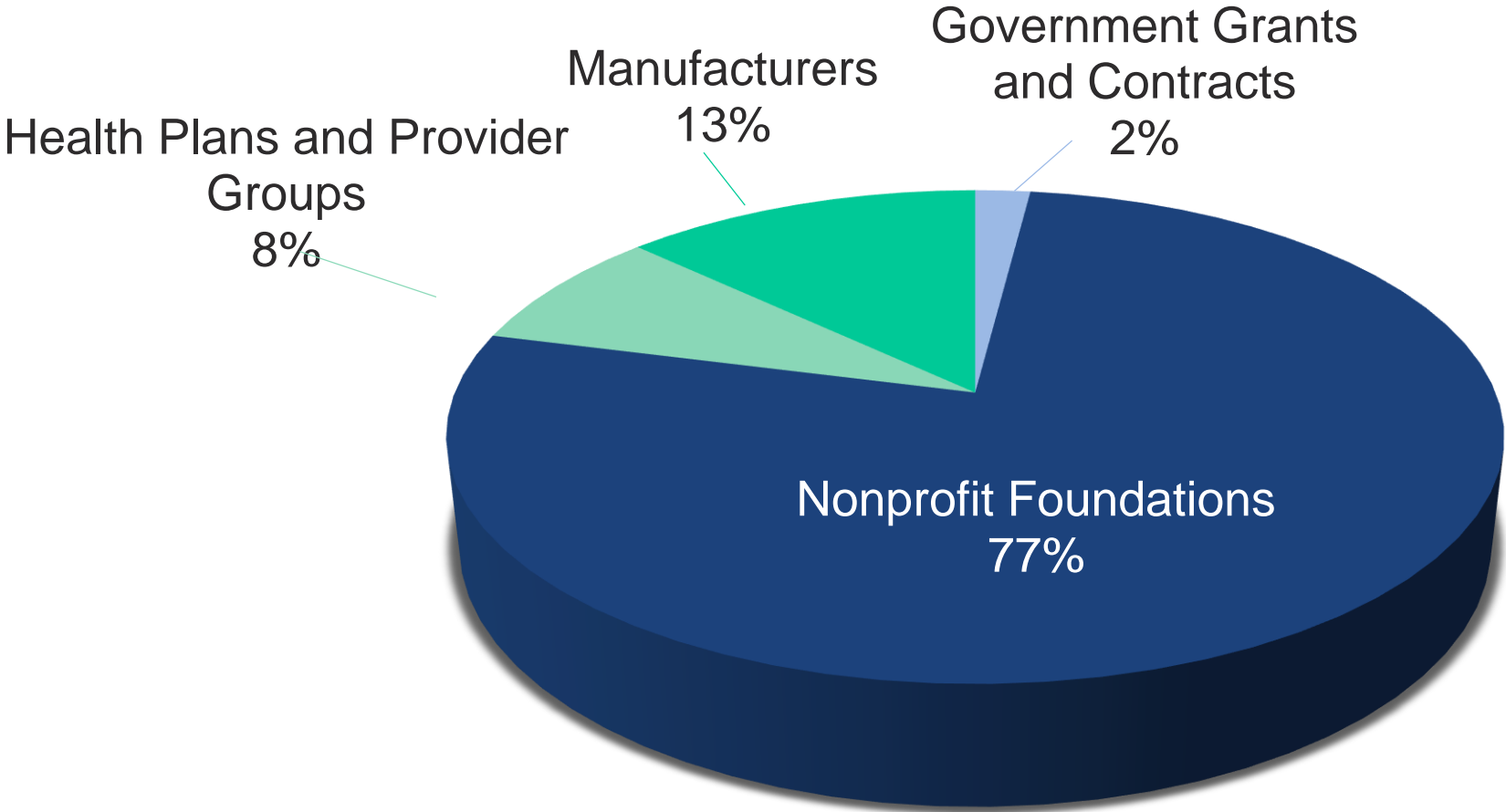
Why are we here today?

- What happens the day these treatments are approved by the FDA?
- The historical context and the challenge we all face today
- Patients can have difficulty accessing drugs
 - Coverage eligibility
- The goals for today's meeting

Organizational Overview

- Midwest Comparative Effectiveness Public Advisory Council (CEPAC)
- Institute for Clinical and Economic Review (ICER)

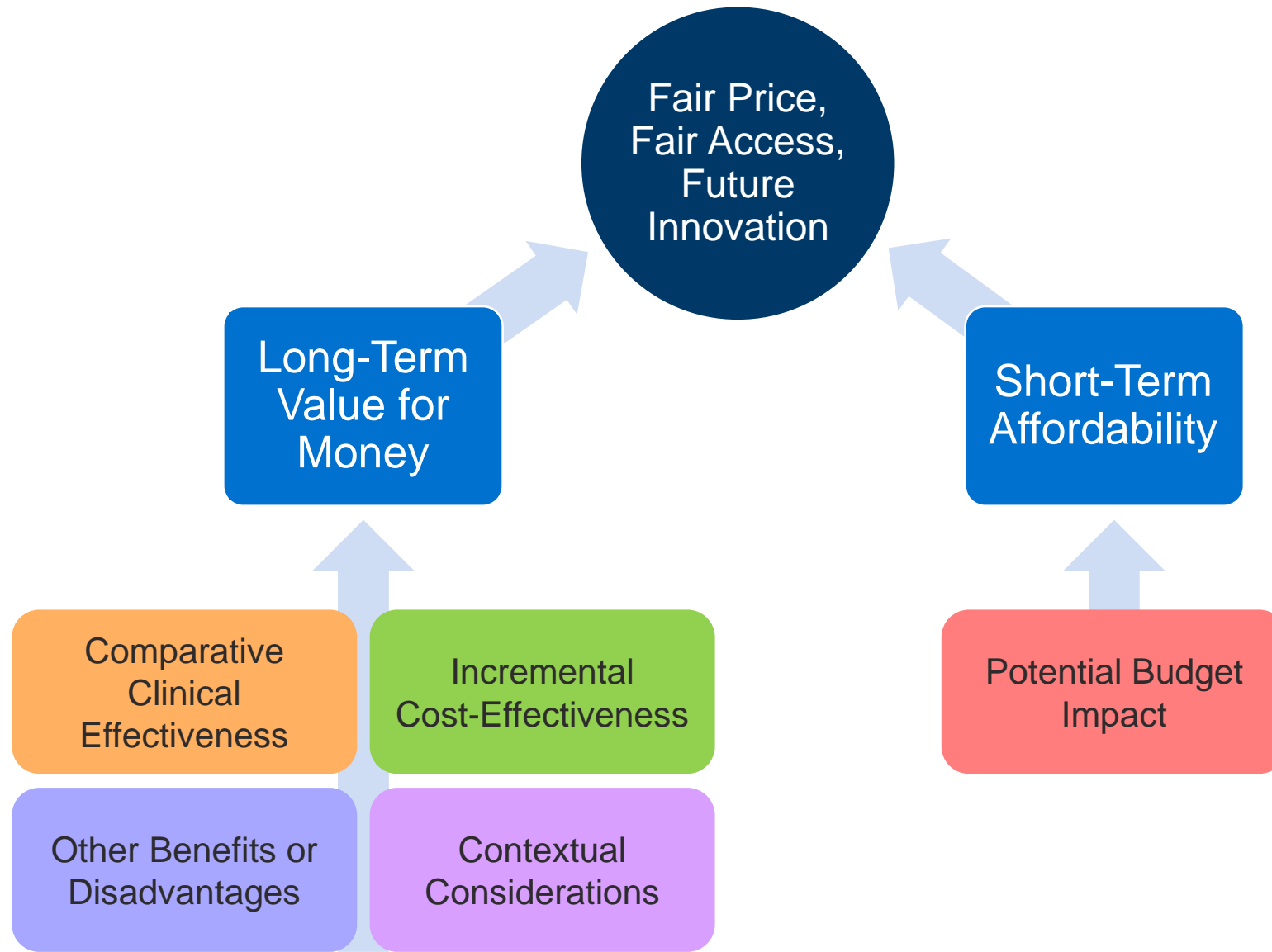
2019 Funding Sources



■ ICER Policy Summit and Non-Report activities only

How was the ICER Report Developed?

- Scoping with guidance from patient groups, clinical experts, manufacturers, and other stakeholders
- Internal ICER staff evidence analysis
- University of Colorado cost-effectiveness modeling
- Public comment and revision
- Expert reviewers
 - **Robert A. Harrington, MD**, Professor of Medicine, Stanford University
 - **Patrick T. O’Gara, MD**, Distinguished Chair in Cardiology, Brigham and Women’s Hospital; Professor of Medicine, Harvard Medical School
- How is the evidence report structured to support CEPAC voting and policy discussion?



Agenda

| | |
|-----------------|---|
| 10:00 am | Meeting Convened and Opening Remarks |
| 10:15 am | Presentation of the Evidence |
| 11:15 am | Manufacturer Public Comments and Discussion |
| 11:40 am | Public Comments and Discussion |
| 12:00 pm | Lunch |
| 1:00 pm | Midwest CEPAC Panel Vote |
| 2:00 pm | Break |
| 2:15 pm | Policy Roundtable Discussion |
| 3:30 pm | Reflections from Midwest CEPAC Panel |
| 4:00 pm | Meeting Adjourned |

Clinical Experts

Jeremy Sussman, MD, MS, Assistant Professor, University of Michigan Medical School

- *No conflicts of interest to disclose*

Jason Wasfy, MD, MPhil, Assistant Professor, Harvard Medical School; Director, Quality and Outcomes Research, Massachusetts General Hospital Heart Center; Medical Director, Massachusetts General Hospital Physician Organization

- *Received speaking fees (<\$5,000) for participation at the iHEAR conference sponsored by Biotronik*

Patient Experts

Andrea Baer, MS, MCPA, Executive Director, Mended Hearts

- *Mended Hearts has received more than \$5,000 in funding from both Janssen and AstraZeneca.*

Marie Warshauer, MS, Support Network Program Director, WomenHeart, The National Coalition for Women with Heart Disease

- *No conflicts of interest to disclose*

Evidence Review

David M. Rind, MD
Chief Medical Officer
ICER



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AND ECONOMIC REVIEW**

Key Collaborators

- **Daniel A. Ollendorf, PhD**, Evidence Author, Tufts Medical Center
- **Katherine Fazioli**, Research Lead, ICER
- **Serina Herron-Smith**, Research Assistant, ICER
- **Patty Synnott, MALD, MS**, Director, Evidence Review, ICER

Disclosures:

Dr. Ollendorf received funding from ICER for this evaluation and report. We have no other conflicts of interest relevant to this report.

Background

- Cardiovascular disease (CVD):
 - Coronary artery disease (CAD)
 - Peripheral artery disease (PAD)
 - Cerebrovascular disease
- Risks of angina, claudication, MI, stroke, etc.
- Affects one-half of all adults in the US

Impact on Patients

- Leading cause of death in US across all races and ethnicities:
 - ~850k deaths annually
- Potential for long-term disability and other complications of care following MI or stroke
- Significant financial burden:
 - ~\$350 billion in direct and indirect costs
 - Expected to exceed \$1 trillion by 2035

Standard of Care & Management

- Behavioral and lifestyle modification (e.g., diet, exercise, smoking cessation)
 - Control of hypertension and diabetes
 - Aspirin (ASA)
 - Statins
 - (Other newer medications aimed at CV risk)
-
- Despite these, many patients at high residual event risk

Scope of Review

Populations:

1. Adults with CVD currently receiving optimal medical management (anti-hypertensives, moderate/high-intensity statins, management of diabetes, and other comorbidities)
2. Adults without known CVD but at elevated risk due to age/comorbidity (Vascepa only)

Intervention: Rivaroxaban

- Anticoagulant (Factor Xa inhibitor)
- Initial indications for AF and VTE like other DOACs
- Indicated (in combination with ASA) to reduce risk of major adverse CV events (MACE) in CAD and/or PAD
- Compared to:
 - ASA alone
 - Dual antiplatelet therapy (DAPT) (ASA+oral P2Y₁₂ inhibitor such as clopidogrel or ticagrelor)

Intervention: Vascepa

- An ethyl ester of eicosapentaenoic acid (EPA)
- Current indication for reduction of triglyceride levels in patients with severe hypertriglyceridemia (≥ 500 mg/dL)
- FDA filing for MACE risk reduction
- Studied as addition to optimal medical management (including statins) in:
 - Patients with established CVD
 - Those without known CVD but age ≥ 50 , with diabetes +1 additional risk factor
 - Patients had triglycerides between 135 and 500 mg/dL and LDL-C between 40 and 100 mg/dL
- Compared to optimal medical management alone (placebo)

Outcomes

- Mortality (CV-related and all-cause)
 - Nonfatal MI and stroke
 - Unstable angina
 - Revascularization
 - CV hospitalization
 - Health-related quality of life
 - Major adverse limb events (MALE)
-
- *Harm of primary interest: major bleeding events*

Insights from Discussions with Patients & Clinicians

- Possible adherence challenges given high levels of comorbidity and polypharmacy in candidate patients
- Increased financial burden from additive therapy
- Need for better physician-patient communication regarding benefit-risk tradeoffs
- Cautious optimism from clinicians:
 - Balance of bleeding risks and clinical benefit
 - Inconsistent findings for other anticoagulant and omega-3 preparations

Clinical Evidence

Rivaroxaban: COMPASS Trial

| Group | Mean F/U | Mean Age | CAD / PAD | Prior MI / Stroke | Outcomes |
|---|-----------|----------|--|--|---|
| 1. Rivaroxaban 2.5 mg BID + ASA 100 mg QD (n=9,152) | 23 months | 68 years | <ul style="list-style-type: none"> CAD: 91% PAD: 27% | <ul style="list-style-type: none"> MI: 62% Stroke: 4%* | <ul style="list-style-type: none"> • <u>Composite</u>: CV death, stroke, MI • Individual events • Major bleeding |
| 2. Rivaroxaban 5 mg BID (n=9,117) | | | | | |
| 3. ASA 100 mg QD (n=9,126) | | | | | |

*Recent stroke was an exclusion criterion

Clinical Benefits: Rivaroxaban

- Composite event rate significantly lower with rivaroxaban+ASA vs. ASA alone:
 - 4.1% vs. 5.4% (HR 0.76, 95% CI 0.66 to 0.86)
- Consistent with reductions in CV mortality (HR 0.78) and all-cause mortality (HR 0.82)
- Reduction in stroke (HR 0.58) and ischemic stroke (HR 0.51)
- Stopped early for benefit with 23 months mean follow up

Other Benefits: Rivaroxaban

- EQ-5D collected in COMPASS, but no data currently available
- Clinical benefits consistent across subgroups of interest

Harms: Rivaroxaban

- Major bleeding* significantly increased with rivaroxaban+ASA:
 - (3.1% vs. 1.9% for ASA alone), HR 1.70, 95% CI 1.40 to 2.05
- No significant differences in fatal bleeding or symptomatic intracranial bleeding
- Analysis of “net clinical benefit” (CV death, MI, stroke, fatal bleeding, or symptomatic bleeding into critical organ) favored rivaroxaban+ASA:
 - HR 0.80; 95% CI: 0.70, 0.91; $p < 0.001$

*Modified definition that included acute care or inpatient intervention

NMA: Rivaroxaban+ASA vs. DAPT in recent MI

| | | | |
|--------------------------|--------------------------------------|--------------------------------------|------------|
| Rivaroxaban + ASA | | | |
| 0.91 (0.61 to 1.36) | Ticagrelor + ASA | | |
| 0.91 (0.58 to 1.40) | 1.00 (0.75 to 1.32) | Clopidogrel + ASA | |
| 0.70 (0.48 to 1.02) | 0.77 (0.66 to 0.90) | 0.77 (0.61 to 0.98) | ASA |

Each box represents the estimated hazard ratio and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in bold signify that the 95% credible interval does not contain one.

Controversies and Uncertainties: Rivaroxaban

- COMPASS entry criteria focused on patients at high event risk but excluded those with high bleeding risk
- Possible overstating of clinical benefit due to stopping early for benefit
- Multiple major bleeding events not reported (only most severe)
- Differences in bleeding definitions precluded full NMA comparing rivaroxaban+ASA to DAPT in patients with recent MI

Vascepa: REDUCE-IT Trial

| Group | Median F/U | Median Age | Secondary/ Primary Prevention | Mod/ High Intensity Statin Use | Outcomes |
|---|------------|------------|--|--------------------------------|--|
| <ul style="list-style-type: none"> Vascepa 2 g BID (n=4,089) Placebo* (n=4,090) | 4.9 years | 64 years | <ul style="list-style-type: none"> Secondary: 71% Primary: 29% | 93% | <ul style="list-style-type: none"> <u>Composite</u>: CV death, stroke, MI, revascularization, unstable angina Serious bleeding |

Clinical Benefits: Vascepa

- Composite event rate significantly lower with Vascepa vs. placebo:
 - 17.2% vs. 22.0% (HR 0.75, 95% CI 0.68 to 0.83)
- Similar for “hard” MACE (HR 0.74)
 - Primary prevention (HR 0.81, 95% CI 0.62 to 1.06)
 - Secondary prevention (HR 0.72, 95% CI 0.63 to 0.82)
- Consistent with reductions in CV mortality (HR 0.80), MI (HR 0.70), stroke (HR 0.71), and all cause mortality (0.87, 95% CI 0.74-1.02)

Triglycerides

| Subgroup | | Primary Composite CV Death, MI, Stroke, Revascularization, and Unstable Angina | Key Secondary Composite CV Death, MI, and Stroke |
|---------------|------------|---|---|
| | | HR (95% CI) | HR (95% CI) |
| Triglycerides | ≥150 mg/dL | 0.75 (0.68-0.83) | 0.74 (0.65-0.84) |
| | <150 mg/dL | 0.79 (0.57-1.09) | 0.66 (0.44-0.99) |
| | ≥200 mg/dL | 0.73 (0.64–0.83) | 0.75 (0.65–0.88) |
| | <200 mg/dL | 0.79 (0.67–0.93) | 0.71 (0.58–0.86) |

Harms: Vascepa

- Rate of serious bleeding disorders trended toward but was not statistically significantly higher with Vascepa
- Statistically higher rates of hospitalization for atrial fibrillation or flutter (3.1% vs. 2.1% for placebo, $p=0.004$) and AF generally (5.3% vs. 3.9%, $p=0.003$) with Vascepa

Controversies and Uncertainties: Vascepa

- Increases in LDL-C and hsCRP in placebo arm related to mineral oil?
 - *Post hoc* analysis showed persistent benefit when stratified by whether placebo patients saw increased LDL-C
 - Unclear why FDA scheduled advisory committee and delayed approval decision
- Challenges with total event analysis when events correlated
- Impressive results of REDUCE-IT vs. mostly negative findings from prior omega-3 trials
- Entry criteria for REDUCE-IT required elevated TGs
- Questions regarding Vascepa performance without optimized statin therapy

Potential Other Benefits or Disadvantages

- Most candidate patients are already taking multiple classes of medication, so these agents potentially increase complexity of CVD management
- Vascepa may complement other commonly-prescribed therapies for CVD that have different mechanism of action

Contextual Considerations

- Both drugs studied in high-risk populations, which suggests significant unmet need
- CVD is both prevalent and associated with a high lifetime burden of illness
- The early termination of the COMPASS trial introduces uncertainty regarding the long-term safety and benefits of rivaroxaban

Public Comments Received

- Total event vs. time-to-event findings
- Appropriateness of comparisons of rivaroxaban to DAPT
- Implied comparisons of rivaroxaban to Vascepa

Summary

- Available Phase III trial evidence for both rivaroxaban+ASA and Vascepa indicate significant reductions in the risk of major CV events in high-risk populations vs. standard treatments
- Residual uncertainties regarding true clinical benefit:
 - Early trial termination (rivaroxaban)
 - Prior negative studies of fish oil (Vascepa)
 - Biomarker changes in placebo arm (Vascepa)
- Full comparison of rivaroxaban+ASA to DAPT not feasible due to differences in bleeding definitions

ICER Evidence Ratings

- Rivaroxaban+ASA vs. ASA alone: B+
- Rivaroxaban+ASA vs. DAPT: I

- Vascepa vs. optimal medical management: B+

Questions?

Cost-Effectiveness

R. Brett McQueen, PhD, Assistant Professor

Department of Clinical Pharmacy

Center for Pharmaceutical Outcomes Research (CePOR)

Skaggs School of Pharmacy and Pharmaceutical Sciences

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University of Colorado Contributors

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- Taryn Quinlan, MS

Disclosures:

Financial support was provided to the University of Colorado from the Institute for Clinical and Economic Review.

University of Colorado researchers have no conflicts to disclose defined as more than \$10,000 in health care company stock or more than \$5,000 in honoraria or consultancies relevant to this report during the previous year from health care technology manufacturers or insurers.

Objective

Estimate the cost-effectiveness of rivaroxaban (Xarelto®, Janssen) and icosapent ethyl (Vascepa®, Amarin Pharma) as additive therapies to optimal medical management in patients with established CVD.

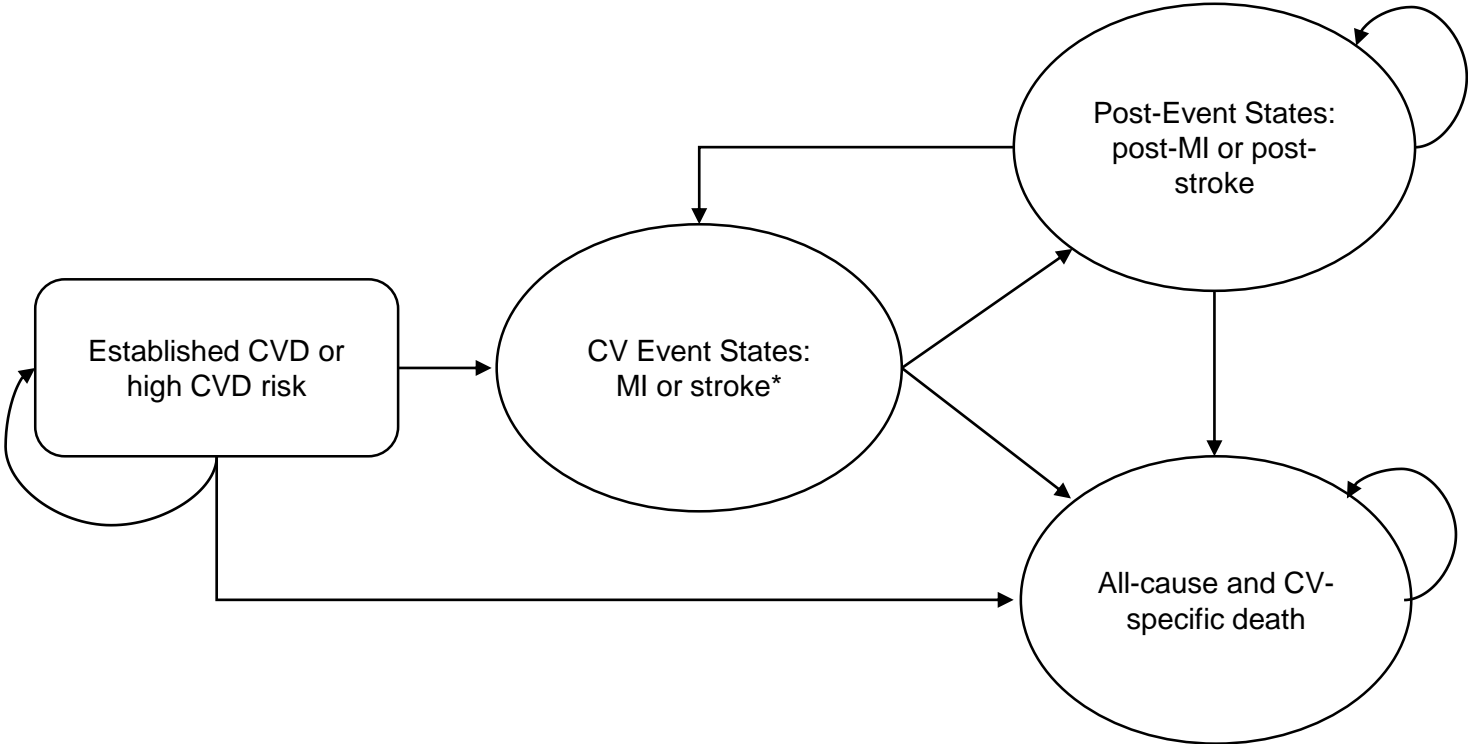
- In the case of Vascepa, we included patients without evidence of CVD but with diabetes and at least one additional risk factor.

Methods in Brief

Methods Overview

- **Model:** Markov
- **Setting:** United States
- **Perspective:** Health care sector (direct medical care and drug costs)
- **Time Horizon:** Lifetime
- **Discount Rate:** 3% per year (costs and outcomes)
- **Cycle Length:** 1 year
- **Outcomes:** Cost per quality-adjusted life year (QALY) gained; equal value of life years gained (evLYG); life year (LY) gained

Model Schematic



Other treatment-specific modeled events include major adverse limb events and other serious adverse events.
* Other CV events such as revascularization and unstable angina included in scenario analysis

Key Model Assumptions

1. Individual hazard ratios (HRs) for each subcomponent of composite endpoint.
2. Subsequent CV events (second, third and fourth events) have the same HR as the first event.
3. Patients may have more than one event in the same cycle.
 - Additive costs and disutilities for multiple events.

Clinical Inputs: Transition Probabilities

- Validated CV risk equations were used to estimate time-varying annualized event rates within the control arm.
- The control arm's risk of CV events was calibrated to be consistent with cumulative CV events observed in the trials.
- Treatment- and event-specific hazard ratios were used in the model's treatment arm in combination with CV risk equations.
 - See Evidence Summary and Report for specific hazard ratios

Discontinuation and Adverse Events

- Treatment discontinuation rates were based on trial-specific data for each comparison.
- All reported treatment-related serious adverse events (AEs) and bleeding events were assigned a cost and disutility.

Key Model Inputs: Treatment Costs

| Drug | WAC per Dose | Discount from WAC | Net Price per Dose | Net Price per Year |
|-----------------------------------|-------------------------|-------------------|--------------------|--------------------|
| Rivaroxaban (Xarelto®, Janssen) | \$7.47 per 2.5mg tablet | 59.41% | \$3.03 | \$2,215 |
| Vascepa (Vascepa®, Amarin Pharma) | \$2.53 per 1g capsule | 56.04% | \$1.11 | \$1,625 |

Wholesale acquisition cost (WAC) per Redbook®; net pricing estimates from SSR Health.

Key Model Inputs: Utilities

| Parameter | Value | Source |
|--|------------------|----------------------------------|
| Treated Population without Observed Events | 0.854* | Cohen, 2011; Stevanovic, 2016 |
| Post-Event MI (Disutility Applied to State) | -0.150 | Sullivan, 2006 |
| Post-Event Stroke (Disutility Applied to State) | -0.204 | Sullivan, 2006 |
| Event Cycle MI (Disutilities Applied to Event) | -0.0409 + -0.150 | Sullivan, 2006 |
| Event Cycle Stroke (Disutilities Applied to Event) | -0.0524 + -0.204 | Sullivan, 2006 |
| Severe Atrial Fibrillation (Disutility Applied to Event) | -0.164 | Wynn, 2014 |
| Major Bleeding (Disutility Applied to Event) | -0.181 | Sullivan, 2006 |
| Acute Non-Fatal MALE (Disutility Applied to Event) | -0.220 | Zomer, 2018 |

MALE: major adverse limb event; MI: myocardial infarction

*Based on average utilities of coronary heart disease patients who had undergone coronary artery bypass grafting (CABG) and percutaneous coronary interventions (PCI) and later stabilized. (CABG=0.847, PCI=0.861)

Results

Rivaroxaban Long-Run Clinical Outcomes (Lifetime time horizon, undiscounted)

| Lifetime Events | | | |
|--|--------------|--------------------|---------------------|
| Event | Intervention | Medical Management | Absolute Difference |
| First Event MI | 20% | 21% | -1% |
| First Event Stroke | 10% | 14% | -4% |
| Death (CV) | 30% | 35% | -5% |
| Cumulative CV Events (MI, Stroke & CV Death) | 61% | 72% | -11% |

Vascepa Long-Run Clinical Outcomes (Lifetime time horizon, undiscounted)

| Lifetime Events | | | |
|--|--------------|--------------------|---------------------|
| Event | Intervention | Medical Management | Absolute Difference |
| First Event MI | 29% | 35% | -6% |
| First Event Stroke | 9% | 11% | -2% |
| Death (CV) | 38% | 46% | -8% |
| Cumulative CV Events (MI, Stroke & CV Death) | 81% | 98% | -17% |

Rivaroxaban Base-Case Discounted Results

| Base-Case Model Outputs | | | | | | |
|-------------------------|--------------------|------------------------|-------------|-------|--------|-------|
| | Intervention Costs | Non-Intervention Costs | Total Costs | LYs | evLYGs | QALYs |
| Rivaroxaban | \$17,000 | \$20,000 | \$38,000 | 10.86 | 9.07 | 9.06 |
| Medical Management | \$200* | \$24,000 | \$24,000 | 10.45 | 8.69 | 8.69 |

LY: life year; evLYG: equal value of life years gained; QALY: quality-adjusted life year.

*Aspirin

Vascepa Base-Case Discounted Results

| Base-Case Model Outputs | | | | | | |
|-------------------------|--------------------|------------------------|-------------|-------|--------|-------|
| | Intervention Costs | Non-Intervention Costs | Total Costs | LYs | evLYGs | QALYs |
| Vascepa | \$15,000 | \$25,000 | \$40,000 | 12.26 | 10.21 | 10.19 |
| Medical Management | \$800* | \$30,000 | \$31,000 | 11.73 | 9.69 | 9.69 |

LY: life year; evLYG: equal value of life years gained; QALY: quality-adjusted life year.

*Statins

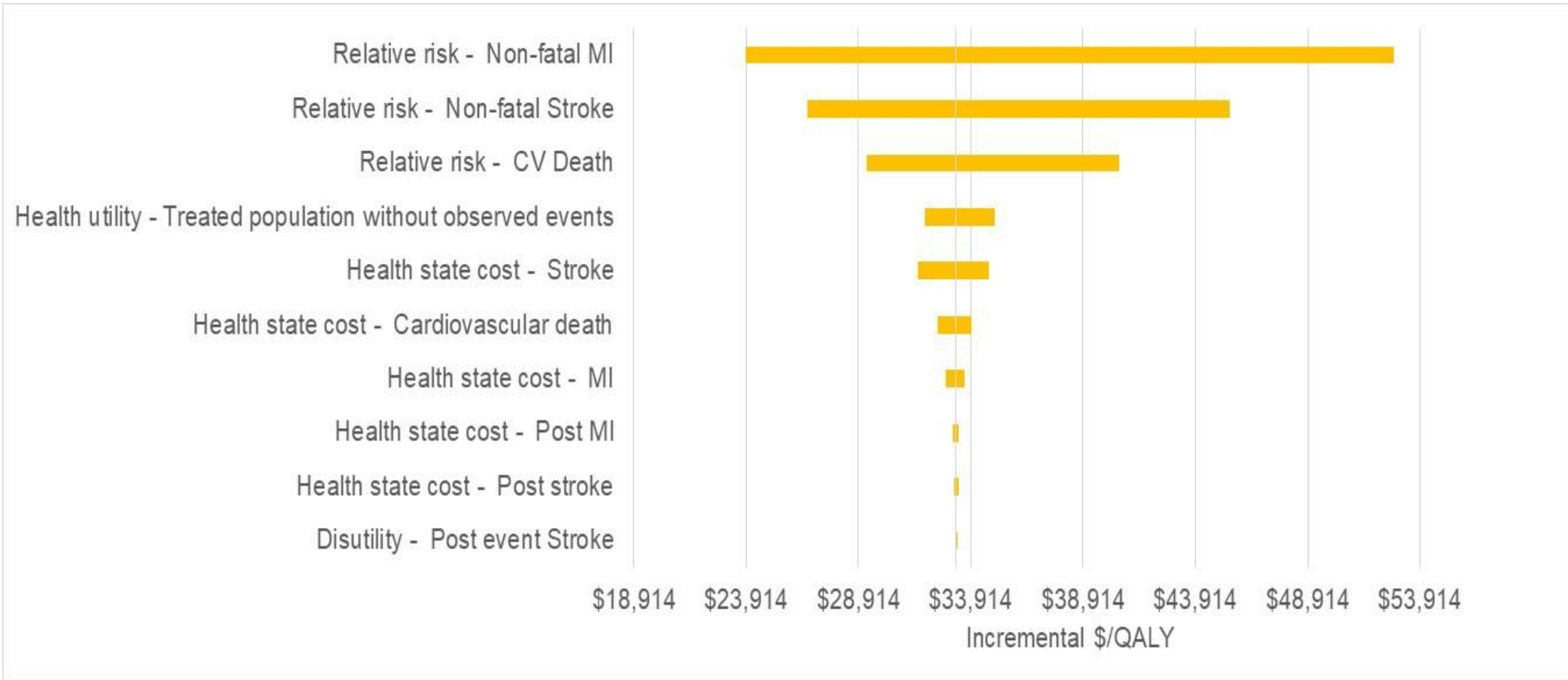
Base-Case Incremental Results

| Intervention* | Incremental Costs | Incremental LYs | Incremental evLYG | Incremental QALYs | Cost per LY | Cost per evLYG | Cost per QALY |
|------------------------------------|-------------------|-----------------|-------------------|-------------------|------------------------|---------------------------|--------------------------|
| Rivaroxaban vs. Medical Management | \$13,000 | 0.41 | 0.38 | 0.37 | \$32,000 per LY gained | \$35,000 per evLYG gained | \$36,000 per QALY gained |
| Vascepa vs. Medical Management | \$9,000 | 0.54 | 0.52 | 0.50 | \$17,000 per LY gained | \$17,000 per evLYG gained | \$18,000 per QALY gained |

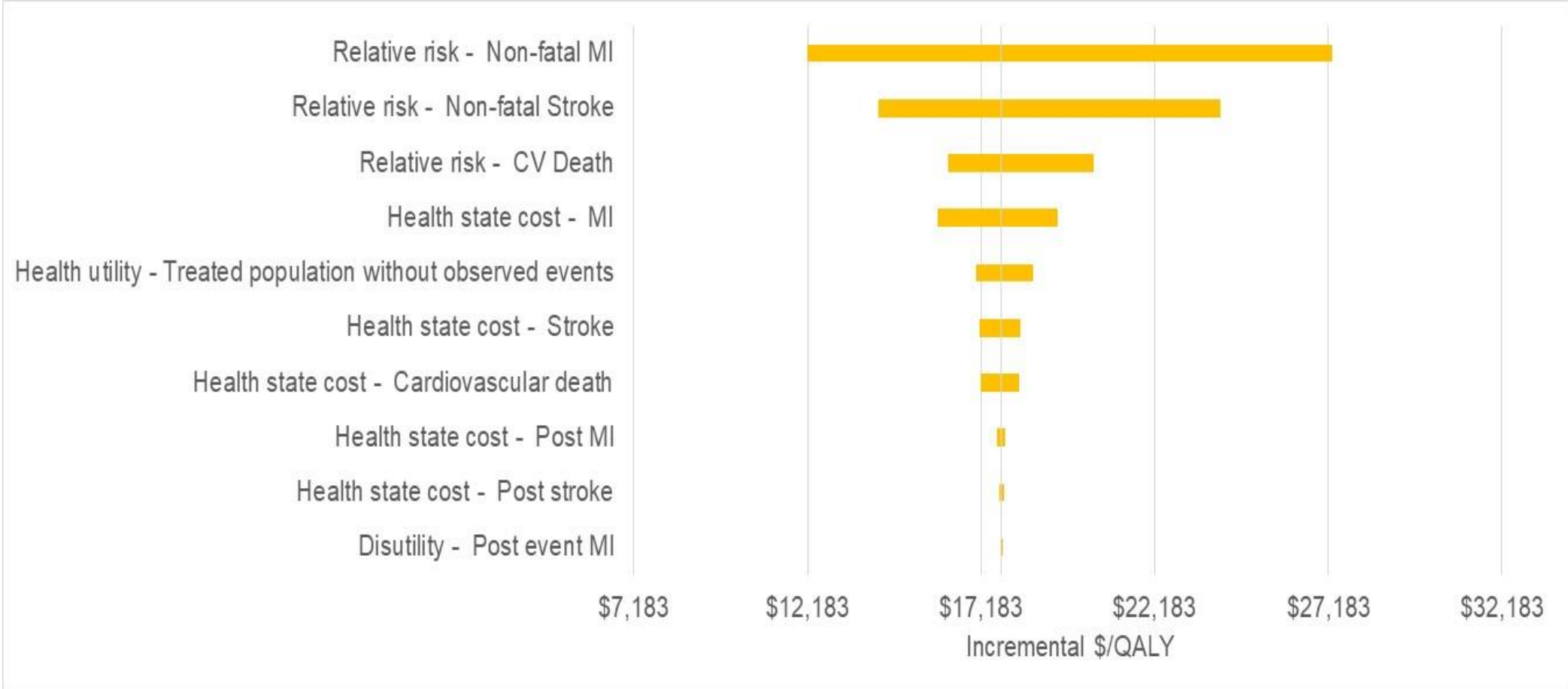
ICER: incremental cost-effectiveness ratio, LY: life year, QALY: quality adjusted life year, evLYG: equal value of life years gained,

*Modeled populations differed across interventions; results for the interventions are not directly comparable

One-Way Sensitivity Analyses: Rivaroxaban versus Medical Management



One-Way Sensitivity Analyses: Vascepa versus Medical Management



Probabilistic Sensitivity Analysis

| Comparison* | Cost-Effective at \$50,000 per QALY | Cost-Effective at \$100,000 per QALY | Cost-Effective at \$150,000 per QALY |
|------------------------------------|-------------------------------------|--------------------------------------|--------------------------------------|
| Rivaroxaban vs. Medical Management | 92% | 100% | 100% |
| Vascepa vs. Medical Management | 100% | 100% | 100% |

QALY: quality-adjusted life year

*Modeled populations differed across interventions; results for the interventions are not directly comparable.

Limitations

- Efficacy \neq Effectiveness
 - We assumed constant treatment benefits and long-run treatment duration that mirrors the trial evidence.
- History built within the model allowed for differentiation between first and subsequent events
 - Model did not differentiate across subsequent events (2nd vs. 3rd vs. 4th events), but all events were counted
- This analysis did not forecast future market disruptions or alternative interventions/comparators.

Comments Received

- Use of 3-point MACE versus 5-point MACE for Vascepa
- Concern over how subsequent MACE events were modeled
- Concern over heterogeneity within MACE events (i.e. stroke severity) and how this was modeled

Conclusions

- Rivaroxaban and Vascepa provide gains in quality-adjusted and overall survival over optimal medical management
- Costs for treatment with either rivaroxaban or Vascepa would fall below commonly cited thresholds for cost-effectiveness

Questions?

Efficacy Estimates for Rivaroxaban

| Parameter | Rivaroxaban + ASA n (%) | ASA Alone n (%) | HR (95% CI) | P-Value | Source |
|---|----------------------------|--------------------|------------------|---------|-----------------|
| Composite Primary Outcome: Stroke, CV Death, MI* | 379 (4.1) | 496 (5.4) | 0.76 (0.66-0.86) | <0.001 | Eikelboom, 2017 |
| Stroke† | 83 (0.9) | 142 (1.6) | 0.58 (0.44-0.76) | <0.001 | |
| CV Death† | 160 (1.7) | 203 (2.2) | 0.78 (0.64-0.96) | 0.02 | |
| MI† | 178 (1.9) | 205 (2.2) | 0.86 (0.70-1.05) | 0.14 | |
| MALE‡ | 30 (1) | 56 (2) | 0.54 (0.35-0.84) | 0.0054 | Anand, 2018 |

*Only *p*-values for the primary outcome are confirmatory.

†As the statistical analysis plan for the trial did not specify modifications to the pre-specified control of multiple testing of other efficacy outcomes in the case of early termination of the study, any HRs, corresponding CIs, and *P*-values reported for other efficacy outcomes cannot be interpreted as statistically significant.

‡MALE was defined as acute or chronic limb ischemia and included all major amputations. MALE was a pre-specified outcome for patients with PAD in the COMPASS trial.

Efficacy Estimates for Vascepa

| Parameter | Vascepa n (%) | Comparator/ Placebo n (%) | HR (95% CI) | P-Value | Source |
|--|------------------|---------------------------------|----------------------|---------|----------------|
| Composite Outcome: CV Death, Nonfatal Stroke, Nonfatal MI | 459 (11.2) | 606 (14.8) | 0.74 (0.65- 0.83) | <0.001 | Bhatt, 2019 |
| Secondary Prevention | 559 (19.3) | 738 (25.5) | 0.73 (0.65- 0.81) | | |
| Primary Prevention | 146 (12.2) | 163 (13.6) | 0.88 (0.70- 1.10) | | |
| Non-Fatal Stroke | 85 (2.1) | 118 (2.9) | 0.71 (0.54- 0.94) | 0.01 | |
| CV Death | 174 (4.3) | 213 (5.2) | 0.80 (0.66- 0.98) | 0.03 | |
| Non-Fatal MI | 237 (5.8) | 332 (8.1) | 0.70 (0.59- 0.82) | <0.001 | |
| Total Events (Primary Composite Endpoint) | 1076 | 1546 | 0.70 (0.62- 0.78) | <0.0001 | Bhatt, 2019 |

Key Model Inputs: Healthcare Utilization Costs

| Input | 2019 USD Mean Value* | Source |
|--|----------------------|--------------------------------------|
| MI Treatment and Event Year Cost | \$55,316 | Kazi, 2016 and supporting references |
| Stroke Treatment and Event Year Cost | \$58,932 | |
| Post-MI Annual Cost (Assumed the Same as Subsequent Years of Coronary Heart Disease) | \$2,728 | |
| Post-Stroke Annual Cost | \$5,742 | |
| CV Death Cost | \$18,341 | O'Sullivan, 2011 |
| Major Bleeding Cost (Applied to Event Year) | \$3,367 | Zomer, 2018 |
| Acute Non-Fatal MALE Cost (Cost Applied to Event) | \$17,979 | |
| Hospitalization for Atrial Fibrillation | \$9,957 | AHRQ, 2019 |

*Estimates varied in sensitivity analyses using the 2.5th and 97.5th percentiles of evidence-based probability distributions.

Manufacturer Public Comment and Discussion

Manufacturer Public Commenters

| Speaker | Title | Affiliation |
|-------------------------|---|-------------|
| Daniel Dadourian, MD | Senior Medical Director | Janssen |
| Alina Kolomeyer, PharmD | Associate Director, Corporate Alliances | Amarin |

Public Comment and Discussion

Andrea Baer, MS, BCPA

Executive Director, Mended Hearts

Conflicts of Interest:

- Mended Hearts has received more than \$5,000 in funding from both Janssen and AstraZeneca.

Taylor Kelly, JD

Law Clerk, DCBA Law & Policy LLP

Conflicts of Interest:

- Taylor Kelly is an employee of DCBA Law & Policy, a law firm whose practice is focused on corporate, drug and device, and health law. The majority of DCBA's clients are health care companies, health care professionals, biopharmaceutical companies, and not-for-profit organizations, and it consequently receives more than 25% of its funding from these organizations and individuals. Aimed Alliance is a client of DCBA.

Marie Warshauer, MS

Support Network Program Director, WomenHeart, The National Coalition for Women with Heart Disease

Conflicts of Interest:

- No conflicts of interest to disclose.

Lunch

Meeting will resume at 1:00 PM

Voting Questions

WIFI **Network: TritonNet**
Login ID: gst-icer
Password: TransformLives2019!

0. St. Louis consumes more _____ per capita than any city in the United States.

- A. Iced tea
- B. BBQ sauce
- C. 7-Up
- D. Donuts

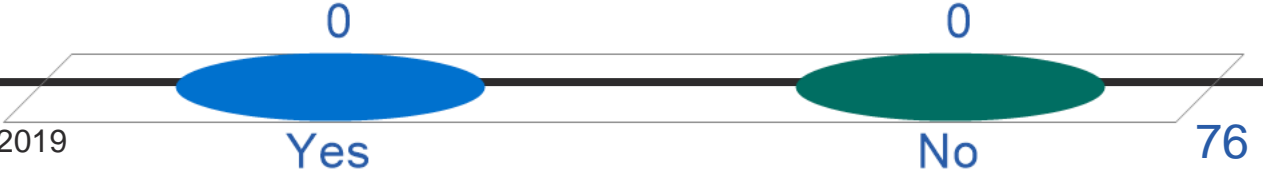


Patient population for all questions relating to:

- ***Rivaroxaban:*** Adults with established cardiovascular disease who are currently being treated with optimal medical management
- ***Vascepa:*** Adults with either established cardiovascular disease or at high risk for cardiovascular disease who are currently being treated with optimal medical management (including statins)

1. Is the evidence adequate to demonstrate that the net health benefit of rivaroxaban plus ASA is superior to that provided by ASA alone?

- A. Yes
- B. No



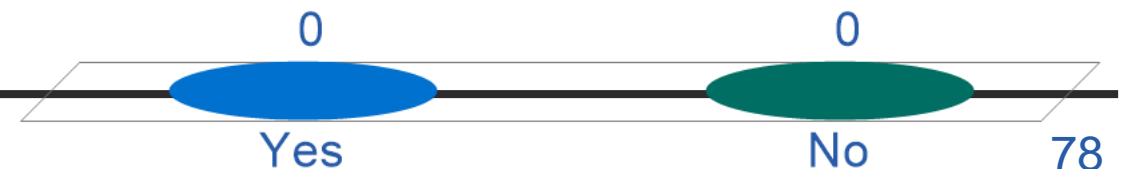
2. Is the evidence adequate to demonstrate that the net health benefit of rivaroxaban plus ASA is superior to that provided by ASA as part of dual antiplatelet therapy (DAPT) with an oral P2Y₁₂ inhibitor (e.g., ticagrelor or clopidogrel)?

- A. Yes
- B. No



3. Is the evidence adequate to demonstrate that the net health benefit of Vascepa added to optimal medical management (including statin therapy) is superior to that provided by optimal medical management (including statin therapy) alone?

- A. Yes
- B. No



4. Does treating patients with rivaroxaban plus ASA offer one or more of the following potential “other benefits or disadvantages” compared to ASA alone?

- A. This intervention will significantly reduce caregiver or broader family burden.
- B. This intervention offers a novel mechanism of action or approach that will allow successful treatment of many patients for whom other available treatments have failed.
- C. This intervention will have a significant impact on improving patients’ ability to return to work and/or their overall productivity.
- D. There are other important benefits or disadvantages that should have an important role in judgments of the value of this intervention.



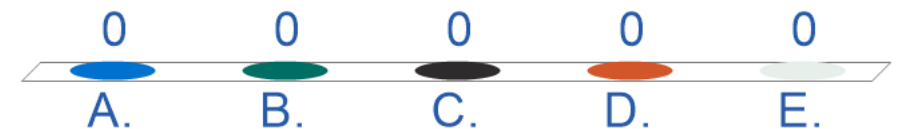
5. Does treating patients with Vascepa offer one or more of the following potential “other benefits or disadvantages” compared to optimal medical management (including statin therapy) alone?

- A. This intervention will significantly reduce caregiver or broader family burden.
- B. This intervention offers a novel mechanism of action or approach that will allow successful treatment of many patients for whom other available treatments have failed.
- C. This intervention will have a significant impact on improving patients’ ability to return to work and/or their overall productivity.
- D. There are other important benefits or disadvantages that should have an important role in judgments of the value of this intervention.



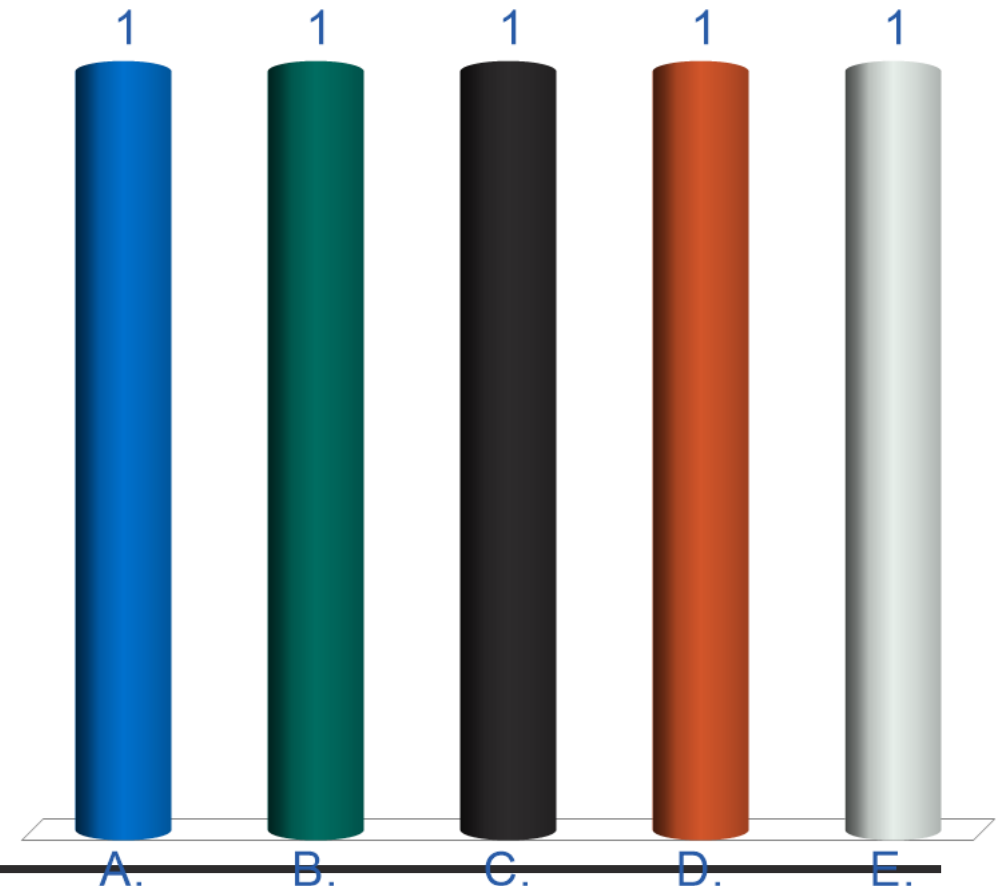
6. Are any of the following contextual considerations important in assessing the long-term value for money for rivaroxaban plus ASA?

- A. This intervention is intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life.
- B. This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.
- C. There is significant uncertainty about the long-term risk of serious side effects of this intervention.
- D. There is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention.
- E. There are additional contextual considerations that should have an important role in judgments of the value of this intervention.



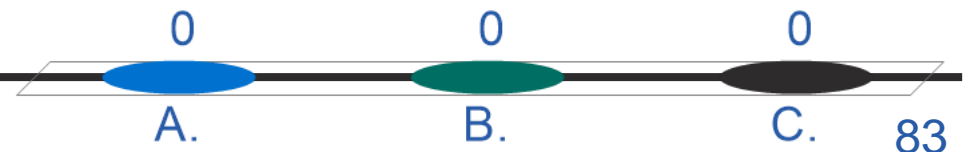
7. Are any of the following contextual considerations important in assessing the long-term value for money of Vascepa?

- A. This intervention is intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life.
- B. This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.
- C. There is significant uncertainty about the long-term risk of serious side effects of this intervention.
- D. There is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention.
- E. There are additional contextual considerations that should have an important role in judgments of the value of this intervention.



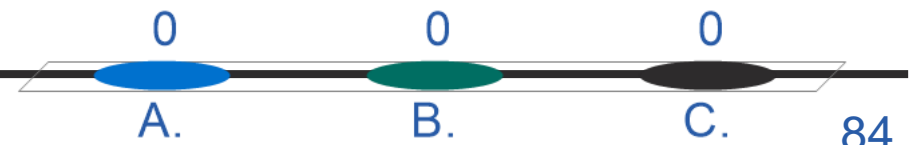
8. Given the available evidence on comparative effectiveness and incremental cost-effectiveness, and considering other benefits, disadvantages, and contextual considerations, what is the long-term value for money of treatment with rivaroxaban plus ASA versus ASA alone?

- A. Low long-term value for money at current pricing
- B. Intermediate long-term value for money at current pricing
- C. High long-term value for money at current pricing



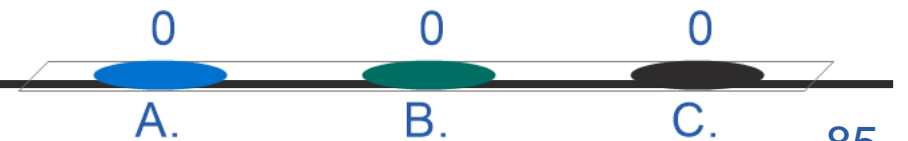
9. Given the available evidence on comparative effectiveness and incremental cost-effectiveness, and considering other benefits, disadvantages, and contextual considerations, what is the long-term value for money of treatment with rivaroxaban plus ASA versus ASA as part of DAPT with clopidogrel?

- A. Low long-term value for money at current pricing
- B. Intermediate long-term value for money at current pricing
- C. High long-term value for money at current pricing



10. Given the available evidence on comparative effectiveness and incremental cost-effectiveness, and considering other benefits, disadvantages, and contextual considerations, what is the long-term value for money of treatment with Vascepa in addition to optimal medical management (including statin therapy) versus optimal medical management (including statin therapy) alone?

- A. Low long-term value for money at current pricing
- B. Intermediate long-term value for money at current pricing
- C. High long-term value for money at current pricing



Break

Meeting will resume at 2:15 PM

Policy Roundtable

Policy Roundtable Participants

| Participant | Title and Affiliation | Conflict of Interest |
|---------------------------------------|--|---|
| Andrea Baer, MS, BCPA | Executive Director, Mended Hearts | Mended Hearts has received more than \$5,000 in funding from both Janssen and AstraZeneca. |
| Chester “Bernie” Good, MD, MPH | Senior Medical Director, UPMC Health Plan | Full-time employee of UPMC Health Plan. |
| Craig Granowitz, MD, PhD | Senior Vice President, Chief Medical Officer, Amarin Corporation | Full-time employee of Amarin. |
| Kayla Leeser, PharmD | Clinical Pharmacist, IngenioRx | Full-time employee of IngenioRx. |
| Jeremy Sussman, MD, MS | Assistant Professor, University of Michigan Medical School | No conflicts of interest to disclose. |
| Marie Warshauer, MS | Support Network Program Director, WomenHeart, The National Coalition for Women with Heart Disease | No conflicts of interest to disclose. |
| Jason Wasfy, MD, MPhil | Assistant Professor, Harvard Medical School; Director, Quality and Outcomes Research, Massachusetts General Hospital Heart Center; Medical Director, Massachusetts General Hospital Physician Organization | Received speaking fees (<\$5,000) for participation at the iHEAR conference sponsored by Biotronik. |

Midwest CEPAC Panel Reflections

Next Steps

- Meeting recording posted to ICER website next week
- Final Report published on or around October 17
 - Includes description of Midwest CEPAC votes, deliberation, policy roundtable discussion
- Materials available at:

<https://icer-review.org/topic/cardiovascular-disease/>

Adjourn

References