NATIONAL FORUM
FOR HEART DISEASE & STROKE PREVENTION
1150 Connecticut Ave. NW, Ste. 300, Washington, DC 20036

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Mr. Matt Seidner
Program Manager
Institute for Clinical and Economic Review
Two Liberty Square, 9th Floor
Boston, MA 02109

Dear Mr. Seidner,

Thank you for your willingness to receive feedback from the National Forum for Heart Disease and Stroke Prevention's Value & Access Initiative Steering Committee on ICER's June 13th PCSK9 Inhibitors for High Cholesterol – New Evidence Update[1].

What follows is a summary of feedback from members of the Steering Committee and other partners engaged in the value & access space whose reflections represent the spectrum of stakeholder groups (patients, providers, public health, payers and pharma/biotech). Some members of this Steering Committee indicated that their organizations' respective scientific advisory councils and project review and development committees are reviewing the update, and may respond as individual organizations.

We appreciate being engaged in this process and look forward to continuing to facilitate dialogue between the Steering Committee and ICER; and hope that the feedback provided will constructively inform how evidence review updates evolve.

Positives:

The Steering Committee felt that the following were positive aspects of the New Evidence Update (NEU):

- FOURIER[2] cited as a good quality trial
- Acknowledgement that the 2.2-year duration possibly limited the effect size
- Inclusion of landmark analyses and IMPROVE-IT[3]

Concerns:

The Steering Committee had concerns with the following aspects within the NEU:

- The NEU statement that there was not a trend in the reduction of cardiovascular deaths and that mortality was higher in year 2 than in year 1 is statistically problematic.
    - Concern with NEU interpretation of direction and magnitude of CVD death in second year, when the 95% confidence intervals were wide (HR 1.22, 95% CI 0.88-1.42).
    - Although not specifically stated in the report, the moderate-versus high-intensity statin trials also failed to show reduction in cardiovascular death. So, a lack of CVD death reduction is not necessarily unexpected in a 2.2-year trial evaluating patients already on maximal statin therapy.

- Even though evolocumab reduced heart attack and stroke, and translated into an incremental or better (corresponding to a B+ rating), the NEU gave a therapy rating of a C+ (comparable or better).
    - The conservative C+ rating has been recommended by ICER on the basis of the non-significant trend in cardiovascular death. A hazard ratio of 1.12 in the second year with wide confidence intervals does not constitute a statistically significant trend, as noted above.
    - Insufficient consideration was given to the heterogeneity of treatment benefit based on:[4]
        - (1) the greater absolute reduction in LDL-C levels in patients with higher baseline LDL-C levels, which would be expected to translate into higher reductions in relative risk
        - (2) the absolute risk of the patients being treated, which influences the potential for events prevented, and
        - (3) the number of events prevented drives estimation of cost/benefit.
    - Evidence for a greater CVD risk reduction benefit when LDL-C levels are higher comes from the SPIRE-2 trial[5] of another drug in this class (bococizumab). SPIRE-2 enrolled very high-risk patients with LDL-C $\geq$100 mg/dl (mean 134 mg/dl) and did show CVD event reduction more similar to that observed in the Cholesterol Treatment Trialists' (CTT) meta-analysis (2010) at 1 year.[6] SPIRE-2 included people with cardiovascular disease or diabetes with additional risk factors; 17% were statin intolerant and 4% had familial hypercholesterolemia.
    - Failure to consider the heterogeneity of benefit results in underestimation of benefit in those patients most likely to benefit from PCSK9 monoclonal antibodies (e.g., familial or genetic hypercholesterolemia, or very high or high-risk statin-intolerant patients).
- In addition to the factors for low uptake listed in the NEU, it cites other evidence (two abstracts by Baum et al[7,8]), as well as another report,[9] that support varying and complex approval processes as reasons for limited uptake of the PCSK9.
- The FOURIER population was <25% female, therefore women were underrepresented.

Recommendations:

The Steering Committee offers the following recommendations:

- Factors other than mortality are important to patients (and other stakeholders), including preventing heart attack and stroke. These factors should be weighted more heavily than they are in the NEU.
    - The 2013 ACC/AHA cholesterol guidelines made individuals with clinical ASCVD a Class 1a recommendation ("must treat") with high intensity statins up to age 75, on the basis of 3 clinical trials that showed a reduction in cardiovascular events without a total mortality benefit. It is a major US guideline that considers non-fatal events as criteria for treatment.

- The focus on death is a high standard. The trials are not powered to detect a reduction in mortality (neither total mortality nor cardiovascular mortality). So, it seems unreasonable to expect these trials to meet that standard if that is not what they were powered to do.
- A trial covering a period of 2 years does not constitute a trend. The confidence intervals are very wide, which is an over-interpretation of the data.

- Consider evidence from SPIRE-2, which enrolled people with LDL-C levels over 100 mg/dl and very CVD high-risk with the same annual event rate in the placebo group as FOURIER. Even though the compound used in this trial is not FDA approved, there is information to be learned about this class of drugs from SPIRE-2. That is, very high-risk patients with LDL-C levels $\geq$ 100 mg/dl received the expected CVD risk reduction benefit from a PCSK9 inhibiting monoclonal antibody.

- The NEU should address the specific populations whom treatment with PCSK9 mAbs is most likely to benefit: High-risk people whose LDL–C remains elevated despite maximally-tolerated statin therapy.
  - Several types of patients have numbers needed to treat (NNT) that may provide cost-effectiveness at currently acceptable levels with discounting, and there are some patients at very high risk and high LDL-C levels where PCSK9 mAbs appear to be cost effective without discounting[10]. This is lost in the evidence summary.

Sincerely,

Members of the Value & Access Steering Committee representing the following organizations:

National Forum for Heart Disease & Stroke Prevention (convener)
Academy of Managed Care Pharmacy
American Association of Heart Failure Nurses
American Pharmacists Association Foundation
American Society for Preventive Cardiology
Association of State and Territorial Health Officials
BallengeRx Consulting
FH Foundation
Independent Health
Mended Hearts
National Association of Chronic Disease Directors
National Lipid Association
Partnership to Improve Patient Care
Preventive Cardiovascular Nurses Association
University of Michigan Center for Value-Based Insurance Design
U.S. Food & Drug Administration – Dr. Fred Senatore
WomenHeart

References

[1] Institute for Clinical and Economic Review. 2017. PCSK9 Inhibitors for High Cholesterol – New Evidence Update. https://icer-review.org/wp-content/uploads/2017/06/ICER_PCSK9_NEU_Clinical_061317.pdf

[2] Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. *New England Journal of Medicine* 2017;376(18):1713-22. doi: 10.1056/NEJMoa1615664

[3] Cannon CP, Blazing MA, Giugliano RP, et al. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. *New England Journal of Medicine* 2015;372(25):2387-97. doi:10.1056/NEJMoa1410489

[4] Robinson J, Huijgen R, Ray K, et al. Determining When to Add Constantin Therapy: A Quantitative Approach. *J Am Coll Cardiol* 2016;68:2412-21.

[5] Ridker PM, Revkin J, Amarenco P, et al. Cardiovascular Efficacy and Safety of Bococizumab in High-Risk Patients. *New England Journal of Medicine* 2017;376(16):1527-39. doi: 10.1056/NEJMoa1701488

[6] Cholesterol Treatment Trialists Collaboration. Efficacy and Safety of More Intensive Lowering of LDL Cholesterol: a Meta-analysis of Data From 170,000 Participants in 26 Randomised Trials. *Lancet* 2010;376:1670-81.

[7] Baum S, Chen C, Rane PB, et al. Characteristics of Patients Approved and Denied Access to PCSK9i Therapy by Payers. American College of Cardiology; March 17-19, 2017, 2017; Washington, D.C.

[8] Baum S, Chen C, Rane PB, et al. Time to Approval in Patients Requesting Access to PCSK9i Therapy by Payers. American College of Cardiology; March 17-19, 2017, 2017; Washington, D.C.

[9] Knowles JW, Howard WB, Karayan L, et al. Access to Nonstatin Lipid-Lowering Therapies in Patients at High Risk of Atherosclerotic Cardiovascular Disease. *Circulation* 2017;135(22):2204-06. doi: 10.1161/circulationaha.117.027705

[10] Robinson J, Huijgen R, Ray K, et al. Determining When to Add Nonstatin Therapy: A Quantitative Approach. *J Am Coll Cardiol* 2016;68:2412-21.