MARCH 2021

Summary

WHAT IS ATHEROSCLEROTIC CARDIOVASCULAR DISEASE (ASCVD)?

ASCVD encompasses a set of common, complex, and burdensome conditions with coronary artery disease, peripheral artery disease, and cerebrovascular disease as the three most prevalent types. Almost 1 in 10 people are estimated to have some form of ASCVD, and ASCVD remains the leading cause of death in the United States. There are significant disparities in ASCVD burden by race and sex, with Hispanic and non-Hispanic Black men and women at higher risk of death compared with White men. One important condition that predisposes people to ASCVD, often much earlier than the general population, is familial hypercholesterolemia (FH), a genetic disease that causes very high cholesterol levels.

Treatment of patients with FH and established ASCVD includes risk factor modification such as dietary and lifestyle changes and smoking cessation, medical therapy (including lipid-lowering therapies), and when necessary, percutaneous or surgical revascularization.

INTERVENTIONS OF INTEREST

ICER evaluated two new lipid-lowering treatment options in patients with heterozygous FH (HeFH) and established ASCVD:

Bempedoic acid with or without ezetimibe (Nexlizet™ and Nexletol®, Esperion Therapeutics, Inc.): an inhibitor of adenosine triphosphate (ATP) citrate lyase that lowers LDL-C by reducing cholesterol synthesis upstream of HMG Co-A reductase (statin enzyme) and up-regulating LDL receptors.

Inclisiran (Novartis): a double-stranded small interfering RNA agent that inhibits hepatic PCSK9 synthesis. Inclisiran is currently undergoing FDA review, with an anticipated decision expected at the end of this year.

KEY REPORT FINDINGS

- Bempedoic acid provides a new oral treatment option that may be helpful particularly for patients who are not able to take statins; however, a discount of at least 36% discount off its list price would be needed to reach the top end of ICER's benchmark range of $1,600-$2,600 per year.
- Inclisiran substantially lowers LDL-C with limited safety concerns, and with a less frequent regimen that may enhance therapy adherence; ICER recommends an annual health-benefit price benchmark range of $3,600-$6,000.

KEY POLICY RECOMMENDATIONS

- All stakeholders should ensure that the introduction of new therapies for high cholesterol do not exacerbate existing health inequities and should strive to decrease inequity in the health care system by decreasing cost and access barriers for patients to access effective therapies.
- Payers should develop consistent prior authorization criteria for lipid-lowering drugs and assure that the documentary burden and other administrative elements of prior authorization do not create an unreasonable burden on clinicians and patients.
- Manufacturers should seek to set prices that will foster affordability and good access for all patients by aligning prices with independent assessments of the therapeutic value of their treatments. In particular, until cardiovascular outcomes data are available from ongoing trials, Novartis should fulfill its stated intent to set the price of inclisiran at or below the cost-effective range of pricing for PCSK9 inhibitors.

Clinical Analyses

ICER EVIDENCE RATINGS

How strong is the evidence that these therapies improve outcomes in patients with HeFH and established ASCVD?

- The evidence suggests that adding bempedoic acid to usual care with maximally tolerated oral lipid lowering drugs provides a comparable or small incremental net health benefit when compared to background usual care alone ("C+"). This rating, which also applies to bempedoic acid/ezetimibe versus ezetimibe alone, is attributed to the treatment's modest ability to lower LDL-C levels, its safety concerns, and the pending results of ongoing studies. Bempedoic acid may provide an even larger reduction in LDL-C levels among the statin-intolerant sub-population.
- There is uncertainty about the net health benefit is due in part to the lack of data from ongoing clinical outcomes trials that will evaluate the extent to which reductions in LDL-C levels translate into tangible patient benefits. The evidence suggests that adding inclisiran to usual care with maximally tolerated oral lipid lowering therapy provides a net health benefit over usual care alone that is at least small and could be substantial given the substantial reduction in LDL-C and a mechanism of action that suggests a very low risk for significant side effects.

KEY CLINICAL BENEFITS STUDIED IN CLINICAL TRIALS

How effective are these therapies?

	Bempedoic acid vs. usual care		Inclisiran vs. usual care
	Overall Population†	Patients with statin-associated side effects (statin intolerance‡)	Overall Population†
LDL-C Reduction	⬇ Moderate LDL-C reduction (19%)	⬇ Moderate LDL-C reduction, slightly greater than the overall population (24%)	⬇ Substantial LDL-C reduction
Health Related Quality of Life	*No Data*		*No Data*

* Estimated by the placebo arms of clinical trials.

†Overall population: Patients with established ASCVD and/or HeFH who have elevated LDL-C levels despite treatment with maximally tolerated oral lipid-lowering therapy.

‡ Defined in the clinical trials as the inability to tolerate at least two statins at moderate or high doses

Clinical Analyses (continued)

HARMS

Bempedoic acid: Overall, there were more adverse events (AEs) and discontinuation due to adverse events associated with bempedoic acid compared with placebo. AEs of particular interest occurring with more frequency in the bempedoic acid group than the placebo group were tendon rupture, hyperuricemia, gout, and elevated liver enzymes (ALT, AST).

Inclisiran: Overall, there was no difference in the incidence of AEs, serious AEs, and AEs leading to discontinuation of the drug in patients receiving inclisiran compared with those on placebo. The most common treatment-related AE was injection site reaction, which occurred in 5.4% of patients in the inclisiran group versus 0.8% in the placebo group.

SOURCES OF UNCERTAINTY

Bempedoic acid

Trial population: Data are limited to short-term (12 weeks) LDL-lowering in selected populations (trials included very few patients with HeFH or from minority populations).

Lack of outcome data: Impact of the drug on reduction of CV events has not been demonstrated, as outcomes trials are ongoing.

Real world safety: Bempedoic acid's safety profile raises questions about whether the increased risk seen in early trials of hyperuricemia and gout, as well as a risk of tendon rupture, will be important real-world problems.

Inclisiran

Trial population: Trials did not include many patients with statin intolerance or from minority populations, so we are unable to determine if there may be differential effects of treatment or on safety events in these populations.

Lack of outcome data: Outcomes trials are ongoing, and thus there remains some uncertainty regarding whether treatment with inclisiran will translate into reduction in MACE rates comparable to those seen with statins or those with PCSK9 inhibitors.

Economic Analyses

LONG-TERM COST EFFECTIVENESS

Do these treatments meet established thresholds for long-term cost effectiveness?

Drug (compared to statin + ezetimibe)	Bempedoic Acid + Ezetimibe + Statin	Inclisiran* + Ezetimibe + Statin
Cost Per QALY Gained	$186,000	$157,000
Cost Per evLYG	$168,000	$142,000

*We used a hypothetical annual placeholder price of $5,644 based on equivalent pricing to PCSK9 inhibitor drugs from the Federal Supply Schedule as of September 1, 2020 and assuming 2 doses per year. Initial treatment year requires 3 doses.

Economic Analyses (continued)

HEALTH-BENEFIT PRICE BENCHMARKS

What is a fair price for these therapies based on its value to patients and the health care system?

	Annual or Estimated Price	Annual Price to Achieve $100,000 - $150,000 cost-effectiveness threshold range	Change from WAC Required to Reach Threshold Prices	Estimated Net Price within or below range?
Bempedoic acid	$4,018	$1,600 to $2,600	Discounts of 36%-60%	NO
Inclisiran	$5,644 (assumed price)	$3,600 to $6,000	No discount required at placeholder price	YES

The Health Benefit Price Benchmark (HBPB) is a price range suggesting the highest price a manufacturer should charge for a treatment, based on the amount of improvement in overall health patients receive from that treatment, to avoid disproportionately greater losses in health among other patients in the health system due to rising overall costs of health care and health insurance. In short, it is the top price range at which a health system can reward innovation and better health for patients without doing more harm than good. The HBPB for a drug is defined as the price range that would achieve incremental cost-effectiveness ratios between $100,000 and $150,000 per QALY gained or per evLYG.

The HBPB for the annual price for bempedoic acid/ezetimibe in the broad population of eligible patients is from approximately $1,600 to $2,600, representing discounts from WAC of 36% to 60%.

The corresponding HBPB for the annual price of inclisiran in the broad population of eligible patients is from $3,600 to $6,000.

POTENTIAL SHORT-TERM BUDGET IMPACT

How many patients can be treated before crossing ICER's $819 million budget impact threshold?

Bempedoic acid: At the current WAC price, approximately 8% of eligible patients could be treated in a given year without crossing the ICER annual budget impact threshold of $819 million.

Inclisiran: At assumed placeholder price ($5,644 per year), approximately 4.5% of eligible patients could be treated in a given year without crossing the ICER annual budget impact threshold of $819 million.

Voting Results

The Midwest CEPAC deliberated on key questions raised by ICER's report at a public meeting on February 5, 2020. The results of the votes are presented below. More detail on the voting results is provided in the full report.

CLINICAL EVIDENCE

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

A majority of panelists found the following:

- The evidence is not adequate to demonstrate a net health benefit over the entire eligible population when adding bempedoic acid to usual care compared to usual care alone.
- In patients who have statin-associated side effects ("statin-intolerant"), the evidence is adequate to demonstrate a net health benefit when adding bempedoic acid to usual care compared to usual care alone.
- In patients with HeFH, the evidence is adequate to demonstrate a net health benefit when adding bempedoic acid to usual care compared to usual care alone.
- The evidence is adequate to demonstrate a net health benefit when adding inclisiran to usual care compared to usual care alone.

LONG-TERM VALUE FOR MONEY

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

A majority or plurality of panelists found the following:

- At the current pricing, adding **bempedoic acid with ezetimibe** to usual care versus usual care with ezetimibe represents a **low long-term value for money** (low – 13 votes, intermediate – 1 vote, high – 0 votes).
- At the current estimated pricing, adding inclisiran to usual care versus usual care alone represents **a low long-term value for money** (low – 10 votes, intermediate– 4 votes, high value – 0 votes).

Patient population: All adult patients with established ASCVD who have elevated LDL-C levels and are unable to take statins due to statin-associated side effects ("statin intolerant"):

- At the current pricing, adding **bempedoic acid with ezetimibe** to usual care versus usual care with ezetimibe represents **an intermediate long-term value for money** (low – 0 vote, intermediate– 12 votes, high – 2 votes).
- At the current estimated pricing, adding **inclisiran** to usual care versus usual care alone represents **an intermediate long-term value for money** (low – 1 vote, intermediate– 13 votes, high – 0 votes).

Voting Results (continued)

LONG-TERM VALUE FOR MONEY

Patient population: All adult patients with HeFH who have elevated LDL-C levels despite treatment with maximally tolerated lipid lowering therapy:

- At the current pricing, adding **bempedoic acid with ezetimibe** to usual care versus usual care with ezetimibe represents **an intermediate long-term value for money** (low – 0 vote, intermediate– 12 votes, high – 2 votes).
- At the current estimated pricing, adding **inclisiran** to usual care versus usual care alone represents **an intermediate long-term value for money** (low – 1 vote, intermediate– 13 votes, high – 0 votes).

OTHER BENEFITS AND CONTEXTUAL CONSIDERATIONS

Key Takeaways:

- When making judgements of overall long-term value for money for secondary prevention of ASCVD, policymakers should give high priority to the magnitude of the lifetime impact on individual patients of the condition being treated.
- When considering the overall long-term value of money for the effects of BEMPEDOIC ACID when added to maximally tolerated oral lipid-lowering therapy on the following outcome(s), important benefits include the impact on caregivers' quality of life and/or ability to achieve major life goals related to education, work, or family life.

Voting Results (continued)

Contextual Considerations: Relative Priority for all Treatments for ASCVD

	Very Low Priority	Low Priority	Average Priority	High Priority	Very High Priority
Acuity of need for treatment of individual patients based on the severity of the condition being treated	0 votes	5 votes	7 votes	2 votes	0 votes
Magnitude of the lifetime impact on individual patients of the condition being treated	0 votes	2 votes	5 votes	5 votes	2 votes

Voting Results (continued)

Potential Other Benefits or Disadvantages: Adding Bempedoic Acid to Usual Care

	Major negative effect	Minor negative effect	No Difference	Minor positive effect	Major positive effect
Patients' ability to achieve major life goals related to education, work, or family life	0 votes	0 votes	5 votes	9 votes	0 votes
Caregivers' quality of life and/or ability to achieve major life goals related to education, work, or family life	0 votes	0 votes	3 votes	11 votes	0 votes
The problem of health inequity	1 votes	4 votes	9 votes	0 votes	0 votes
Other (as relevant): New treatment option for patients with statin intolerance	0 votes	0 votes	1 votes	9 votes	4 votes

Voting Results (continued)

Potential Other Benefits or Disadvantages: Inclisiran vs. PCSK9 Inhibitors

	Major negative effect	Minor negative effect	No Difference	Minor positive effect	Major positive effect
Patients' ability to achieve major life goals related to education, work, or family life	0 votes	1 votes	10 votes	2 votes	0 votes
Caregivers' quality of life and/or ability to achieve major life goals related to education, work, or family life	0 votes	1 votes	12 votes	1 votes	0 votes
The problem of health inequity	0 votes	0 votes	13 votes	1 votes	0 votes

Policy Recommendations

For All Stakeholders

- All stakeholders should ensure that the introduction of new therapies for high cholesterol do not exacerbate existing health inequities and should strive to decrease inequity in the health care system by decreasing cost and access barriers for patients to access effective therapies.

- All stakeholders should act to help increase awareness about the diagnosis and treatment of high cholesterol and, in particular, address the underdiagnosis and undertreatment of familial hypercholesterolemia (FH).

- Along with encouraging steps to improve diet and exercise, all stakeholders should seek to increase utilization of effective therapies such as statins and ezetimibe for patients with established ASCVD and HeFH. These therapies are backed by extensive evidence, are safe for the vast majority of patients, and are far less expensive than other treatment options.

For Payers

- Payers should develop consistent prior authorization criteria for lipid-lowering drugs and assure that the documentary burden and other administrative elements of prior authorization do not create an unreasonable burden on clinicians and patients.

- Payers should work with clinical experts and patient groups to develop consistent criteria and procedures for demonstrating drug intolerance due to statin associated side effects (SASE).

- Payers should ensure that coverage criteria reflect the status of higher-risk subpopulations for whom therapies may be both more clinically effective and cost effective.

For Manufacturers

- Manufacturers should seek to set prices that will foster affordability and good access for all patients by aligning prices with independent assessments of the therapeutic value of their treatments. In particular, until cardiovascular outcomes data are available from ongoing trials, Novartis should fulfill its stated intent to set the price of inclisiran at or below the cost-effective range of pricing for PCSK9 inhibitors.

- Manufacturers should include measurement of a broad set patient-important outcomes in clinical trials.

For Researchers

- Researchers should seek to standardize definitions of ASCVD, major adverse cardiovascular events (MACE), and SASE (statin intolerance) in clinical trials to facilitate comparison of drugs and assist payers, clinicians, and patients in understanding which groups may benefit from a particular drug therapy.

- Researchers should use real world data to standardize definitions of “adherence to therapy” as part of trials that evaluate adherence and its impact on clinical outcomes.

About ICER

The Institute for Clinical and Economic Review (ICER) is an independent nonprofit research institute that produces reports analyzing the evidence on the effectiveness and value of drugs and other medical services. ICER's reports include evidence-based calculations of prices for new drugs that accurately reflect the degree of improvement expected in long-term patient outcomes, while also highlighting price levels that might contribute to unaffordable short-term cost growth for the overall health care system.

ICER's reports incorporate extensive input from all stakeholders and are the subject of public hearings through three core programs: the California Technology Assessment Forum (CTAF), the Midwest Comparative Effectiveness Public Advisory Council (Midwest CEPAC) and the New England Comparative Effectiveness Public Advisory Council (New England CEPAC). These independent panels review ICER's reports at public meetings to deliberate on the evidence and develop recommendations for how patients, clinicians, insurers, and policymakers can improve the quality and value of health care.

For more information about ICER, please visit ICER's website (www.icer.org).