POEMs

Semaglutide Reduces CV Events in High-Risk Patients with Type 2 Diabetes Mellitus

Clinical Question

Does semaglutide reduce the likelihood of subsequent cardiovascular (CV) events in patients with type 2 diabetes mellitus and known CV or chronic kidney disease?

Bottom Line

Semaglutide significantly reduced the composite outcome of CV death, nonfatal myocardial infarction, and nonfatal stroke (number needed to treat [NNT] = 43 over 2.1 years). It was generally well tolerated, and it reduced body weight by approximately 6.4 to 9.5 lb (2.9 to 4.3 kg). Although pricing is not available, similar drugs are priced at approximately $700 per month in the United States. One harm was a small increase in complications of retinopathy, especially vitreous hemorrhage. It is important to remember that this was a very high-risk group with a mean age of 65 years; most had known ischemic heart disease. (Level of Evidence = 1a)

Synopsis

Semaglutide is a glucagon-like peptide-1 analogue that has a long half-life, allowing once-weekly administration as a subcutaneous injection. This study was designed as a noninferiority trial to demonstrate that the drug does not increase the risk of adverse CV events. The authors recruited a high-risk group of patients: 50 years or older with known CV disease or chronic kidney disease, or 60 years or older with at least one CV risk factor. The authors screened 4,346 patients for inclusion and ultimately included 3,297 patients who were randomized to receive semaglutide or matching placebo injections once weekly.

Patients were started at a dosage of 0.25 mg per week for four weeks, and then half of those in the intervention group were escalated to a final dosage of 0.5 mg per week and the other half to a final maintenance dosage of 1.0 mg per week. Groups were balanced at baseline with a mean age of 65 years and a mean duration of type 2 diabetes of 14 years; 61% were men. Most (93%) had hypertension, and 60% had documented ischemic heart disease. Patients were followed for a median of 2.1 years, and analysis was by intention to treat.

The primary outcome was a composite of CV death, nonfatal myocardial infarction, or nonfatal stroke, and occurred significantly less often in the semaglutide group than in those given placebo (6.6% vs. 8.9%; $P = .02$ for superiority; NNT = 43 over 2.1 years). The reduction was primarily due to fewer nonfatal events; there was no difference in CV deaths (2.7% vs. 2.8%; P = not significant). Glycemic control was better in the intervention group, with A1C decreasing from 8.7% to 7.3% or 7.6% (depending on the dosage) compared with a decrease from 8.7% to 8.3% in the placebo group. Body weight decreased by 6.4 to 9.5 lb in the intervention group. The need for revascularization was lower in the semaglutide group (5.0% vs. 7.6%; $P = .003$; NNT = 38), but the likelihood of complications of retinopathy was higher (3.0% vs. 1.8%; $P = .02$; number needed to treat to harm = 83). Death from any cause was unchanged. There was no difference in severe hypoglycemic events, but gastrointestinal symptoms were more common in the intervention group (withdrawal because of gastrointestinal symptoms: 1.1% in the placebo group, 5.7% in the 0.5-mg group, and 9.4% in the 1.0-mg group).

Study design: Randomized controlled trial (double-blinded)

Funding source: Industry

Allocation: Uncertain

Setting: Outpatient (any)

Reference: *Marso SP, Bain SC, Consoli A, et al.; SUSTAIN-6 Investigators. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes.* N Engl J Med. *2016;375(19):1834-1844.*

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