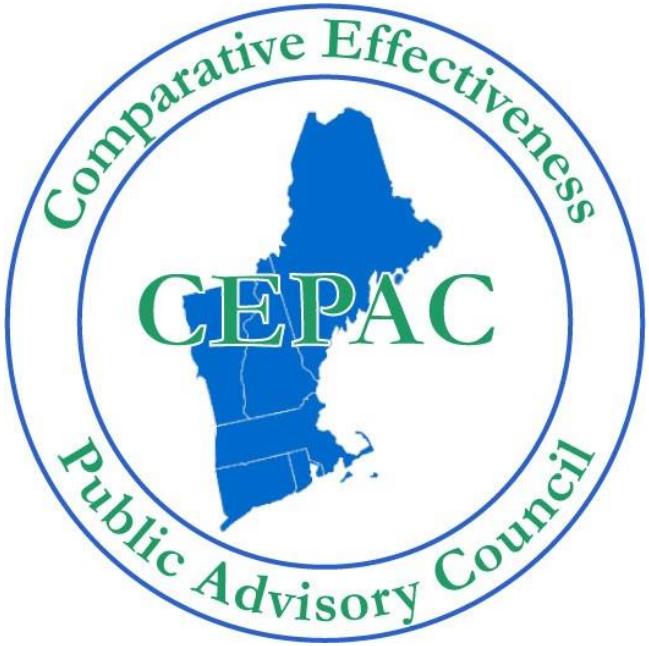


PCSK9 Inhibitors for Treatment of High Cholesterol

Public Meeting – October 27, 2015

Agenda

- **Meeting Convened and Opening Remarks** | 10:00 AM- 10:15 AM
  - Steven Pearson, MD, MSc, President, Institute for Clinical and Economic Review
- **Presentation of the Evidence** |10:15 AM- 11:30 AM
  - Jeffrey Tice, MD, Associate Professor, UCSF School of Medicine
  - Dhruv S. Kazi, MD, MSc, MS, Assistant Professor, UCSF
  - Kirsten Bibbins-Domingo, MD, PhD, MAS, Professor, UCSF
  - Daniel Ollendorf, PhD, Chief Review Officer, Institute for Clinical and Economic Review
- **Public Comments and Discussion** | 11:30 AM-12:00 PM
  - Members of the public pre-registered to deliver oral remarks
- **Break for Lunch** | 12:00 PM – 12:30 PM
- **CEPAC Q&A with Experts/Deliberation and Votes**| 12:30 PM – 2:30 PM
- **Policy Roundtable** | 2:30 PM-3:50 PM

New England CEPAC Overview

- A core program of the Institute for Clinical and Economic Review (ICER)
  - CEPAC is an independent panel that reviews objective evidence reports and holds public meetings to develop recommendations for how patients, clinicians, insurers, and policymakers can improve the quality and value of health care.
- Goal: To improve the application of evidence to guide practice and policy in New England
- Structure:
  - Evidence review from ICER
  - Deliberation and voting by CEPAC– independent clinicians, methodologists, and leaders in patient engagement and advocacy
- Supported by grants from the New England States Consortium Systems Organization (NESCSO) and the Laura and John Arnold Foundation

New England CEPAC Overview

- CEPAC recommendations designed to support aligned efforts to improve the application of evidence to:
  - Practice
    - Patient/clinician education
    - Quality improvement efforts
    - Clinical guideline development
  - Policy
    - Coverage and reimbursement
    - Medical management policies
    - Benefit design

EVIDENCE REVIEW

Jeffrey A. Tice, MD
Division of General Internal Medicine
Department of Medicine
University of California San Francisco

I have no conflicts of interest.

Topic in Context

- Cardiovascular disease is the most common cause of death in the U.S.
- LDL hypothesis: “Lower is better”
  - True for statins and ezetimibe
  - Not true for estrogen, niacin, fibrates, others
- Example: RCT torcetrapib x 5 years, n > 15,000
  - LDL **decreased** by 25%, HDL increased
  - CVD events **increased** 25%; total mortality **increased** 58%

Guidelines

- ACC/AHA 2013
  - High intensity statins for known CVD or 10-year risk > 7.5%
  - Moderate intensity statins for DM
- Prior NCEP guidelines
  - Goal LDL < 100 mg/dL if CVD or risk > 20%
  - Goal LDL < 130 if risk < 20%
- Europe 2011
  - Goal LDL < 70 if CVD or DM
  - Goal LDL < 100 for high risk primary prevention

Unmet needs

- Familial hypercholesterolemia
  - High LDL despite statin and ezetimibe therapy
- Patients with cardiovascular disease
  - High LDL despite statin and ezetimibe therapy
- Indication for statin, but intolerant
  - 5-10% of patients with muscle symptoms
  - Controversial (ODYSSEY ALTERNATIVE)
    - 50% in placebo run-in reported intolerable symptoms
    - 70% randomized to statin tolerated statin x 12 weeks

PCSK9

- Proprotein convertase subtilisin/kexin type 9
- Binds to LDL receptors and prevents recycling
  - Fewer LDL receptors
  - More LDL in blood
- Genetics
  - Gain of function: high LDL, early strokes and MIs
  - Loss of function: low LDL, less CVD

PCSK9 inhibitors

- Alirocumab (Praluent, Sanofi and Regeneron)
  - 75 mg SC every 2 weeks
  - 150 mg SC every 2 weeks
- Evolocumab (Repatha, Amgen)
  - 140 mg SC every 2 weeks
  - 420 mg SC every 4 weeks

Methods

- Two systematic reviews
  - Navarese *et al*., Annals IM, 2015
  - Zhang *et al*., BMC Medicine, 2015
- Updated search using Navarese search criteria
- Phase 2 or 3 randomized trials
- Alirocumab or evolocumab

Results – Study Description

- 25 randomized trials: low risk of bias
  - Alirocumab
    - 13 RCTs, n = 5,137
  - Evolocumab
    - 11 RCTs, n = 5,022
    - Plus OSLER re-randomized patient from earlier trials
  - 1 trial HoFH: TESLA Part B, N = 49
  - 3 trials of patients with statin intolerance
  - Control: placebo in 14 trials, ezetimibe in 7, both in 3

Results: LDL reduction

Comparator	Placebo	Ezetimibe
	58.8%	36.2%

- Similar for alirocumab and evolocumab
- Similar for background statin intensity

Outcomes: CVD

- No trials designed to evaluate CVD outcomes
  - CVD outcomes were adverse events in trials designed to evaluate LDL lowering
  - 2 large CVOTs to report in 2017

	OR (95% CI)
Mortality	0.45 (0.23-0.86)
CVD mortality	0.50 (0.23-1.10)
MI	0.49 (0.26-0.93)
Stroke	1.97 (0.69-5.65)
Unstable angina	0.61 (0.06-6.14)

Other adverse events

	OR (95% CI)
Serious AE	1.01 (0.87-1.18)
AE discontinuation	1.03 (0.84-1.26)
Myalgias	1.16 (0.91-1.49)
Neurocognitive AE	1.08 (0.57-1.24)
ALT elevation	0.82 (0.54-1.24)
CK elevation	0.72 (0.54-0.96)
Injection site AE	1.30 (1.03-1.65)
Hypersensitivity AE	0.69 (0.23-2.08)

Summary of the Evidence: Promising, but inconclusive

- High certainty of LDL lowering with the PCSK9 inhibitors (59% versus placebo; 36% versus ezetimibe)
- Low to moderate certainty of improvements in CVD outcomes
  - Outcomes studies in progress (n > 40,000; 5 year FU)
  - Borderline significant benefits when all trials combined
- Clear evidence of injection site reactions; no other AEs clearly associated with PCSK9 inhibitors, but the person-years of experience is modest
- The magnitude of the net benefit is either incremental or substantial

Public Comments Received

- The uncertainty due to the lack of clinical outcomes trials and the limited number of cardiovascular events has not been emphasized enough
- There is a lack of real world data on adverse events
- There are more patients with HoFH and HeFH than reported in the assessment
- Only about 10% of individuals with FH have been diagnosed

COST-EFFECTIVENESS OF PCSK9 INHIBITORS

AN ANALYSIS FROM THE CVD POLICY MODEL

Kirsten Bibbins-Domingo, MD, PhD, MAS

Professor of Medicine and of Epidemiology and Biostatistics

University of California, San Francisco

I have no conflicts of interest.

CVD Policy Model Team

- Dhruv S. Kazi, MD, MSc, MS
  - Assistant Professor of Medicine and Cardiology, UCSF
- Pamela Coxson, PhD
  - Math Specialist, UCSF
- Andrew Moran, MD, MAS
  - Assistant Professor of Medicine, Columbia College of Physicians and Surgeons
- David Guzman, MS
  - Programmer, UCSF
- Joanne Penko, MS, MPH
  - Project Manager, UCSF

Objective

To estimate the cost-effectiveness of PCSK9 inhibitors in the populations for which their use is currently approved:

- Familial hypercholesterolemia (FH)
- Atherosclerotic cardiovascular disease (ASCVD) who require additional lipid lowering

CVD Policy Model

- Dynamic, population-based simulation model of cardiovascular disease in US adults
- Validated and extensively peer-reviewed
- Previously used to address key clinical and health policy questions

JAMA. 1997;277(7):535-542
N Engl J Med. 2002;346(23):1800-1806
N Engl J Med. 2007;357(23):2371-2379
Ann Intern Med. 2009;150(4):243-254
N Engl J Med. 2010;362(7):590-599
Ann Intern Med. 2015;162(8):533-541
N Engl J Med. 2015;372(5):447-455

CVD Policy Model

- Incident CHD from Framingham Heart and Framingham Offspring Studies
- CV risk factor prevalence from US NHANES
- Other key inputs to the model from Census, Vital Statistics, other national data & cohort studies.
- Outputs of the CVD Policy Model are calibrated to reproduce:
  - 2010 US estimates for MIs, strokes, CHD deaths, stroke deaths, and deaths from all causes within 1%
  - Results of clinical trials of statins

Calibration to National Targets

Comparisons of selected CVD Policy Model simulation outputs for 2010 (model base year) with national clinical outcomes for 2010.

Clinical outcomes	Total myocardial infarctions Target source: NHDS	Total strokes Target source: NHDS	CHD deaths Target source: national vital statistics	Stroke deaths Target source: national vital statistics	All-cause deaths Target source: national vital statistics
Model variance from actual events	**-0.26%**	**0.39%**	**0.27%**	**0.12%**	**-0.14%**

Validation

- Event rates in the model accurately reproduced those seen in statin trials

Event Type	CVD Policy Model	CTT statin trials
	Annual rate (%)	
Nonfatal MI	1.0	0.9 – 1.3
Cardiovascular death	1.0	1.0
Stroke	1.0	0.6 – 0.7
Major Coronary Event (nonfatal MI + CHD death)	1.8	1.3-1.9

Target Populations

- FH population
  - LDL-C ≥ 200mg/dL on statins or LDL-C ≥ 250mg/dL off statins
- Atherosclerotic CVD requiring additional lipid lowering
  - On statins but not at goal (LDL ≥ 70mg/dL)
  - Statin-intolerant (subset of those not using statins), LDL ≥ 70mg/dL

Interventions

- FH population and CVD population on statins but not at goal
  - Control: Statin therapy as treated according to NHANES
  - Intervention: Addition of PCSK9 inhibitor
- CVD population with statin intolerance
  - Control: no change in care
  - Intervention: Addition of PCSK9 inhibitor
- Key assumption
  - Based on review of cohort and clinical trial data, assumed that every 1 mg/dL reduction in LDL-C by PCSK9 inhibitors produces a reduction in cardiovascular events identical to that seen with statins

Costs

- Annual drug costs = average wholesale acquisition costs:
  - Statin: $812
  - PCSK9 inhibitor: $14,350 (average of two agents)

Outcomes

- Major Adverse Clinical Outcomes (MACE):
  - Nonfatal myocardial infarction, nonfatal stroke, CVD death
- Number-needed-to-treat over 5 years (NNT_5)
- Health care costs related to cardiovascular disease
- Quality-adjusted life years (QALYs)
- Incremental cost-effectiveness ratio: $/QALY

Perspective and analytic horizon

- Health system perspective
- Life-time analytic horizon
  - Modeled adults 35-74 until all reached 95 years

Sensitivity Analysis

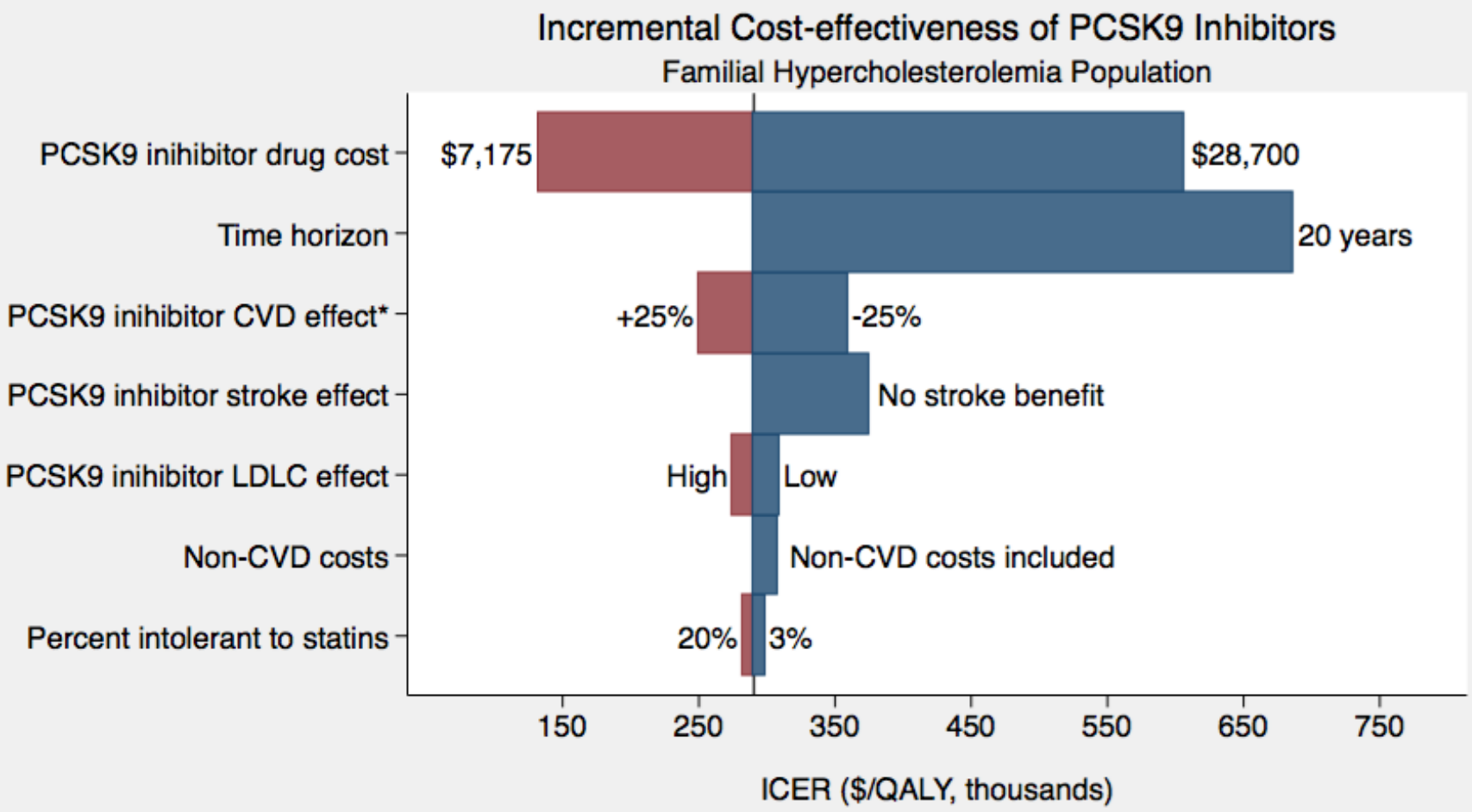
- Atherosclerotic CVD:
  - Focus on highest risk patients by restricting to those who experienced their first-ever MI at the start of the simulation

Results: FH

- 605,000 patients in 2015

	Total MACE averted	NNT_5	QALYs gained	Incremental Drug Costs (million $)	Incremental Costs, Other CV Care (million $)	ICER ($/QALY)
Statin (as treated in NHANES)	comparator					
Statin + PCSK9 inhibitor	324,200	28	665,200	$210,516	-$17,304	$290,000

Results: FH


Incremental Cost-effectiveness of PCSK9 Inhibitors
Familial Hypercholesterolemia Population
PCSK9 inihibitor drug cost
$7,175
$28,700
Time horizon
20 years
PCSK9 inihibitor CVD effect*
+25%
-25%
PCSK9 inhibitor stroke effect
No stroke benefit
PCSK9 inihibitor LDLC effect
High
Low
Non-CVD costs
Non-CVD costs included
Percent intolerant to statins
20%
3%
150
250
350
450
550
650
750
ICER ($/QALY, thousands)

Results: CVD on statins, not at goal

- 7,271,000 patients in 2015

	Total MACE averted	NNT_5	QALYs gained	Incremental Drug Costs (million $)	Incremental Costs, Other CV Care (million $)	ICER ($/QALY)
Statin	comparator					
Statin + PCSK9 inhibitor	5,621,800	21	10,573,800	$3,406,692	-$210,702	$302,000

Results: CVD, statin-intolerant

- 1,460,000 patients in 2015

	Total MACE averted	NNT_5	QALYs gained	Incremental Drug Costs (million $)	Incremental Costs, Other CV Care (million $)	ICER ($/QALY)
Control (no statin treatment)	comparator					
PCSK9 inhibitor	1,254,400	21	2,366,000	$693,450	-$44,627	$274,000

Sensitivity Analysis: CVD (restricting to first MI)

- 169,000 patients in 2015

	Total MACE averted	NNT_5	QALYs gained	Incremental Drug Costs (million $)	Incremental Costs, Other CV Care (million $)	ICER ($/QALY)
Statin	comparator					
Statin + PCSK9 inhibitor	43,200	15	159,200	$35,287	-$2,692	**$204,000**

Threshold Analyses

Patient Subpopulation	Willingness-to-pay threshold		
	$50,000/QALY	$100,000/QALY	$150,000/QALY
FH - Main simulation	$3,400	$5,700	$8,000
FH - Additional Scenario Analysis (first treat all with statin)	$3,000	$5,000	$7,000
ASCVD - Statin intolerant LDL-C ≥ 70 mg/dL	$3,400	$5,800	$8,300
ASCVD on statins LDL-C ≥ 70 mg/dL	$3,100	$5,300	$7,600
ASCVD, restricting to first-ever MI	$4,300	$7,600	$10,800
ALL SUBPOPULATIONS	$3,166	$5,404	$7,735

Discussion

- Strengths:
  - Lifetime simulation of a nationally representative cohort
- Potential limitations:
  - Uncertainty about true long-term clinical effectiveness and safety
  - Did not model changes in adherence over time
  - Uncertainty about CV risk in FH
  - Modeled US adults age 35-74 in 2015

Conclusion

- Assuming that LDL-C lowering observed with PCSK9 inhibitors translates into clinical benefit consistent with that observed with statins, PCSK9 inhibitors are likely to yield considerable reductions in CV morbidity and mortality
  - NNT_5 for FH = 28
  - NNT_5 for ASCVD = 21
- Incremental cost-effectiveness ratios at list price
  - Range from $274,000-$302,000 per QALY for all three subpopulations
  - Even hypothetical use in population immediately following MI produces cost/QALY > $150,000

Public Comments Received

- CVD Policy Model underestimates CVD risk
- Model architecture and assumptions lack transparency
- Extend model time horizon to lifetime

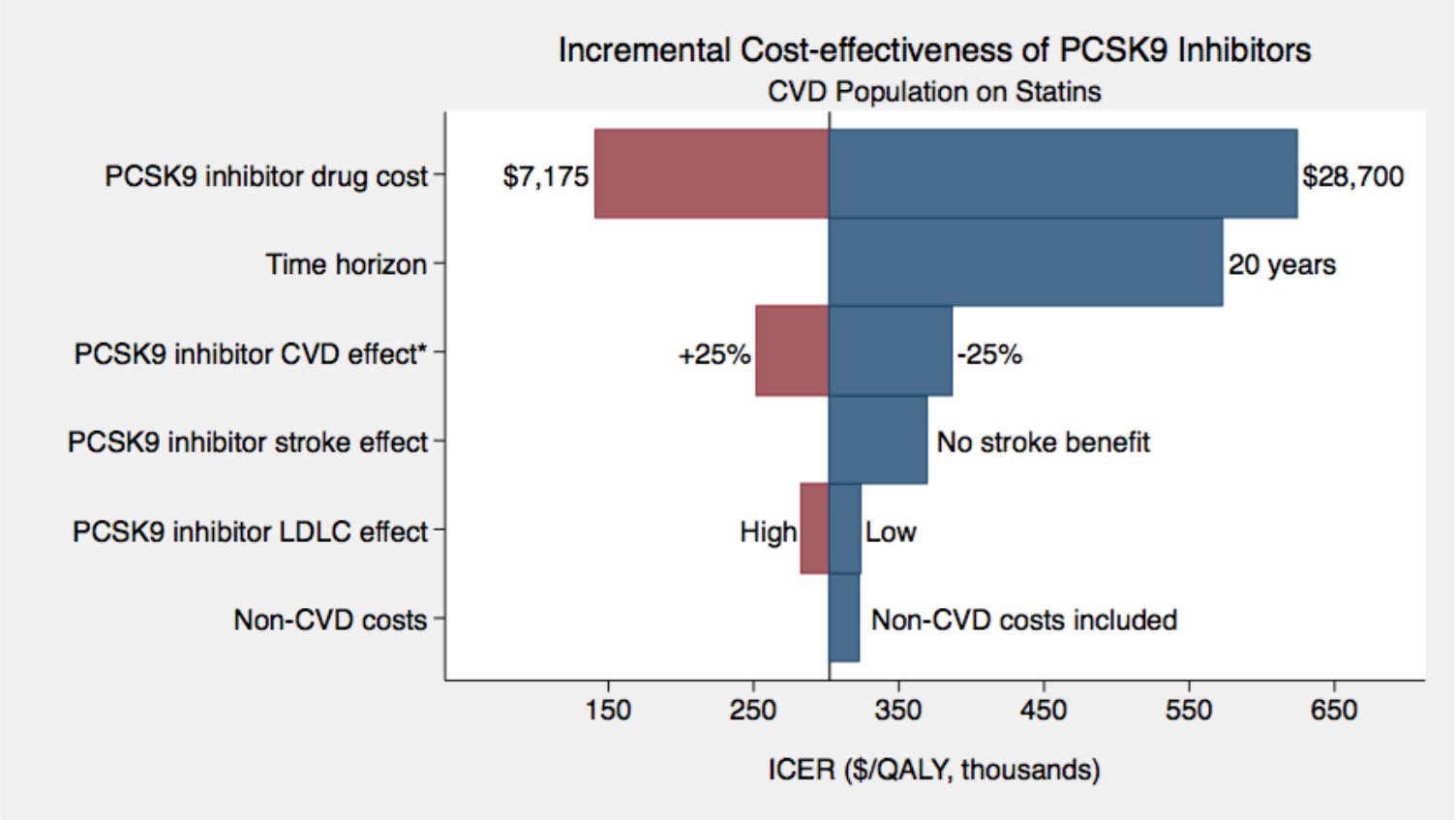
BACKUP SLIDES

Additional Scenario Analysis: FH (entire population treated with statins)

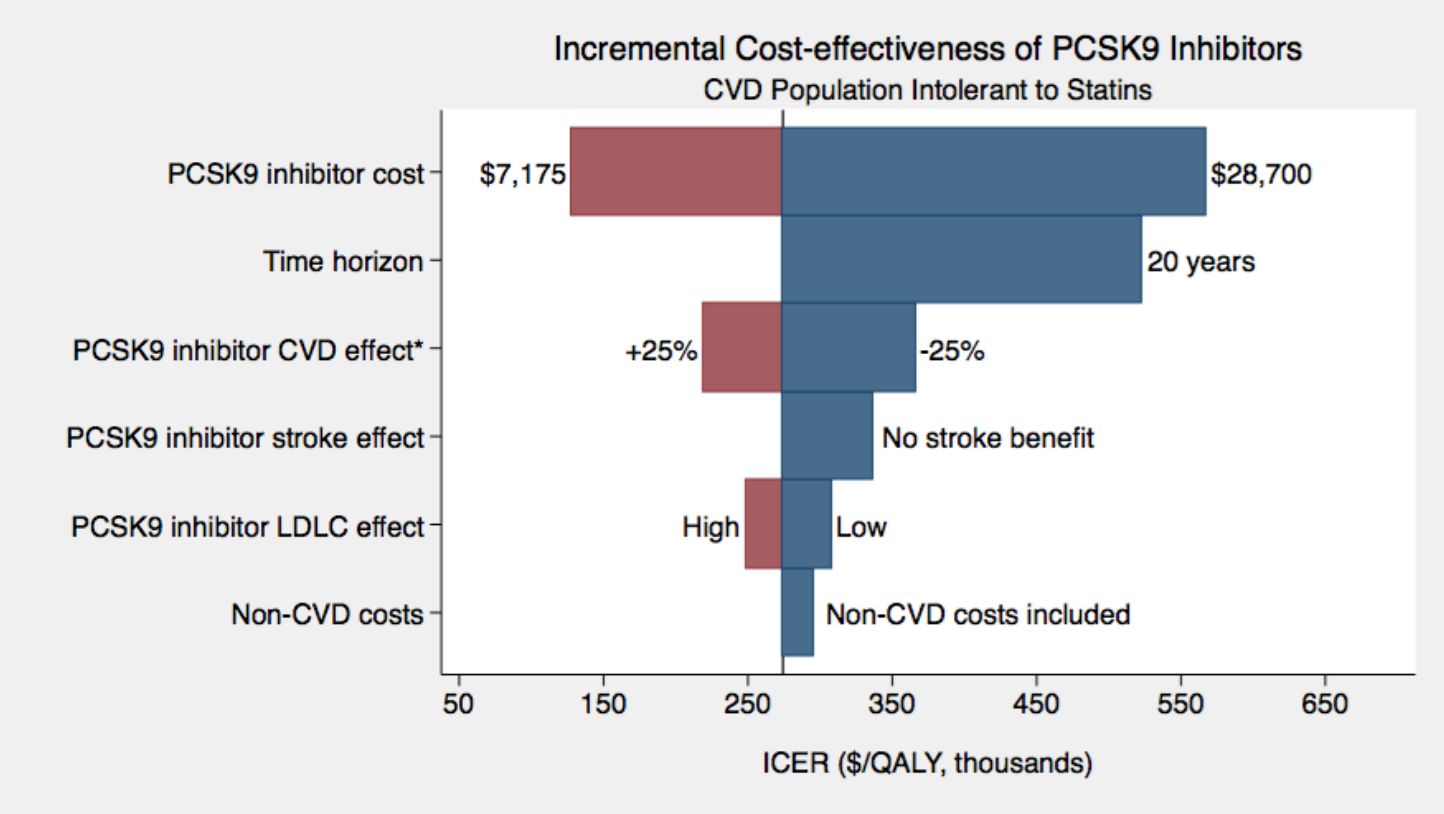
- 748,000 patients in 2015

	Total MACE averted	NNT_5	QALYs gained	Incremental Drug Costs (million $)	Incremental Costs, Other CV Care (million $)	ICER ($/QALY)
Statin (as treated)	comparator					
Statin (Full Treatment)	84,300	25	160,500	$1,889	-$3,286	Cost-Saving
Statin + PCSK9 inhibitor	335,300	33	680,800	$245,111	-$17,833	$334,000

Results: CVD on statins, not at goal



Results: CVD, statin-intolerant



POTENTIAL BUDGETARY IMPACT

Dan Ollendorf, PhD
Chief Review Officer
Institute for Clinical and Economic Review

I have no conflicts of interest.

Key review team members:

Rick Chapman, PhD

Budget Impact: Methods

- Size of key subpopulations from CVD Policy Model:
  - FH: 605,000
  - CVD: 1.5 million & 7.3 million for statin-intolerant and not at LDL-C goal
- Assumed 5-year uptake: 75% for FH, 25% for CVD subpopulations
- Year 5 treated estimates:
  - FH: 453,000
  - CVD statin-intolerant: 365,000
  - CVD not at goal: 1,818,000
  - TOTAL 2,636,000

Annual Budget Impact Threshold: Methods

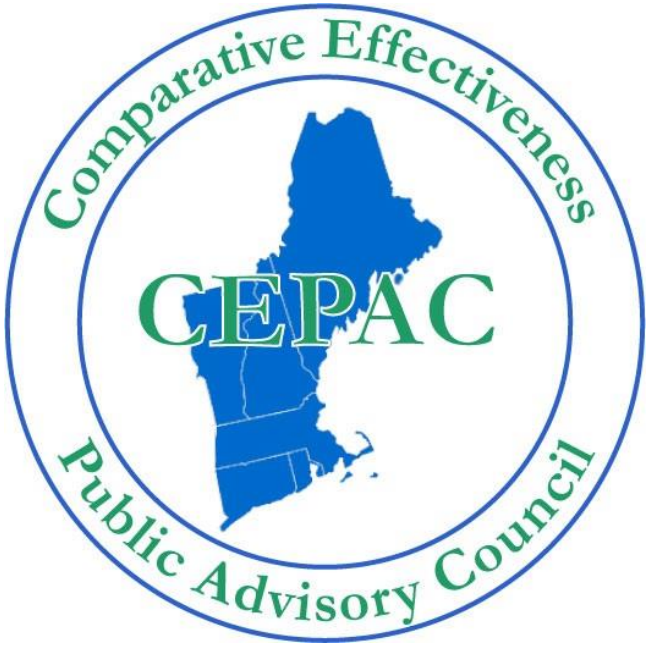
- Based on calculations involving:
  - Target for overall health care cost growth (GDP+1%)
  - Number of new drug/device approvals annually
  - Contribution of drug/device spending to overall health care spending
- Serves as “policy trigger” for discussion of managing cost of new interventions
- 2015-2016 thresholds are $904 million and $603 million for drugs and devices respectively

Budget Impact: Results at 5 Years

Population	Number Treated (thousands)	Annualized Budget Impact (billions)	Discount to Match Annual Budget Impact Threshold
FH	453	$3.7	28.4%
CVD, Statin-intolerant	365	$3.0	10.1%
CVD, Not at goal	1,818	$14.7	79.3%
TOTAL	**2,636**	**$21.4**	**84.8%**

Public Comments Received

- Budget impact assumptions not based on evidence
- Benchmark pricing based on arbitrary caps that do not adequately reflect long-term benefit



Questions for Deliberation

PCSK9 Inhibitors for Treatment of High Cholesterol

Comparative *Clinical Effectiveness* Example Question

Is the evidence "**adequate**" to demonstrate that "**intervention A**" is superior to "**comparator B**" for patients with "**condition X**"?

- **Yes**
- **No**

Care Value Example Question

What is the care value of "**intervention A**" vs "**comparator B**"?

A. Low

B. Intermediate

C. High

Provisional Health System Value Example Question

Assuming baseline pricing and payment mechanisms, what would be the provisional **health system value** of "**intervention A**"?

A. Low

B. Intermediate

C. High

COMPARATIVE CLINICAL EFFECTIVENESS

Praluent vs. Repatha: Net Health Benefits

1. Is the evidence adequate to distinguish between the overall net health benefits of the PCSK9 inhibitors Praluent® and Repatha™, excluding use in homozygous familial hypercholesterolemia for which only Repatha has an indication?
    - Yes: 0 votes (0%)
    - **No: 12 votes (100%)**

Sub populations include:

- Individuals with heterozygous familial hypercholesterolemia (HeFH) who are not at goal (LDL <160mg/dL)
- Individuals with a history of atherosclerotic cardiovascular disease who cannot take statins or who take statins but are not at goal (LDL < 70mg/dL)

PCSK9 Inhibitors for Patients with HeFH

For individuals with heterozygous familial hypercholesterolemia (HeFH) who are statin intolerant or who take statins but are not at goal (<160mg/dL):

2. Is the evidence adequate to demonstrate that adding PCSK9 inhibitors to treatment improves net health benefits?

- **Yes: 7 votes (58%)**
- No: 5 votes (42%)

PCSK9 Inhibitors for Patients with ASCVD and Statin Intolerance

For individuals with a history of atherosclerotic cardiovascular disease who are statin intolerant:

3. Is the evidence adequate to demonstrate that adding PCSK9 inhibitors to treatment improves net health benefits?

- Yes: 4 votes (33%)
- **No: 8 votes (67%)**

PCSK9 Inhibitors for Patients with ASCVD Taking Statins but Not at Goal

For individuals with a history of atherosclerotic cardiovascular disease who take statins but are not at goal (LDL < 70mg/dL):

4. Is the evidence adequate to demonstrate that adding PCSK9 inhibitors to treatment improves net health benefits?

- Yes: 3 votes (25%)
- **No: 9 votes (75%)**

COMPARATIVE VALUE

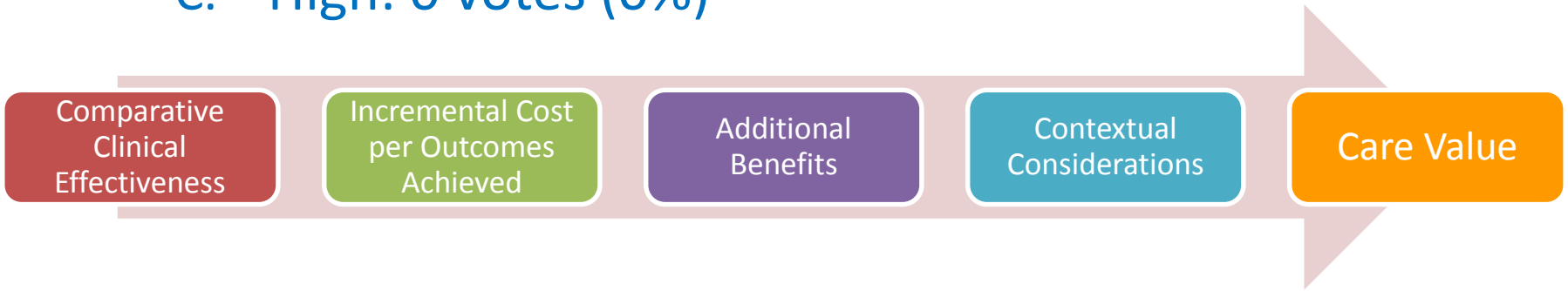
CARE VALUE

Care Value: HeFH

For individuals with heterozygous familial hypercholesterolemia (HeFH) who are statin intolerant or who take statins but are not at goal (LDL <160mg/dL):

5. Given the available evidence, what is the *care value* of adding ***PCSK9 inhibitors vs. no additional treatment***?

A. Low: 4 votes (33%)
B. Intermediate: 8 votes (67%)
C. High: 0 votes (0%)



Care Value: ASCVD, Statin Intolerant

For individuals with a history of atherosclerotic cardiovascular disease who are statin intolerant:

6. Given the available evidence, what is the *care value* of adding ***PCSK9 inhibitors vs. no additional treatment***?

   A. **Low: 7 votes (58%)**
   B. Intermediate: 5 votes (42%)
   C. High: 0 votes (0%)

Care Value: ASCVD with Statins, Not at Goal

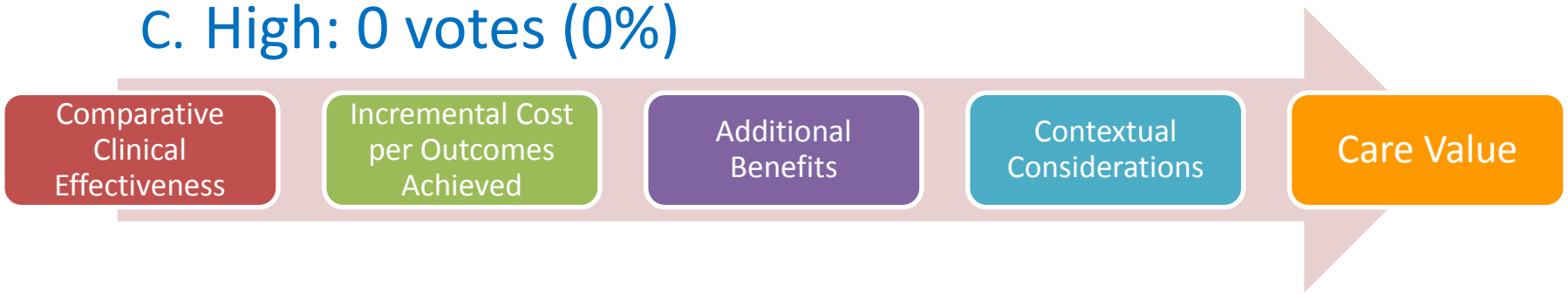
For individuals with a history of atherosclerotic cardiovascular disease who take statins but are not at goal (LDL < 70mg/dL):

7. Given the available evidence, what is the *care value* of adding ***PCSK9 inhibitors vs. no additional treatment***?

   A. Low: 10 votes (83%)

   B. Intermediate: 2 votes (17%)

   C. High: 0 votes (0%)



Care Value: Combined Populations

For the combined population of all patients in these groups:

8. Given the available evidence, what is the *care value* of adding ***PCSK9 inhibitors vs. no additional treatment***?

A. **Low: 9 votes (75%)**

B. Intermediate: 3 votes (25%)

C. High: 0 votes

COMPARATIVE VALUE

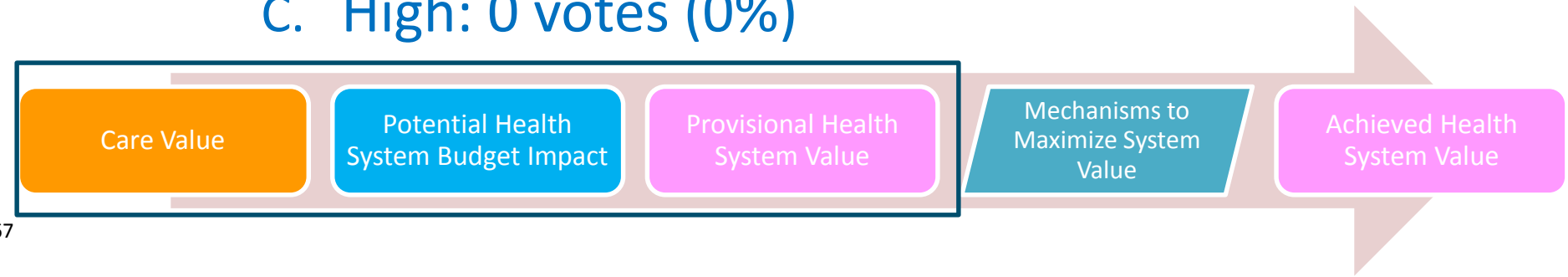
PROVISIONAL HEALTH SYSTEM VALUE

Provisional Health System Value: HeFH

For individuals with heterozygous familial hypercholesterolemia (HeFH) who are statin intolerant or who take statins but are not at goal (LDL <160mg/dL):

9. Given the available evidence, what is the provisional *health system value* of adding ***PCSK9 inhibitors vs. no additional treatment***?

A. **Low: 10 votes (83%)**
B. Intermediate: 2 votes (17%)
C. High: 0 votes (0%)

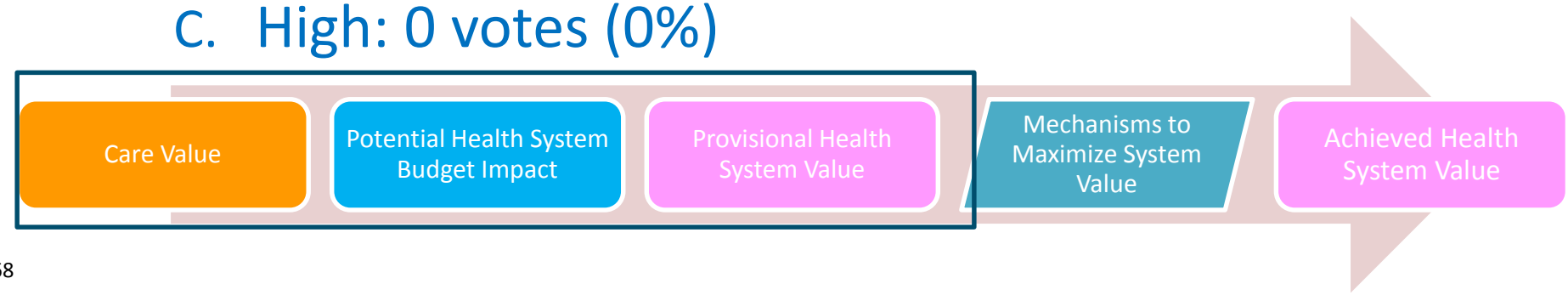


Provisional Health System Value: ASCVD and Statin Intolerant

For individuals with a history of atherosclerotic cardiovascular disease who are statin intolerant:

10. Given the available evidence, what is the provisional *health system value* of adding ***PCSK9 inhibitors vs. no additional treatment***?

   A. **Low: 12 votes (100%)**
   B. Intermediate: 0 votes (0%)
   C. High: 0 votes (0%)

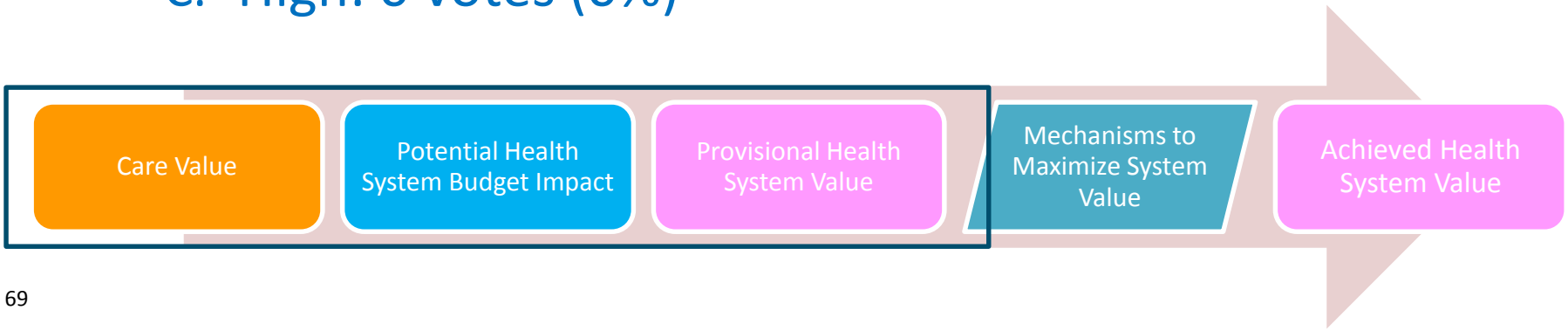


Provisional Health System Value: ASCVD with Statins, Not at Goal

For individuals with a history of atherosclerotic cardiovascular disease who take statins but are not at goal (LDL < 70mg/dL):

11. Given the available evidence, what is the provisional *health system value* of adding ***PCSK9 inhibitors vs. no additional treatment***?

A. **Low: 12 votes (100%)**
B. Intermediate: 0 votes (0%)
C. High: 0 votes (0%)

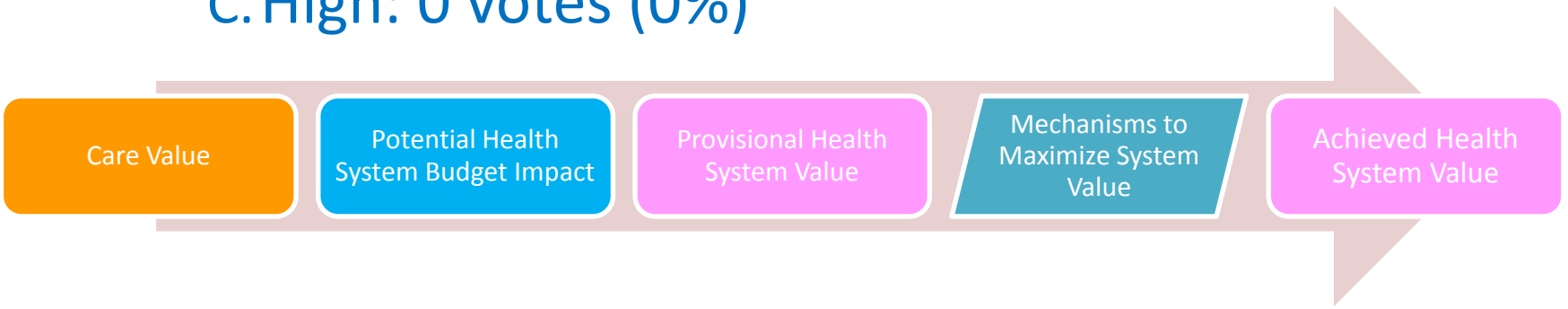


Provisional Health System Value: Combined Populations

For the combined population of all patients in these groups:

Given the available evidence, what is the provisional *health system value* of adding ***PCSK9 inhibitors vs. no additional treatment***?

A. **Low: 12 votes (100%)**
B. Intermediate: 0 votes (0%)
C. High: 0 votes (0%)



POLICY ROUNDTABLE

Policy Roundtable Participants

Policy Roundtable Participants	
Leslie Fish, PharmD Vice President of Pharmacy, Fallon Health	**William Shrank, MD, MSHS** Senior Vice President, Chief Scientific Officer and Chief Medical Officer, Provider Innovation and Analytics, CVS Health
Dolores Mitchell Executive Director, Group Insurance Commission	**Thomas Siepka, RPh, MS FACHE** Vice President, System Pharmacy and Outreach, Dartmouth Hitchcock
Jonathan Karas Patient Representative	**Paul Thompson, MD** Chief of Cardiology, Hartford Hospital Professor of Medicine, University of Connecticut
Patrick O'Gara, MD Senior Physician, Brigham and Women's Hospital Professor of Medicine, Harvard Medical School	

Meeting Adjourned

Next Steps

- Final Report and accompanying materials: Expected in early December.
- Meeting materials and outputs: http://tinyurl.com/o7krgs7

For more information please visit cepac.icer-review.org