Bempedoic Acid and Inclisiran for Patients with Heterozygous Familial Hypercholesterolemia and for Secondary Prevention of ASCVD: Effectiveness and Value

Public Meeting — February 5, 2021

Meeting materials available at: https://icer.org/assessment/high-cholesterol-2021/

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Why are we here today?

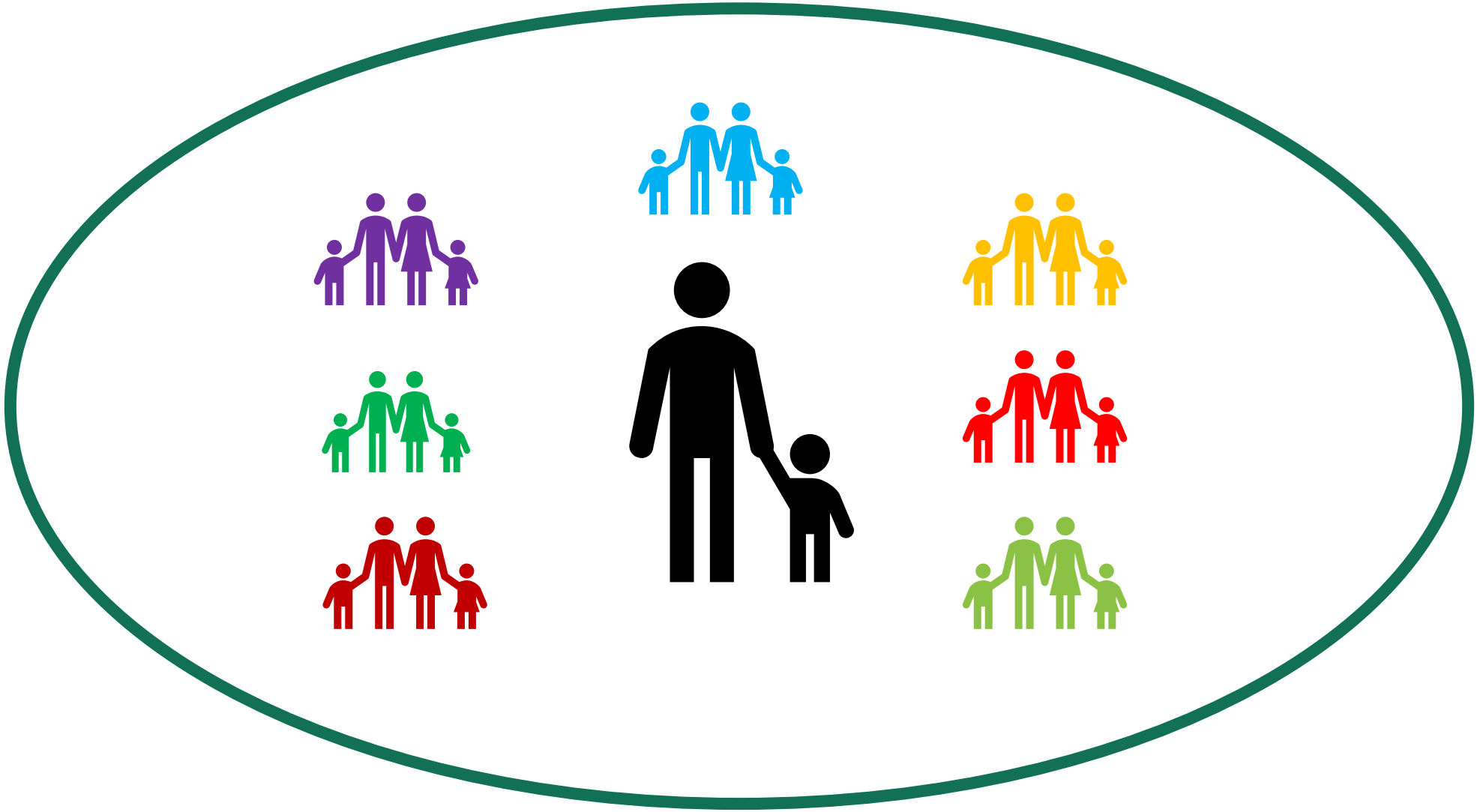
“I have not had any cardiovascular events so far … but I do worry every day that I didn't do enough, early enough in life to prevent heart disease. I almost lost my father at age 57 when he had sudden cardiac death in the middle of a tennis tournament … but we always expected that to happen - not if, but when.

Patient with HeFH

Why Are We Here Today?

- What happens the day these treatments are approved by the FDA?
- Patients can have difficulty accessing drugs
  - Coverage eligibility
  - Costs (out-of-pocket and insurance premiums)
- What happens to patients and others in the health care “system”?

When There Isn’t Enough Money For Health Insurance

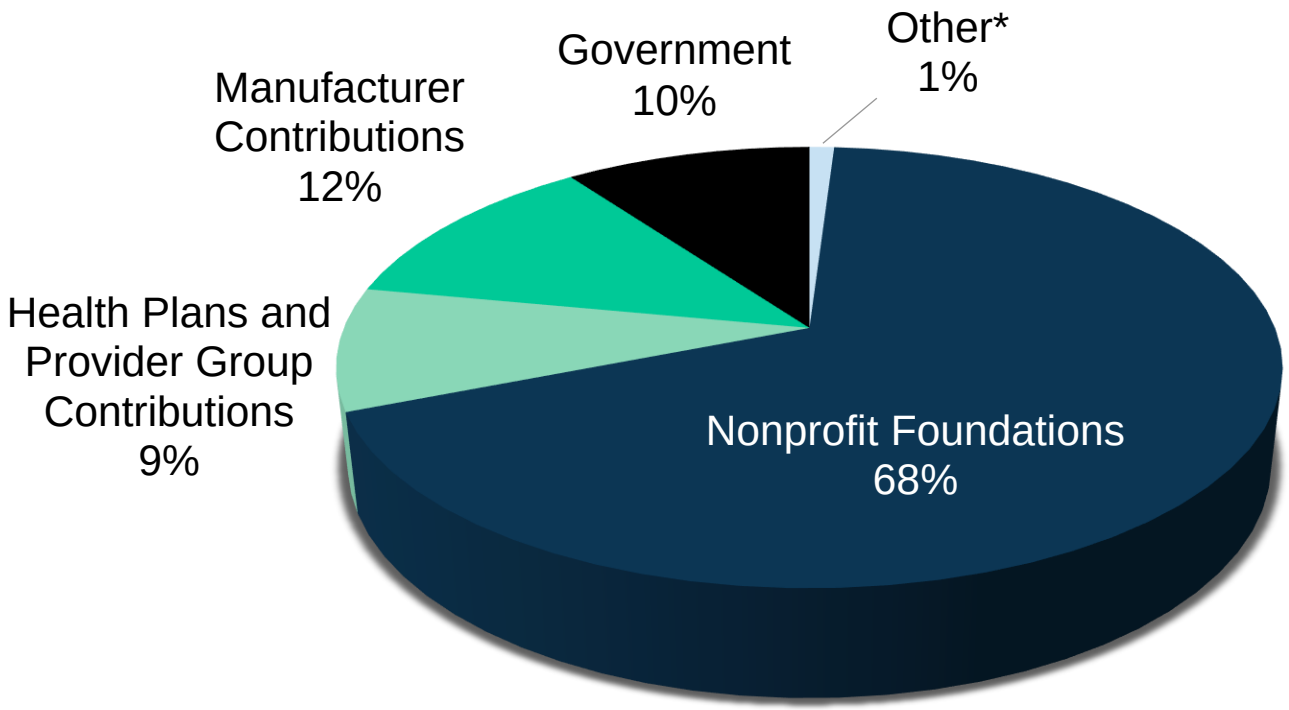


Organizational Overview

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

Sources of Funding, 2021

https://icer.org/who-we-are/independent-funding/



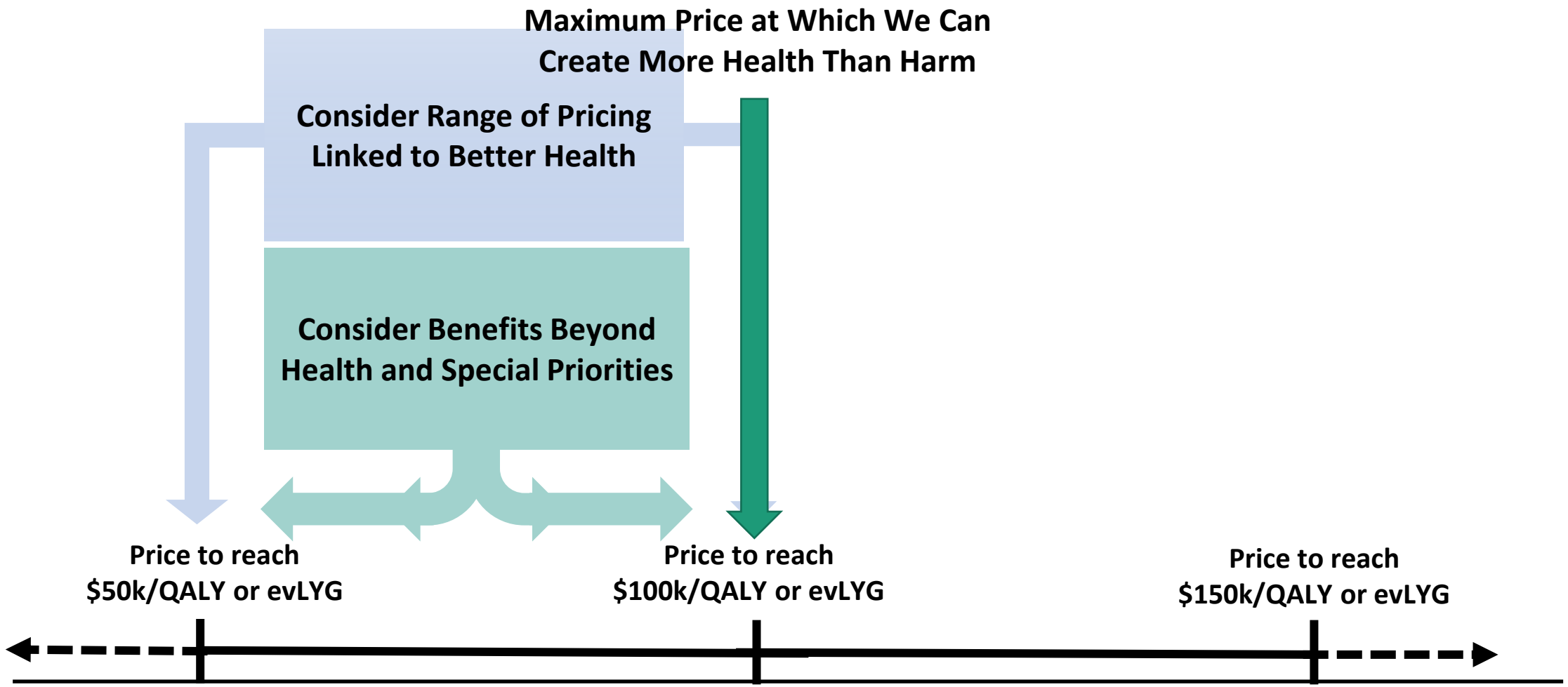
*Individual / matching contributions and speech stipends

How was the ICER report developed?

- Scoping with guidance from patient groups, clinical experts, manufacturers, and other stakeholders
- Internal ICER staff evidence analysis
- External cost-effectiveness modeling
- Public comment and revision
- Expert reviewers
  - Cat Davis Ahmed, MBA, Vice President of Policy and Outreach, FH Foundation
  - Keith C. Ferdinand, MD, Gerald S. Berenson Endowed Chair in Preventive Cardiology and Professor of Medicine, Tulane University School of Medicine
  - Salim S. Virani, MD, PhD, Professor in Cardiology and Cardiovascular Research Sections, Baylor College of Medicine
- How is the evidence report structured to support CEPAC voting and policy discussion?

Components of Long-Term Value for Money

Integrating the Elements of Long-term Value for Money



Agenda

Time (CT)	Activity
10:00am – 10:20am	**Meeting Convened and Opening Remarks** Steven D. Pearson, MD, MSc
10:20am – 10:50am	**Presentation of the Clinical Evidence** Grace A. Lin, MD, MAS
10:50am – 11:20am	**Presentation of the Economic Model** Dhruv S. Kazi, MD, MSc, MS
11:20am – 12:00pm	**Public Comments and Discussion**
12:00pm – 12:45pm	**Lunch Break**
12:45pm – 2:00pm	**Midwest CEPAC Vote on Clinical Effectiveness and Value**
2:00pm – 2:15pm	**Break**
2:15pm – 3:30pm	**Policy Roundtable**
3:30pm – 4:00pm	**Reflections from Midwest CEPAC**
4:00pm	**Meeting Adjourned**

Presentation of the Clinical Evidence

Grace A. Lin, MD, MAS

Associate Professor of Medicine and Health Policy

University of California, San Francisco

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Key Collaborators

- Jane Jih, MD, MPH, Associate Professor, UCSF
- Foluso Agboola, MBBS, MPH, Vice President of Research, ICER
- Avery McKenna, BS, Research Assistant, Evidence Synthesis, ICER

Disclosures:

Grace Lin and Jane Jih receive funding support from ICER. We have no conflicts of interest relevant to this report

Atherosclerotic Cardiovascular Disease (ASCVD): A Common and Deadly Disease

- Includes coronary artery disease, stroke, peripheral vascular disease
- Most common cause of death in US
- High cholesterol is major risk factor
  - Familial hypercholesterolemia (FH) most common associated genetic disease, results in premature ASCVD and high risk of cardiovascular events
- Black men and women are disproportionately affected compared with White counterparts

Management of High Cholesterol for HeFH and Secondary Prevention of ASCVD

- Guidelines recommend treatment with high-intensity statin to lower LDL-C by at least 50%
  - If LDL remains > 70 mg/dL, reasonable to add ezetimibe, then PCSK9 inhibitor
  - For HeFH patients, for primary prevention, add above medications at LDL > 100 mg/dL
  - European guidelines recommend LDL target of ≤ 55 mg/dL
- Statin-associated side effects (“statin intolerance”)
  - Adverse events (e.g., muscle aches, lab abnormalities) related to statin therapy that lead to lower dosage or discontinuation of statin
  - In clinical trials, often defined as inability to tolerate at least two different statins at moderate doses
  - Prevalence 5-20%

What We Learned From Patients

Awareness

- FH is underdiagnosed, undertreated
- Women have missed, delayed diagnosis

Access and Affordability

- Prior authorization/step therapy make access difficult
- Potentially high out-of-pocket costs

Health Equity

- Racial/ethnic minorities bear disproportionate burden of ASCVD
- Disparities in treatment
- Clinical trials not diverse (gender, race/ethnicity)

Scope of Review: Two New Drugs

- Clinical and cost effectiveness of adding bempedoic acid with or without ezetimibe (Nexletol®, Nexlizet™) or inclisiran (Leqvio®) to maximally tolerated oral lipid-lowering therapy for lowering cholesterol
- Patient populations: HeFH and established ASCVD
  - Patients with HeFH with and without ASCVD
  - Patients with established ASCVD at higher risk (e.g., recent MI)
  - Patients with statin intolerance
- Comparator: maximally tolerated oral lipid-lowering therapy (placebo arms in trials)

Clinical Evidence: Bempedoic Acid

Bempedoic Acid: Mechanism of Action

- Bempedoic acid with or without ezetimibe
  - Reduces cholesterol synthesis and upregulates LDL receptors through novel mechanism
  - Acts upstream of HMG-CoA reductase (statin pathway)
  - Once daily oral therapy
  - Approved by FDA in February 2020

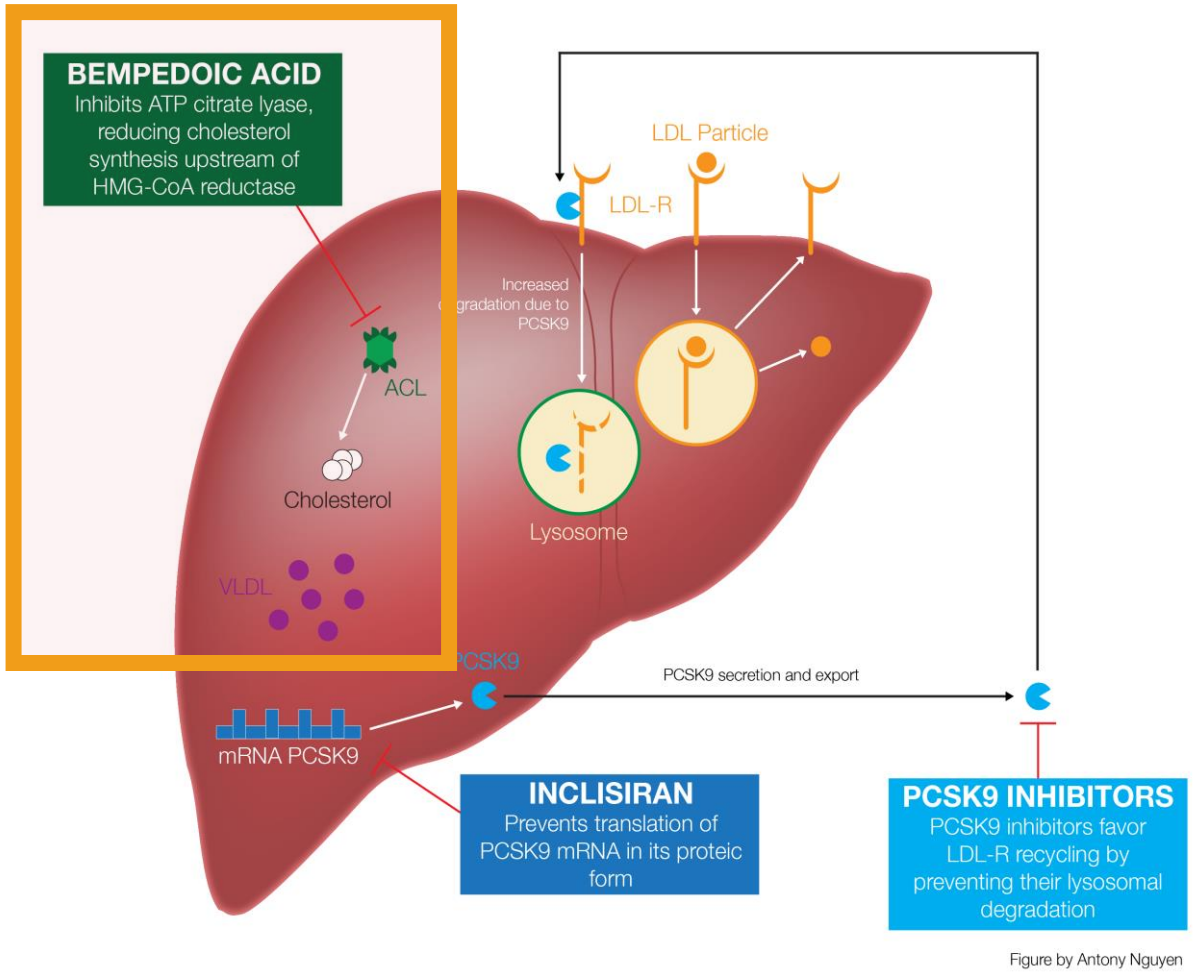


Figure by Antony Nguyen

Bempedoic Acid: Key Clinical Trials

- CLEAR Wisdom (n=779) & CLEAR Harmony (n=2230)
  - Bempedoic acid vs. placebo
  - Population: Established ASCVD (95-97%) and HeFH (3-5%); baseline LDL-C 103-120 mg/dL
- CLEAR Serenity (n=345) & CLEAR Tranquility (n=269)
  - Bempedoic acid vs. placebo
  - Population: Statin intolerant patients (established ASCVD 25-37%, few HeFH); baseline LDL-C 127-157 mg/dL
- Ballantyne 2020 (n=301)
  - 4 arm study of (1) bempedoic acid/ezetimibe; (2) bempedoic acid; (3) ezetimibe; (4) placebo
  - Population: ASCVD and/or HeFH (62%), statin intolerance (35%); baseline LDL-C 150 mg/dL

Bempedoic Acid: Trial & Meta-Analysis Results

Trials	Percent Reduction in LDL-C from Baseline to Week 12 Between-Arm Difference
Bempedoic Acid vs. Placebo	
CLEAR Wisdom	-17.4 (-21.0, -13.9)
CLEAR Harmony	-18.1 (-20.0, -16.1)
Ballantyne 2020*	-19.0 (-27.8, -10.2)
CLEAR Serenity	-21.4 (-25.1, -17.7)
CLEAR Tranquility	-28.5 (-34.4, -22.5)
Bempedoic Acid/Ezetimibe Combination Pill vs. Ezetimibe	
Ballantyne 2020*	-13.0 (-19.7, -6.5)
Summary Estimate: Random Effect Meta-Analysis BA vs. Placebo	-19.5 (-22.7, -16.4); p<0.0001; I^2 =69%

*Ballantyne 2020 was 4 arm trial so presented as comparisons: 1) BA vs. PBO and 2) BA/EZE vs. EZE

Bempedoic Acid: Subpopulations

HeFH (primary & secondary prevention)	• 1-5% of population in trials • Possible greater LDL-C lowering in HeFH population (p=NS)
High-risk established ASCVD	• Excluded from trials
Statin intolerance	• Greater decrease in LDL-C than overall population (24% vs. 17%, p<0.0001)

Bempedoic Acid: Clinical Outcomes

Outcome	RR (95% CI)	No. of Events (%)	
		Bempedoic Acid (N=2009)	Placebo (N=999)
All-Cause Mortality	2.25 (0.76 - 6.67)	19 (1.0)	4 (0.4)
CV Mortality	1.52 (0.41 -5.70)	10 (0.5)	3 (0.3)
Non-Fatal Stroke	1.11 (0.34 -3.61)	9 (0.5)	4 (0.4)
Non-Fatal MI	0.54 (0.25 -1.15)	25 (1.2)	22 (2.2)
MACE*	0.79 (0.58 -1.07)	100 (5.0)	63 (6.3)

*MACE: pre-specified exploratory outcome including CV death, non-fatal MI, non-fatal stroke, coronary revascularization, hospitalization for unstable angina

Bempedoic Acid: Harms

- More adverse events (AEs) and discontinuation due to AEs in BA group vs. placebo
- Most AEs mild to moderate
  - Uric acid and gout:
    - 4x incidence of increased uric acid (2.1% vs. 0.5%, p<0.001)
    - 3x incidence of gout (1.4% vs. 0.4%, p=0.008), higher risk in patients with history of gout
  - Tendon rupture: 11 patients (0.5%) of patients in BA arm experienced tendon rupture compared vs. none in placebo group

Bempedoic Acid: Controversies and Uncertainties

- Data limited to short-term LDL-C lowering in selected populations, no outcomes data
- May offer greater LDL-C reduction in statin intolerant patients; clinical significance?
- Unclear how significant risk of gout and tendon rupture will be in real world

ICER Evidence Ratings for Bempedoic Acid

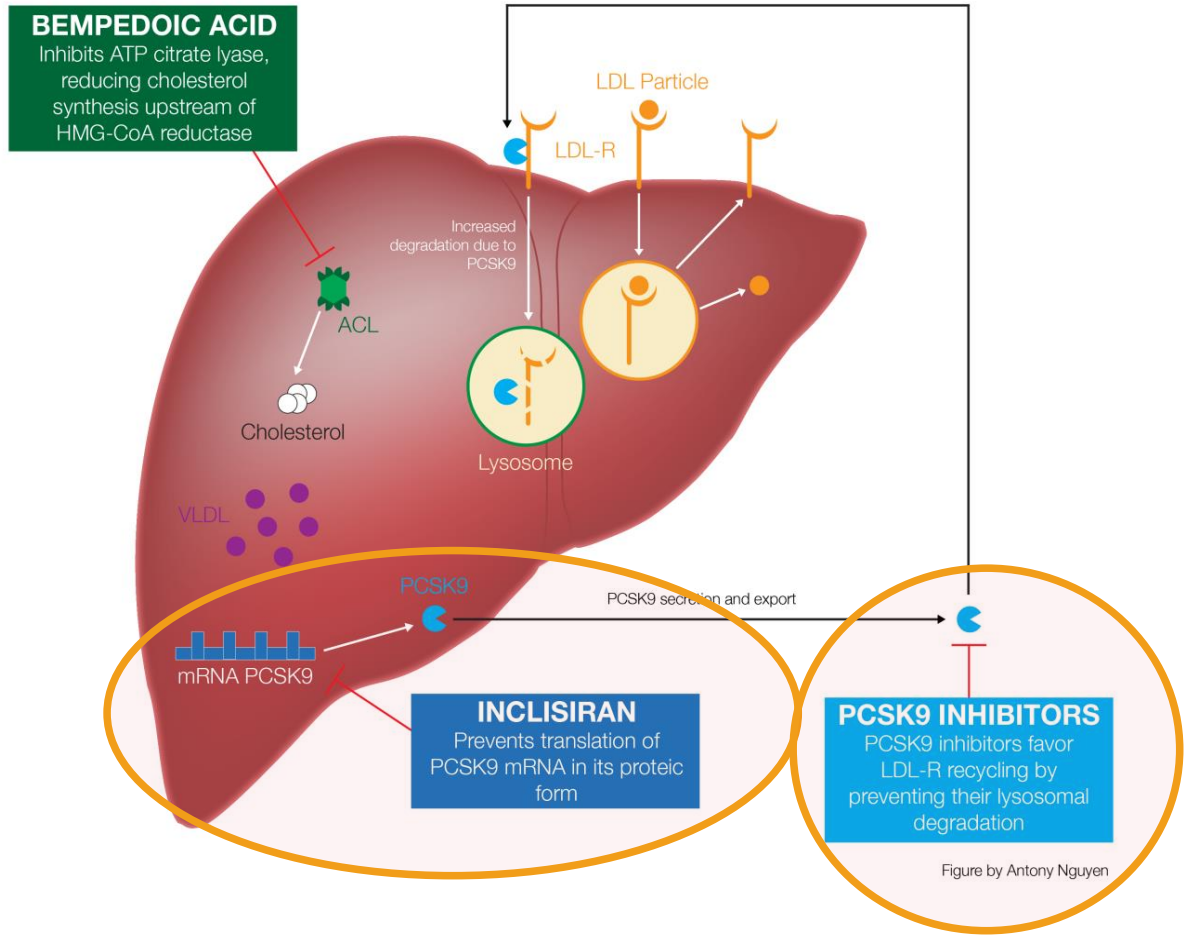
Moderate certainty of comparable or small net health benefit (C+)

- Moderate lowering of LDL-C in short-term, especially statin intolerant patients
- Longer term efficacy data on LDL-C and clinical outcomes are needed
- Limited data in HeFH population
- Risk of moderate to severe adverse events, clinical significance unknown

Clinical Evidence: Inclisiran

Mechanism of Action: Inclisiran

- Inclisiran
  - Small interfering RNA agent inhibiting hepatic PCSK9 synthesis → less LDL receptor degradation → more clearance of LDL
  - Twice yearly subcutaneous injection
  - FDA approval delayed by COVID



Inclisiran: Key Clinical Trials

- ORION 9 (n=482)
  - HeFH with LDL-C ≥ 100 on maximally tolerated statin therapy ± ezetimibe
  - 27% established ASCVD, 10% statin intolerance, baseline LDL-C 153 mg/dL
- ORION 10 (n=1561)
  - Established ASCVD with LDL-C ≥ 70
  - 10% statin intolerance, baseline LDL-C 105 mg/dL
- ORION 11 (n=1617)
  - Established ASCVD or ASCVD risk equivalent with LDL-C ≥ 70 mg/dL
  - 87% established ASCVD, 5% statin intolerance, baseline LDL-C 106 mg/dL

Inclisiran: Trial & Meta-analysis Results

Trials (Population Enrolled)	Percent Reduction in LDL-C from Baseline to Day 510 Between-Arm Difference (95% CI)
ORION 9 (HeFH)	-47.9 (-53.5, -42.3)
ORION 10 (ASCVD)	-52.3 (-55.7, -48.8)
ORION 11 (ASCVD + ASCVD risk equivalent)	-49.9 (-53.1, -46.6)
Summary Estimate: Random Effect Meta-Analysis of Inclisiran vs. Placebo	-50.5 (-55.5, -45.5); p<0.001; I^2=0.00

Inclisiran: Subpopulations

HeFH (primary & secondary prevention)	• ORION-9 trials were HeFH only • Similar LDL-C lowering (48%) to overall population
High-risk established ASCVD	• Excluded from trials
Statin intolerance	• 8% of patients in trials • Similar LDL-C lowering (47%) to overall population

Inclisiran: Clinical Outcomes

Outcome	RR (95% CI)	No. of Events (%)	
		Inclisiran	Placebo
All-Cause Mortality	0.99 (0.59-1.69)	27 (1.4)	27 (1.4)
CV Mortality	1.09 (0.54-2.19)	17 (0.9)	15 (0.8)
Stroke	0.69 (0.12-4.17)	13 (0.7)	15 (0.8)
Fatal and Non-Fatal MI	0.87 (0.12-6.18)	33 (1.8)	41 (2.3)
CV Composite*	0.76 (0.60-0.96)	131 (7.1)	172 (9.4)

*CV composite: pre-specified outcome of CV mortality, cardiac arrest, non-fatal MI, or stroke

Inclisiran: Harms

- Few serious adverse events (AEs)
- Slightly higher discontinuation rate in inclisiran group
- Most common AE was injection site reaction (5.4% in inclisiran group vs. 0.8% in the placebo group)

Inclisiran: Controversies and Uncertainties

- LDL-C lowering substantial and similar to PCSK9 inhibitors
- No outcomes data; will MACE reduction be closer to statins or PCSK9 inhibitors?
- Trial populations are limited (few statin intolerant, lack of racial/ethnic diversity)

ICER Evidence Ratings for Inclisiran

Moderate certainty of at least small net health benefit (B+)

- Demonstrated substantial lowering of LDL-C
- More robust data on clinical outcomes needed; LDL-C lowering produces variable reduction in CV events
- Very few safety concerns
- Similar mechanism to PCSK9 inhibitors, which have demonstrated long-term efficacy and safety

Potential Other Benefits and Contextual Considerations

- Fewer cardiovascular events have greater impact on productivity in FH population
- Fewer cardiovascular events may reduce caregiving needs
- Combination bempedoic acid/ezetimibe may decrease pill burden; inclisiran extended interval dosing may impact adherence
- Availability of more effective therapies may impact health equity - women and minorities less likely to be treated or reach LDL goals

Public Comments Received

- Health inequities are a major concern for treatment of high cholesterol in ASCVD and HeFH patients
  - Disparities in access to care and treatment
  - Disparities in clinical trial representation
  - Patient, clinician, and structural factors (e.g., socioeconomic status, racism in the healthcare system) contribute to disparities
- FH is underdiagnosed & undertreated, and patients are a high-risk population with lifelong impact from their disease
- Real-world use of ezetimibe is low

Questions?

Effectiveness and Value

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Disclosures

Dr. Kazi received funding support for this work from ICER.

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 manufacturers or insurers.

Objective

To evaluate the cost effectiveness of bempedoic acid/ezetimibe and inclisiran compared with maximally tolerated statin plus ezetimibe for the secondary prevention of ASCVD (in the general population as well as among adults with HeFH)

Caveats

- Addition of each therapy to usual care compared with usual care alone
- No outcomes data available – translating LDL-C reduction into reduction in cardiovascular events
- Not making a case that step therapy with ezetimibe is right for every patient

Brief Methods

Methods Overview

- **Population:** Adults with established ASCVD
  - Established ASCD, statin intolerant
  - HeFH (regardless of statin tolerance)
  - Recent ACS
- **Interventions:** Bempedoic acid/ezetimibe, inclisiran
- **Comparators:** Maximally tolerated statin + ezetimibe
- **Outcomes:**
  - Major adverse cardiovascular events (MACE = ACS, stroke, or cardiovascular death)
  - Life years, quality-adjusted life years (QALYs)
  - Total costs
  - Incremental cost-effectiveness ratio (cost per MACE avoided, cost per life-year gained, cost per QALY gained, cost per equal value of life years gained)

Methods Overview

- **Time horizon**: Patient lifetime
- **Setting**: United States
- **Perspective**: Health care sector (direct medical care and drug costs); modified societal
- **Cycle length:** 1 year
- **Discount rate**: 3% per year (costs and outcomes)

Events

- Elective revascularization
- Acute coronary syndrome – medically managed or with urgent revascularization
- Stroke
- Death from cardiovascular causes
- Death from non-cardiovascular causes

Model Cohort Characteristics

- Starting age = 66 years
- Baseline LDL-C level on maximally tolerated statins and ezetimibe = 88.8 ± 1.2 mg/dL
- Statin intolerance = 10%

Exceptions:

Statin-intolerant individuals have a mean baseline LDL-C 127.1±1.7 mg/dL

HeFH individuals start at age 62 years, mean baseline LDL-C 139.2±6.0 mg/dL

Key Assumptions

- Clinical history determines baseline quality of life, costs, and risk of future events
- Patients with statin intolerance have a higher baseline LDL-C and are at increased risk of major adverse cardiovascular events than patients receiving statins
- Patients with HeFH and established ASCVD have 50% higher event rates than the general population with established ASCVD

Key Assumptions

- Real-world adoption will replicate the LDL-C reductions observed in randomized trials, and these reductions will be sustained over the patient's lifetime
- LDL-C reductions will translate into a reduction in MACE:
  - Base case: per statin trials
  - Sensitivity analysis for inclisiran: using data from evolocumab/ alirocumab trials
- Real-world adoption will replicate the rates of adverse outcomes seen in randomized trials
  - BA: Gout
  - Inclisiran: Injection-site reactions

Treatment-Related Efficacy

Strategy	LDL Cholesterol Reduction, %	Range for Sensitivity Analyses	Source, Comment
LDL Cholesterol Reduction, %			
Bempedoic acid,%	17.7% on statins 24.6% not on statins	16.1%-19.3% 17.6%-31.5%	Randomized trials of bempedoic acid compared with placebo, or the combination pill compared with ezetimibe
Inclisiran, %	50.5%	45.4%-55.5%	Randomized trials of inclisiran

Health State Utilities

Input Parameter	Base-Case Value	Range for Sensitivity Analyses
Chronic States		
History of angina	0.9064	(0.8710-0.9360)
History of MI	0.9648	(0.9513-0.9764)
History of stroke	0.8835	(0.8456-0.9133)
History of MI and stroke	0.8524	(0.8083-0.8987)
Transient QoL Tolls for Acute Events		
Acute MI	0.0079	(0.0051-0.0112)
Acute stroke	0.0113	(0.0084-0.0154)

Treatment Costs

Drug	WAC per Dose	Discount from WAC	Net Price per Dose	Net Price per Year
Bempedoic Acid/ Ezetimibe (Nexlizet™)	$11.00	29%	$7.82*	$2,856
Inclisiran	NA	NA	$2,822†	$5,644†

* Federal Supply Schedule (FSS) price as of September 1, 2020.
† Placeholder price per maintenance year estimated using average annual net cost of alirocumab and evolocumab (from FSS, September 1, 2020) and assuming 2 doses per year. Initial treatment year requires 3 doses.

Adverse Events

Parameter	Incidence, %	Disutility	Cost
Gout (Bempedoic Acid)	1.0	0.01 for 1 month (0.005-0.02)	$520 ($260-$1,040)
Injection-Site Reactions (Inclisiran)	4.3	0.0003 (0.0000-0.0020)	0

Results

Results

Over the first five years,

MACE rate in the control arm = 5.06 per 100 person-years

This included:

2.65 fatal and non-fatal ACS

0.87 fatal and non-fatal strokes, and

2.51 deaths from CV causes per 100 person-years

Results: Cost Effectiveness of Bempedoic Acid/Ezetimibe

	Statin + Ezetimibe	Statin + Bempedoic Acid/Ezetimibe
Health Care Outcomes		
Survival, life years		
Mean survival (undiscounted)	15.07	15.35
Mean survival (discounted)	11.48	11.66
Incremental survival	Comparator	**0.18**
Quality-adjusted survival, QALYs		
Mean QALYs	10.57	10.74
Incremental QALYs	Comparator	**0.17**
Direct Health Care Costs		
Lifetime Health Care Costs, 2020 USD	$185,000	$216,000
Spending on Lipid-Lowering Therapies	$4,000	$35,000
Spending on Cardiovascular Care	$106,000	$105,000
Background Health Care Costs	$75,000	$76,000
Incremental health care costs, 2020 USD	Comparator	**$31,000**
ICER, $ per MACE averted	Comparator	$535,000
ICER, $ per life-year gained	Comparator	$175,000
ICER, $ per QALY gained	Comparator	**$186,000**
ICER, $ per evLYG	Comparator	**$168,000**

Probabilistic Sensitivity Analysis

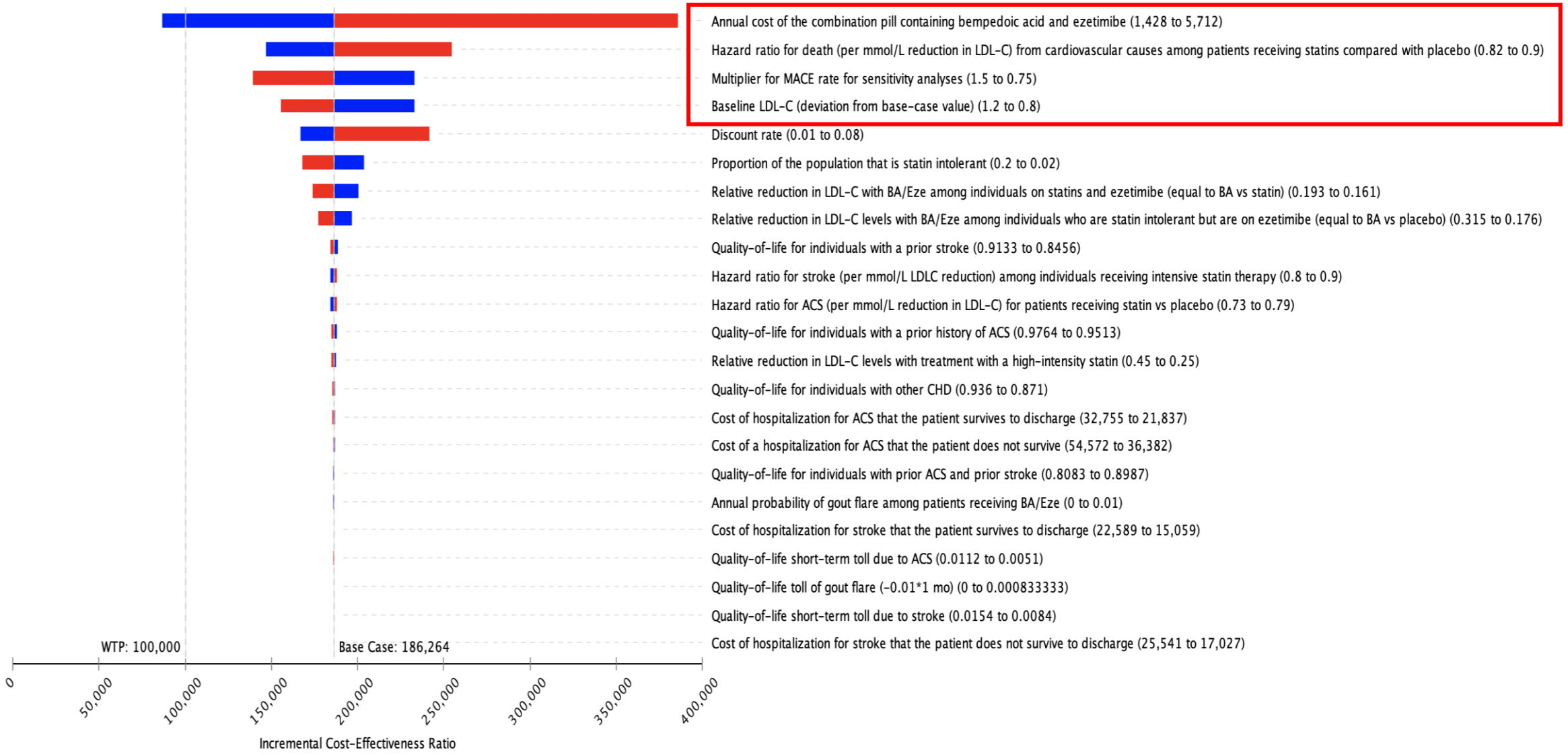
	Cost Effective at $50,000 per QALY	Cost Effective at $100,000 per QALY	Cost Effective at $150,000 per QALY	Cost Effective at $200,000 per QALY
Bempedoic Acid/ Ezetimibe	0%	0%	6.3%	64.8%

Subgroup Analyses

	Base Case (Established ASCVD)	HeFH (Established ASCVD)	Statin-Intolerant (Established ASCVD)	Recent ACS
MACE Rate,* per 100p-y	5.06	7.09	6.11	7.52
Incremental survival	0.18	0.33	0.34	0.18
Incremental QALYs	0.17	0.31	0.32	0.17
Incremental costs, USD	$31,000	$32,000	$30,000	$30,000
ICER, $ per QALY	$186,000	**$101,000**	**$92,000**	$176,000
ICER, $ per evLYG	$168,000	**$92,000**	**$83,000**	$161,000

* Estimated over the first 5 years of the model

Tornado Diagram – Bempedoic Acid+Ezetimibe vs. Control



Results: Cost Effectiveness of Inclisiran

	Statin + Ezetimibe	Inclisiran + Statin + Ezetimibe
Survival, life years		
Mean survival (undiscounted)	15.07	15.80
Mean survival (discounted)	11.48	11.94
Incremental survival	Comparator	**0.46**
Quality-adjusted survival, QALYs		
Mean QALYs	10.57	11.01
Incremental QALYs	Comparator	**0.44**
Direct Health Care Costs		
Lifetime Health Care Costs, 2020 USD	$185,000	$253,000
Spending on Lipid-Lowering Therapies	$4,000	$73,000
Spending on Cardiovascular Care	$106,000	$103,000
Background Health Care Costs	$75,000	$78,000
Incremental health care costs, 2020	Comparator	**$68,000**
ICER, $ per MACE averted	Comparator	$451,000
ICER, $ per life-year gained	Comparator	$147,000
ICER, $ per QALY gained	Comparator	**$157,000**
ICER, $ per evLYG	Comparator	**$142,000**

Probabilistic Sensitivity Analysis

	Cost Effective at $50,000 per QALY	Cost Effective at $100,000 per QALY	Cost Effective at $150,000 per QALY	Cost Effective at $200,000 per QALY
Inclisiran*	0%	0%	35.9%	90.3%

*At a placeholder price of $5,644 per year

Subgroup Analyses

	Base Case (Established ASCVD)	HeFH (Established ASCVD)	Statin-Intolerant (Established ASCVD)	Recent ACS
MACE Rate,* per 100p-y	5.06	7.09	6.11	7.52
Incremental survival	0.46	0.91	0.68	0.47
Incremental QALYs	0.44	0.85	0.64	0.45
Incremental costs, USD	$68,000	$71,000	$66,000	$67,000
ICER, $ per QALY	$157,000	**$84,000**	**$103,000**	$147,000
ICER, $ per evLYG	$142,000	**$76,000**	**$93,000**	$135,000

* Estimated over the first 5 years of the model

Scenario Analysis

Assuming effectiveness of inclisiran is similar to that observed in PCSK9i trials rather than statin trials:

	Base Case (Established ASCVD)	Scenario – Effectiveness ~ PCSK9i (Established ASCVD)
MACE Rate, per 100p-y	5.06	5.06
Incremental survival	0.46	0.12
Incremental QALYs	0.44	0.12
Incremental costs, USD	$68,000	$64,000
ICER, $ per QALY	$157,000	**$522,000**
ICER, $ per evLYG	$142,000	**$464,000**

*At a placeholder price of $5,644 per year

Limitations

- Lack of randomized, controlled clinical trials evaluating clinical outcomes
- Many statin-intolerant patients able to tolerate low-dose statin
- Other side effects of the drug may appear with longer follow-up
- Did not examine primary prevention populations, which typically have lower rates of MACE (HeFH may be an exception)

Public Comments

- Inclusion of ezetimibe in the comparator
- Uncertainty in quality-of-life inputs
- Effect of dosing regimen on long-term adherence
- Out-of-pocket costs may vary considerably

Conclusions

- Assuming that lipid lowering with these new agents has the same effect on outcomes as seen with statins:
  - Bempedoic acid/ezetimibe would not meet conventional cost-effectiveness thresholds at current FSS prices, except in individuals with statin intolerance
  - Inclisiran would meet cost-effectiveness thresholds at the placeholder price (current FSS price of PCSK9i) but not if its effectiveness is equivalent to that observed in PCSK9i trials
- More cost-effective in higher-risk subgroups
- Additional data on efficacy and effectiveness in reducing clinical outcomes, long-term adherence, and impact on quality-of-life are needed

Questions?

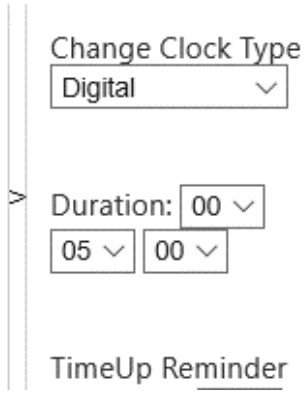
Manufacturer Public Comment and Discussion

Joaquim Cristino, MSc

US Head of Health Economics and Outcomes Research for Cardiovascular, Renal and Metabolism, Novartis Pharmaceuticals

Conflicts of Interest:

- *Joaquim Cristino is a full-time employee of Novartis.*

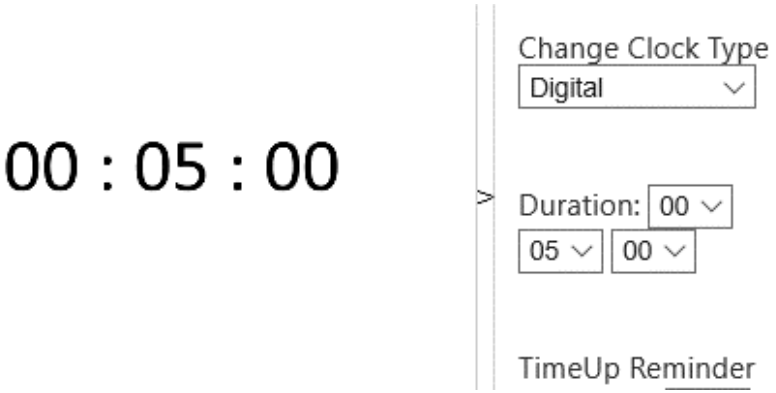


Michael Louie, MD, MPH, MSc

SVP of Clinical Development and Pharmacovigilance, Esperion Therapeutics

Conflicts of Interest:

- *Dr. Michael Louie is a full-time employee of Esperion.*

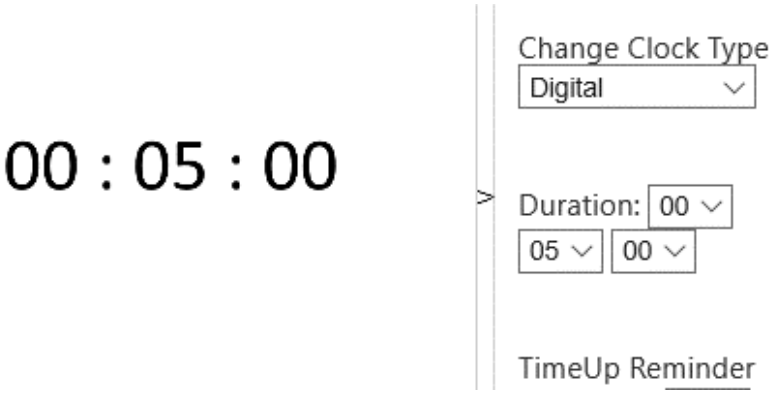


Public Comment and Discussion

Andrea Baer, MS, BCPA
Executive Director, The Mended Hearts, Inc.

Conflicts of Interest:

- *The Mended Hearts, Inc. receives > 25% of their funding from health care companies, including Novartis.*



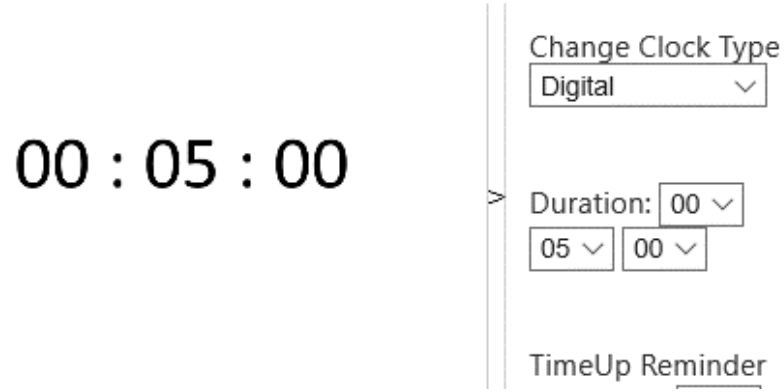
Seth Baum, MD, FACC, FAHA, FNLA, FASPC

Founder & CEO, Excel Medical Clinical Trials

Clinical Affiliate Professor of Cardiology, Florida Atlantic University

Conflicts of Interest:

- *Dr. Seth Baum has served as PI on numerous studies of bempedoic acid and inclisiran. He has served as a consultant and speaker for Esperion and as a consultant for Novartis.*

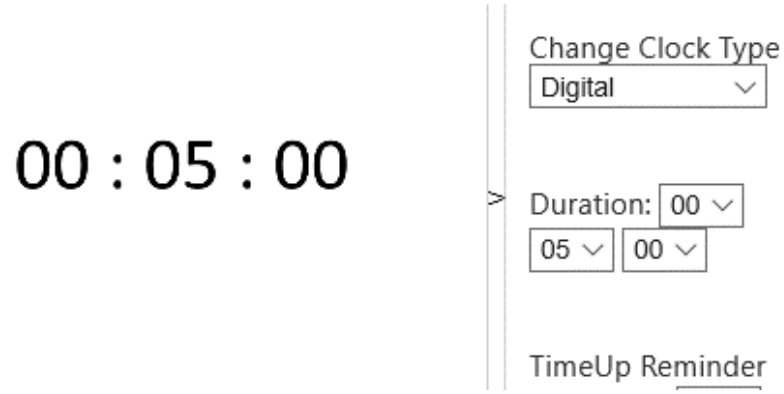


John Clymer

Executive Director, National Forum for Heart Disease & Stroke Prevention

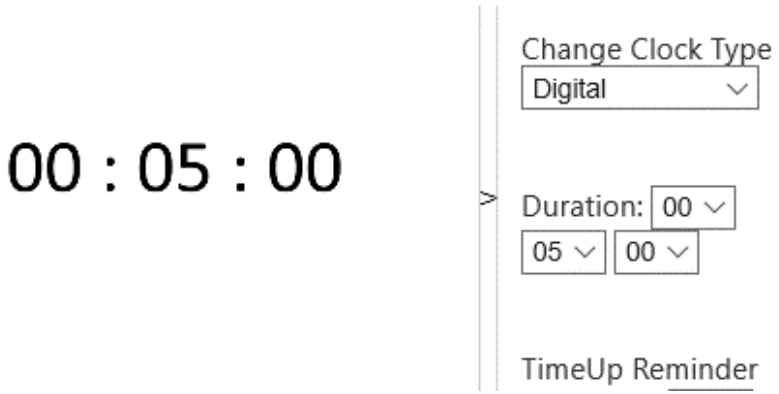
Conflicts of Interest:

- *National Forum for Heart Disease & Stroke Prevention receives >25% of its funding from health care companies*



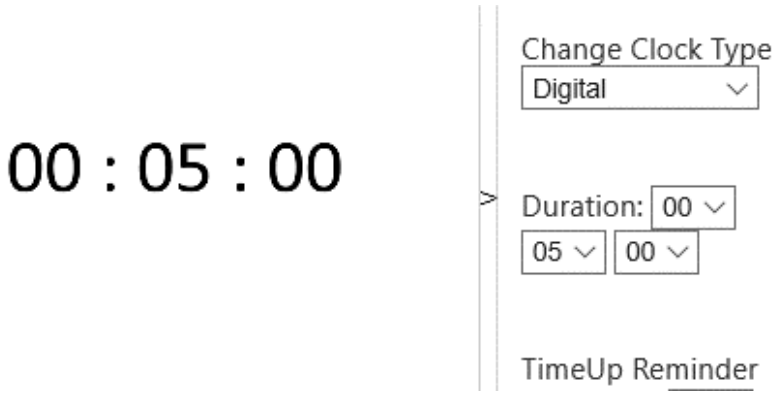
Pat Meredith
Patient Expert

No financial conflicts to disclose.



Lea Parker
Patient Expert

No financial conflicts to disclose.

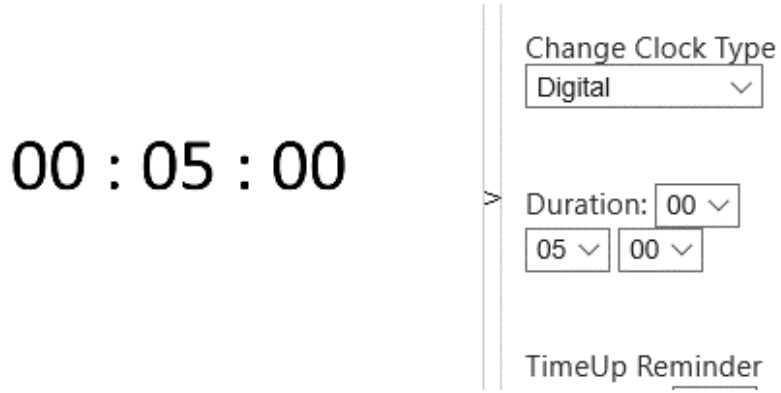


Katherine Wilemon

Founder and Chief Executive Officer, FH Foundation

Conflicts of Interest:

- *The FH Foundation receives funding for its programs from health care companies, including Esperion and Novartis.*



Lunch

Meeting will resume at 12:45pm CT

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Voting Questions

Clinical Evidence

***Patient population for questions 1 and 2**: All adult patients with established ASCVD and/or HeFH who have elevated LDL-C levels despite treatment with maximally tolerated oral lipid-lowering therapy.*

1. Given today's evidence, is the evidence adequate to demonstrate that the net health benefit of adding bempedoic acid alone to usual care is superior to that provided by usual care alone?

A. Yes

B. No

1a. If the answer to question 1 is no, is the evidence adequate to demonstrate the net health benefit of adding bempedoic acid alone to usual care is superior to that provided by usual care alone in patients who have statin-associated side effects (“statin intolerant”)?

A. Yes

B. No

1b. If the answer to question 1 is no, is the evidence adequate to demonstrate the net health benefit of adding bempedoic acid alone to usual care is superior to that provided by usual care alone in patients with HeFH?

A. Yes

B. No

***Patient population for questions 1 and 2**: All adult patients with established ASCVD and/or HeFH who have elevated LDL-C levels despite treatment with maximally tolerated oral lipid-lowering therapy.*

2. Given today's evidence, is the evidence adequate to demonstrate that the net health benefit of adding inclisiran to usual care is superior to that provided by usual care alone?

A. Yes

B. No

Contextual Considerations and Potential Other Benefits or Disadvantages

1. When making judgments of overall long-term value for money, what is the relative priority that should be given to <u>any</u> new effective treatment for SECONDARY PREVENTION OF ASCVD, on the basis of the following contextual consideration:

Acuity of need for treatment of individual patients based on the severity of the condition being treated

A. Very low priority

B. Low priority

C. Average priority

D. High priority

E. Very high priority

2. When making judgments of overall long-term value for money, what is the relative priority that should be given to <u>any</u> new effective treatment for SECONDARY PREVENTION OF ASCVD, on the basis of the following contextual consideration:

Magnitude of the lifetime impact on individual patients of the condition being treated

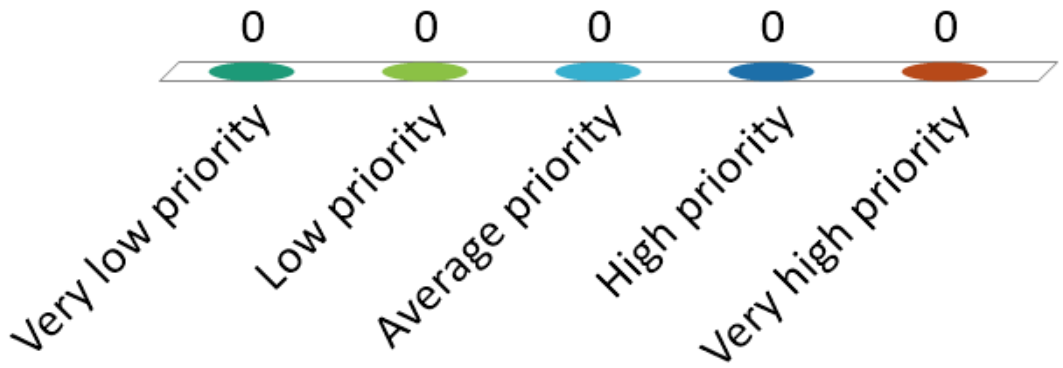
A. Very low priority

B. Low priority

C. Average priority

D. High priority

E. Very high priority



3. What are the relative effects of BEMPEDOIC ACID when added to maximally tolerated oral lipid-lowering therapy on the following outcome(s) that inform judgment of the overall long-term value for money of BEMPEDOIC ACID?

Patients' ability to achieve major life goals related to education, work, or family life

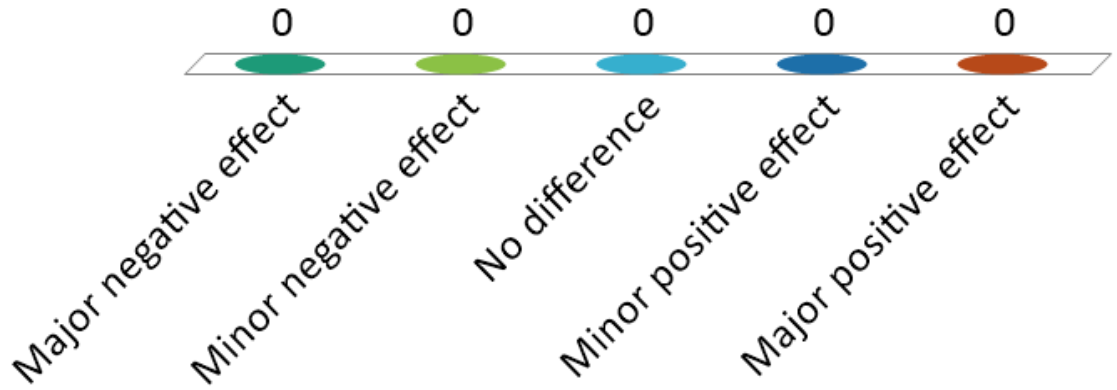
A. Major negative effect

B. Minor negative effect

C. No difference

D. Minor positive effect

E. Major positive effect



4. What are the relative effects of BEMPEDOIC ACID when added to maximally tolerated oral lipid-lowering therapy on the following outcome(s) that inform judgment of the overall long-term value for money of BEMPEDOIC ACID?

Caregivers' quality of life and/or ability to achieve major life goals related to education, work, or family life

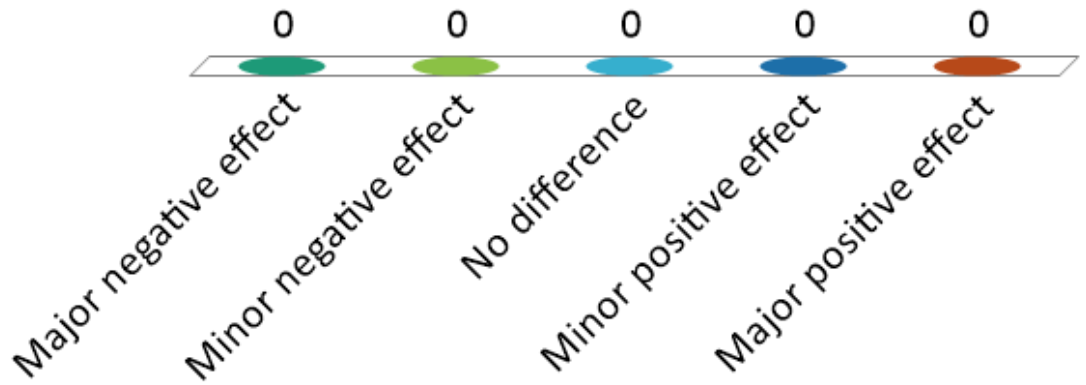
A. Major negative effect

B. Minor negative effect

C. No difference

D. Minor positive effect

E. Major positive effect



5. What are the relative effects of BEMPEDOIC ACID when added to maximally tolerated oral lipid-lowering therapy on the following outcome(s) that inform judgment of the overall long-term value for money of BEMPEDOIC ACID?

Patients' ability to manage and sustain treatment given the complexity of regimen

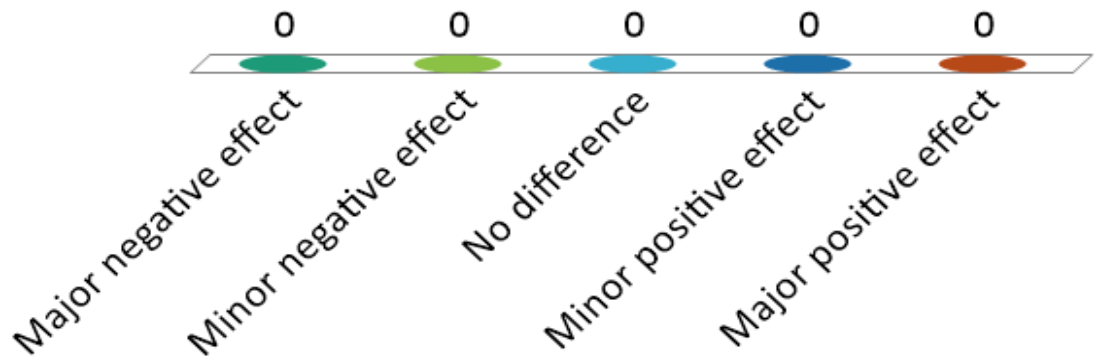
A. Major negative effect

B. Minor negative effect

C. No difference

D. Minor positive effect

E. Major positive effect



6. What are the relative effects of BEMPEDOIC ACID when added to maximally tolerated oral lipid-lowering therapy on the following outcome that informs judgment of the overall long-term value for money of BEMPEDOIC ACID?

The problem of health inequity

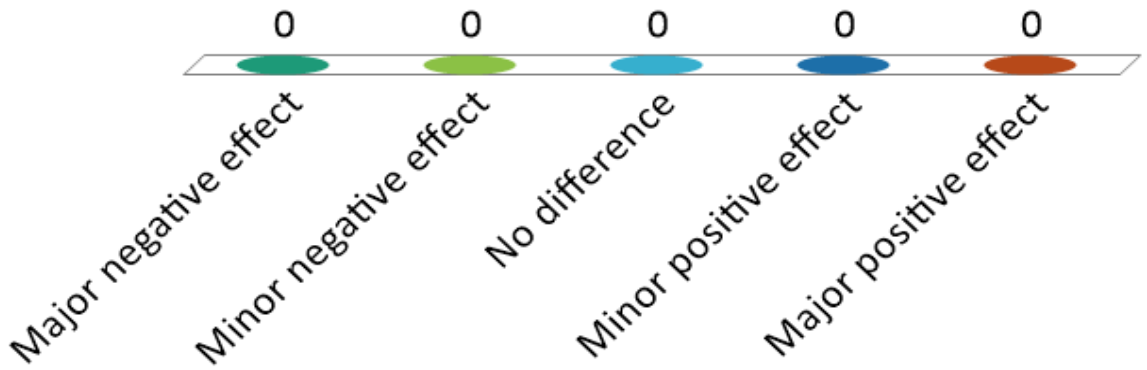
A. Major negative effect

B. Minor negative effect

C. No difference

D. Minor positive effect

E. Major positive effect



7. What are the relative effects of BEMPEDOIC ACID when added to maximally tolerated oral lipid-lowering therapy on the following outcome(s) that inform judgment of the overall long-term value for money of BEMPEDOIC ACID?

Other (as relevant): New treatment option for patients with statin intolerance

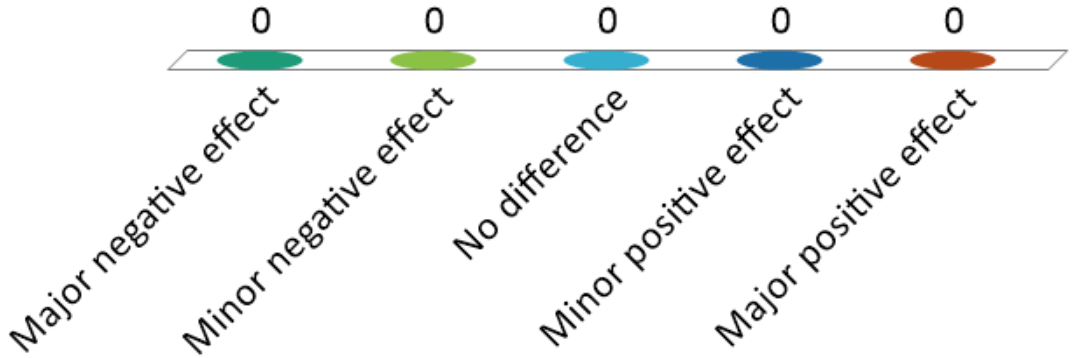
A. Major negative effect

B. Minor negative effect

C. No difference

D. Minor positive effect

E. Major positive effect



8. What are the relative effects of INCLISIRAN versus PCSK9 INHIBITORS on the following outcome(s) that informs judgment of the overall long-term value for money of INCLISIRAN?

Patients' ability to achieve major life goals related to education, work, or family life

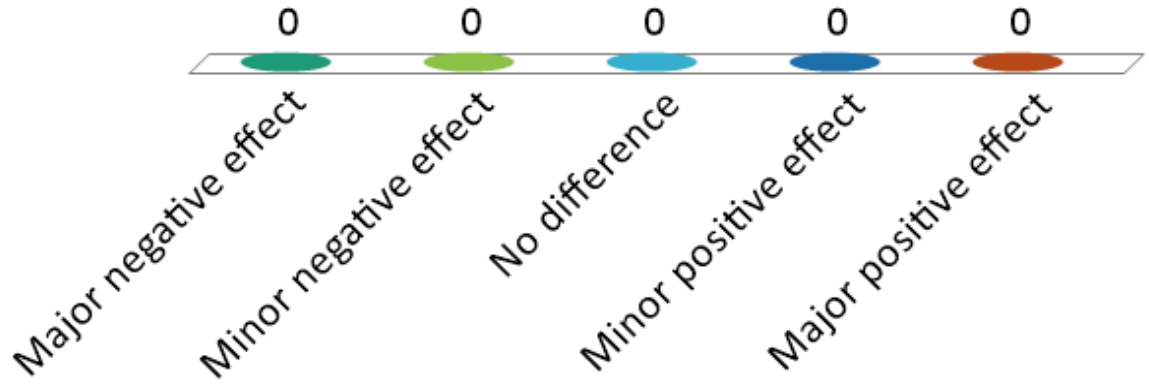
A. Major negative effect

B. Minor negative effect

C. No difference

D. Minor positive effect

E. Major positive effect



9. What are the relative effects of INCLISIRAN versus PCSK9 INHIBITORS on the following outcome(s) that informs judgment of the overall long-term value for money of INCLISIRAN?

Caregivers' quality of life and/or ability to achieve major life goals related to education, work, or family life

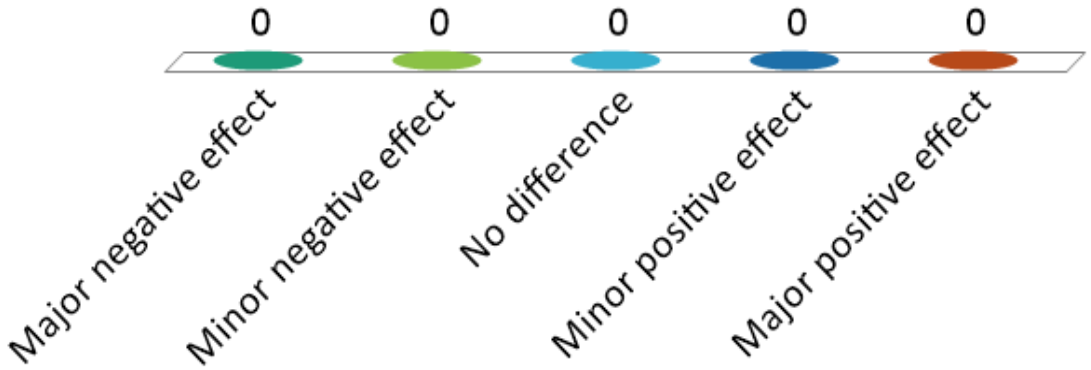
A. Major negative effect

B. Minor negative effect

C. No difference

D. Minor positive effect

E. Major positive effect



10. What are the relative effects of INCLISIRAN versus PCSK9 INHIBITORS on the following outcome that informs judgment of the overall long-term value for money of INCLISIRAN?

Patients' ability to manage and sustain treatment given the complexity of regimen

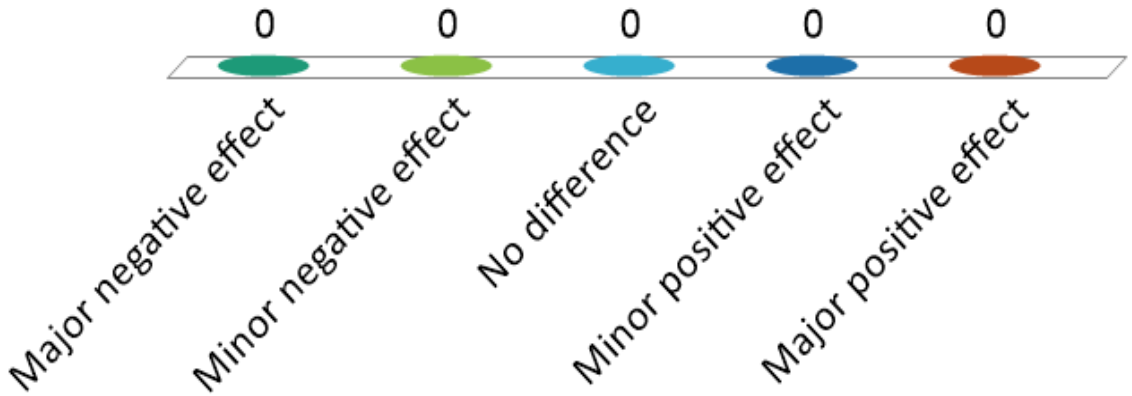
A. Major negative effect

B. Minor negative effect

C. No difference

D. Minor positive effect

E. Major positive effect



11. What are the relative effects of INCLISIRAN versus PCSK9 INHIBITORS on the following outcome that informs judgment of the overall long-term value for money of INCLISIRAN?

The problem of health inequity

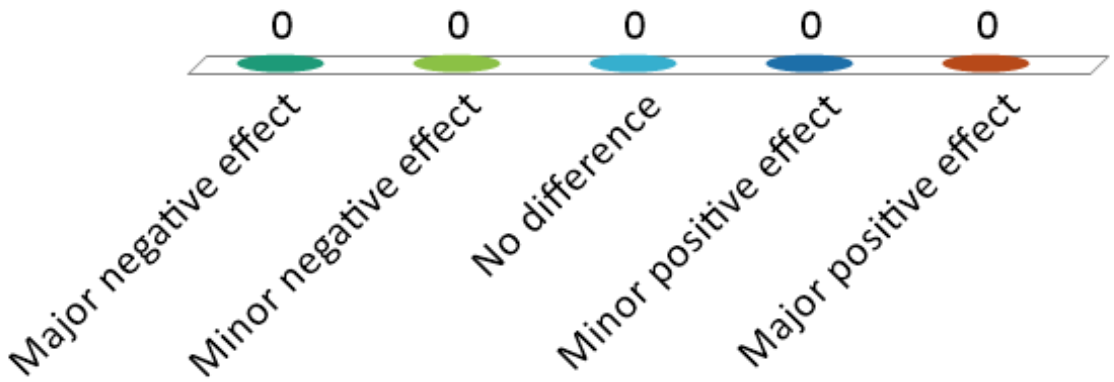
A. Major negative effect

B. Minor negative effect

C. No difference

D. Minor positive effect

E. Major positive effect



12. What are the relative effects of INCLISIRAN versus PCSK9 INHIBITORS on the following outcome that informs judgment of the overall long-term value for money of INCLISIRAN?

Other (as relevant): New treatment option for patients with statin intolerance

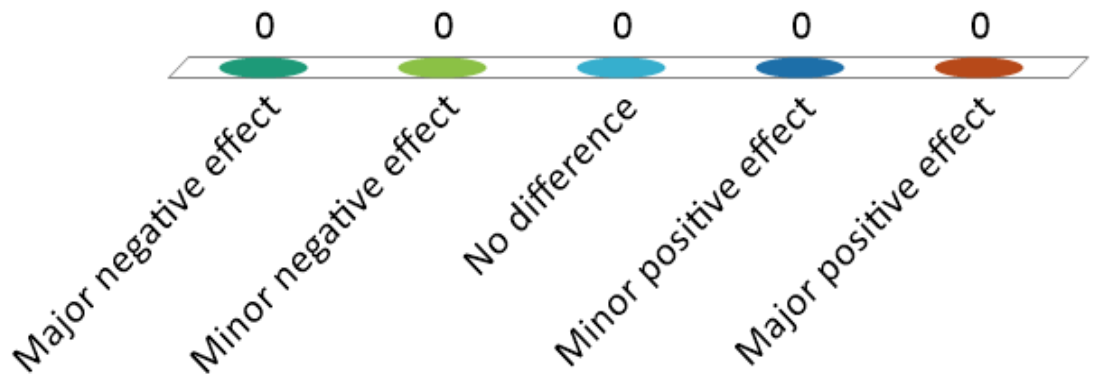
A. Major negative effect

B. Minor negative effect

C. No difference

D. Minor positive effect

E. Major positive effect



Long-Term Value for Money

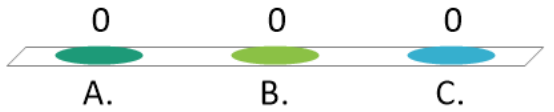
Patient population for question 1: *All adult patients with established ASCVD and/or HeFH who have elevated LDL-C levels despite treatment with maximally tolerated statin therapy.*

1. 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 at current pricing of adding bempedoic acid with ezetimibe to usual care versus usual care with ezetimibe?

A. Low long-term value for money

B. Intermediate long-term value for money

C. High long-term value for money



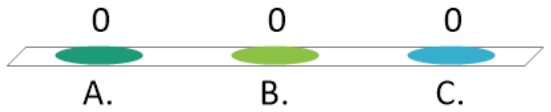
***Patient population for question 2**: All adult patients with established ASCVD – with or without HeFH – who have elevated LDL-C levels and have statin-associated side effects ("statin intolerant").*

2. 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 at current pricing of adding bempedoic acid with ezetimibe to usual care versus usual care with ezetimibe?

A. Low long-term value for money

B. Intermediate long-term value for money

C. High long-term value for money



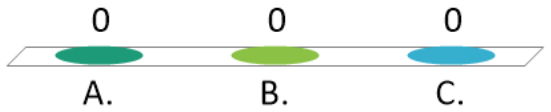
Patient population for question 3: *All adult patients with HeFH who have elevated LDL-C levels despite treatment with maximally tolerated statin therapy.*

3. 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 at current pricing of adding bempedoic acid with ezetimibe to usual care versus usual care with ezetimibe?

A. Low long-term value for money

B. Intermediate long-term value for money

C. High long-term value for money



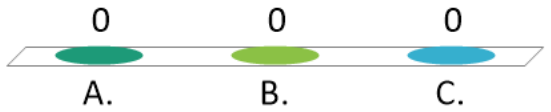
Patient population for question 4: *All adult patients with established ASCVD and/or HeFH who have elevated LDL-C levels despite treatment with maximally tolerated statin therapy.*

4. 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 at current pricing of adding inclisiran to usual care versus usual care alone?

A. Low long-term value for money

B. Intermediate long-term value for money

C. High long-term value for money



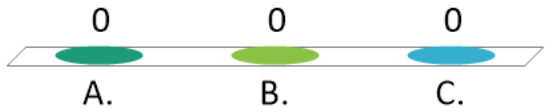
Patient population for question 5: *All adult patients with established ASCVD – with or without HeFH – who have elevated LDL-C levels and have statin-associated side effects ("statin intolerant").*

5. 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 at current pricing of adding inclisiran to usual care versus usual care alone?

A. Low long-term value for money

B. Intermediate long-term value for money

C. High long-term value for money



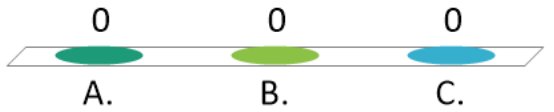
Patient population for question 6: *All adult patients with HeFH who have elevated LDL-C levels despite treatment with maximally tolerated statin therapy.*

6. 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 at current pricing of adding inclisiran to usual care versus usual care alone?

A. Low long-term value for money

B. Intermediate long-term value for money

C. High long-term value for money



Break

Meeting will resume at 2:15pm CT

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Policy Roundtable

Policy Roundtable

Policy Roundtable Member	Conflicts of Interest
Cat Davis Ahmed, MBA Vice President, Policy and Outreach, FH Foundation	The FH Foundation receives > 25% of their funding from health care companies, including: Amgen, Regeneron, Novartis, Esperion, Kaneka Medical Products, Silence Therapeutics, Arrowhead Pharmaceuticals, Verve Therapeutics, Amryt Pharma, and BIO.
Andrea Baer, MS, BCPA Executive Director, The Mended Hearts, Inc.	The Mended Hearts, Inc. receives > 25% of their funding from health care companies, including Novartis.
Dave Busch, RPh, MS Vice President Pharmacy, HealthPartners	Dave Busch is a full-time employee of HealthPartners.
Keith C. Ferdinand, MD, FACC, FAHA, FASH, FNLA Gerald S. Berenson Endowed Chair in Preventive Cardiology and Professor of Medicine, Tulane School of Medicine	Dr. Ferdinand has served as a consultant for Novartis Pharmaceuticals.
Michael Louie, MD, MPH, MSc SVP of Clinical Development and Pharmacovigilance Esperion Therapeutics	Dr. Louie is a full-time employee of Esperion Therapeutics.
David Platt, MD Vice President and Head, Cardiovascular, Renal & Metabolism Medical Unit, US Clinical Development and Medical Affairs, Novartis Pharmaceuticals	Dr. Platt is a full-time employee of Novartis Pharmaceuticals.
Erik Schindler, PharmD, BCPS Director, Emerging Therapeutics and Outcome-Based Contracting, UnitedHealthcare Pharmacy	Dr. Schindler is a full-time employee of UnitedHealthcare Pharmacy.
Salim S. Virani, MD, PhD Professor in Cardiology and Cardiovascular Research Sections, Baylor College of Medicine	Dr. Virani receives grant support from the Department of Veterans Affairs, World Heart Federation, and Tahir and Jooma Family. In addition, Dr. Virani receives honorarium from the American College of Cardiology; Associate Editor for Innovations, acc.org.

Midwest CEPAC Council Reflections

Next Steps

- Meeting recording posted to ICER website next week
- Final Report published on or around March 2, 2021
  - Includes description of Midwest CEPAC votes, deliberation, policy roundtable discussion
- Meeting materials available at: https://icer.org/assessment/high-cholesterol-2021/

Adjourn

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