INDIAN HEALTH SERVICE
National Pharmacy and Therapeutics Committee
Formulary Brief: *Cardiovascular Disease Update*
-January 2025-

Background:

The Indian Health Service (IHS) National Pharmacy and Therapeutics Committee (NPTC) provided a review of bempedoic acid (+/- ezetimibe), colchicine, icosapent ethyl, and semaglutide for the treatment or prevention of major adverse cardiovascular events (MACE). Semaglutide is currently listed on the IHS National Core Formulary. New research supports the additional indication of secondary cardiovascular disease prevention (CVD) in overweight patients without diabetes. Despite initially promising results, the Committee identified too many issues in terms of efficacy and/or safety to recommend bempedoic acid, colchicine, or icosapent ethyl for formulary addition. As such, no modifications were made to the National Core Formulary.

Discussion:

Semaglutide:

The SELECT trail randomized 17,604 patients ≥45 years old with a Body Mass Index (BMI) ≥27 (mean 33.3) with established CVD to either placebo or semaglutide (titrated to a goal of 2.4mg) for a median of 39 months. Patients with diabetes were excluded at the start of the trial, although 66.4% met the A1c criterion for prediabetes. Semaglutide showed efficacy against the MACE primary outcome (HR 0.80, CI: 0.72-0.90, p<0.001). While it narrowly missed a statistically significant reduction in cardiovascular death, it was associated with reductions in death from any cause (HR 0.81, CI: 0.71-0.93) and a heart failure composite (HR 0.82, CI: 0.71-0.96).[1]

Adverse events (AEs) were not increased beyond the well-known issues of gastrointestinal (GI) and gallbladder complications. Reassuringly, there were numerically fewer cases of acute pancreatitis in the semaglutide group, and an essentially equal number of neoplasms in both the treatment and placebo groups.

Bempedoic Acid:

The CLEAR Outcomes trial randomized 13,970 patients 18-85 years old with CVD or at high-risk for CVD to placebo or bempedoic acid (180mg po daily) for a median of 40 months. Patients were required to sign a statement that they were statin unwilling or statin-intolerant due to adverse effects, although they were allowed to take a very low statin dose or any other lipid-lowering therapy. Bempedoic acid demonstrated efficacy against the MACE primary outcome (HR 0.87, CI: 0.79-0.96, p=0.004).[2]

Overall, AEs, serious AEs, and withdrawal AEs did not significantly differ from placebo, but gout and cholelithiasis were increased, with a number needed to harm (NNH) of 100 for each. Bempedoic acid was also associated with an increase in renal impairment events (NNH=34), but the authors do not provide sufficient data to evaluate the significance of this finding.

While current guidelines[3–5] recommend ezetimibe for patients meeting the inclusion criteria of the CLEAR Outcomes trial, and available evidence demonstrates benefit[6], only 11.5% of participants reported taking ezetimibe. While the effect on biomarkers is promising,[7] the point estimate for the ezetimibe subgroup in the CLEAR Outcomes trial suggests minimal benefit (HR 0.94, CI: 0.74-1.2).

There was a significant difference in outcomes between the primary and secondary prevention subgroups (p=0.03). While overall mortality was significantly decreased in the primary prevention group (HR 0.73, CI: 0.54-0.98), an upward trend in mortality was noted in the secondary prevention group (RR 1.15, CI: 0.99-1.33).[8] While these subgroup secondary endpoints may be due to chance alone, the possibility of causing increased death warrants caution.

Icosapent Ethyl:

The REDUCE-IT trial included 8179 patients ≥45 years old with CVD or ≥50 years old with diabetes mellitus plus ≥1 additional CVD risk factor. All patients had fasting triglyceride levels between 200-499mg (median 216) and LDL values between 41-100 mg/dL. They were randomized to either a mineral oil placebo or 2gm twice daily of icosapent ethyl for a median of 4.9 years. Icosapent ethyl reduced the MACE primary outcome (HR 0.75, CI: 0.68-0.83) and was associated with a reduction in cardiovascular death (HR 0.80, CI: 0.66-0.98) but not all-cause mortality.[9] This trial was the first trial of fish oil derivatives to demonstrate benefit after several negative trials. Guidelines recommend icosapent ethyl for patients meeting the inclusion criteria of this study.[3,4,10]

While serious AEs and withdrawal AEs did not differ between treatment groups, patients treated with icosapent ethyl experienced more hospitalizations for atrial fibrillation (AFib) (NNH=71, *p*=0.003). Post hoc subgroup analysis suggests that this risk may be mitigated by excluding patients with a history of AFib.[11]

The mineral oil used in the placebo arm was not biologically inert. For instance, after 2 years of placebo, LDL levels increased over baseline by 11.4%, highly sensitive C-Reactive Protein by 32.3%, and apolipoprotein B by 7.8%. These biomarker changes raise the possibility that the apparent benefits of icosapent ethyl may, in fact, be exaggerated by the added harms from taking mineral oil.

While 6.5% of study participants were reportedly taking ezetimibe, it is not known to have benefit in this clinical setting. Ezetimibe does however have a modest effect on triglycerides.[12]

Colchicine:
The LoDoCo2 trial randomized 5478 patients 35-82 years old with CVD to either placebo or colchicine 0.5mg/day for a median of 28 months. Colchicine reduced the MACE primary outcome (HR 0.69, CI: 0.57-0.83, *p*<0.001).[13] Based on this trial, an FDA indication for the reduction of MACE was granted for colchicine 0.5mg/day. Note that this dosing is not available as a generic in the United States. Generic formulations are 0.6mg, which are approved for gout treatment only.

In contrast, the CLEAR trial randomized 7062 patients who underwent percutaneous coronary intervention for an ST-elevation myocardial infarction (95%) or "large" non-ST elevation MI (5%) to either placebo or colchicine 0.5mg/day or spironolactone 25mg/day in a 2x2 factorial design for a mean of 3 years. In this trial, colchicine had no effect on any endpoint, including the MACE primary endpoint.[14]

Findings:

- Ezetimibe should be considered for patients who are statin-intolerant or unable to meet lipid goals with statins alone.
- Semaglutide decreases MACE when used for secondary CVD prevention in patients with obesity.
- Bempedoic acid decreases MACE for statin intolerant patients, but there is uncertainty regarding long-term renal outcomes, lack of clinical benefit when added to ezetimibe, and increased mortality when used for secondary prevention.
- Icosapent ethyl is superior to mineral oil for primary and secondary prevention of CVD in patients with triglycerides uncontrolled by statins alone, but how much of this superiority is due to the harms of mineral oil is uncertain. Hospitalizations for AFib may possibly be mitigated by avoiding icosapent ethyl in patients with a history of AFib.
- Colchicine studies present contradictory data for CVD prevention.

If you have any questions regarding this document, please contact the NPTC at IHSNPTC1@ihs.gov . For more information about the NPTC, please visit the NPTC website.

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