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Learning objectives	• Describe glucagon-like peptide 1 (GLP-1) receptor agonists mechanism of action, the positive effects in control of diabetes mellitus (DM), obesity/weight loss, cardiovascular, GI, renal, and MSK systems, and the potential complications of treatment. • Discuss the indications and the beneficial effects of dual antiplatelet therapy (DAPT) for transient ischemic attack (TIA) or stroke and the importance of timing the initiation of therapy. • Compare conservative therapies with arthroscopic surgery for meniscal tears. Discuss evidence in support of non-operative treatment for knee pain from meniscal injury or degenerative joint disease. • Explain the role of monoclonal antibody therapy for early Alzheimer's Disease and mild cognitive impairment (MCI). Highlight outcomes of phase III trials using candidate drugs in early Alzheimer's Disease.

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Glucagon-like peptide-1 receptor agonists (GLP-1RA) indications, risks, costs

Several glucagon-like peptide-1 receptor agonists (GLP-1RAs) are available in the United States and share the same mechanisms of action.[1] Examples of these drugs include semaglutide and liraglutide. A third molecule, tirzepatide, has a dual effect combining GLP-1RA with a second mechanism of action via glucose-dependent insulinotropic polypeptide (GIP) agonism.[2]

Mechanism of action and positive effects in control of diabetes mellitus (DM)

These drugs work on receptors in the pancreas to support beta-cells, increasing insulin release and decreasing glucagon release. This leads to lower blood sugar levels but in a glucose-sensitive manner that minimizes risk of hypoglycemia. Additional effects that help treat DM include delayed gastric emptying, increased muscle uptake of glucose, decreased gluconeogenesis and increased satiety. The range of reduction in HbA1c is 0.8%-1.5%.[3]

Mechanism of action and positive effects in obesity or weight loss

Increased satiety and delayed gastric emptying are the predominant beneficial effects when these drugs are used to treat obesity. A significant portion of this increased satiety is related to the direct CNS effects of the GLP-1RAs. Recent trials focused on the use of semaglutide and tirzepatide for obesity in patients without diabetes have demonstrated highly significant median weight loss of 16% with semaglutide at the 2.4 mg weekly dose[4] and 22% total body weight with tirzepatide at the 15 mg weekly dose.[5] Clinically meaningful weight loss effects as well as sustained reductions in HgbA1C have been maintained for over 7 years.[6]

Mechanism of action and positive effects on the cardiovascular, GI, renal and MSK systems

This drug class has positive effects on the cardiovascular system as well, with decreased total cholesterol and blood pressure, and improved left ventricular ejection fraction, coronary artery blood flow, endothelial function, myocardial contractility and cardiac output. It is important to recognize that a class effect of these drugs is an elevation of the heart rate, which may be as much as 6–10 bpm with some drugs in this class.[7] However, adverse effects related to this increased heart rate have not been documented. These beneficial effects are independent of, but may be further augmented by, the glucose-lowering and weight-reduction benefits. Many randomized controlled trials and cohort studies have demonstrated beneficial clinical results of several drugs in these categories in treating DM, DM with cardiovascular disease, diabetic kidney disease, obesity and related complications from adiposity-based chronic diseases such as non-alcoholic fatty liver disease[8, 9, 10] (NAFLD, and metabolic associated fatty liver disease [MAFLD]). Significant and sustained weight loss should reduce severity of hip and knee arthritis as well as the need for hip and knee arthroplasty, and potentially reduce the burden and costs of managing chronic low back pain. Observational studies are ongoing but there are no definitive data at this point.

Potential complications of treatment

Despite the promising results, the side effects and the direct costs of these drugs should temper indiscriminate prescribing. Once started, these drugs may need to be continued indefinitely to maintain any positive results. Data shows the beneficial effects on measures such as BMI, blood pressure and lab results revert to baseline after discontinuation.[11] Side effects include gastrointestinal (GI) upset (nausea/vomiting, constipation or diarrhea and in severe cases, gastroparesis) that commonly results in patient intolerance and discontinuation, with some evidence that over half of patients will stop the medication.[12] These short-term side effects can be managed with slow and careful dose titration and short-term use of ondansetron and laxatives as needed for symptom control. In many patients, the full therapeutic benefit in terms of weight and HbA1c reduction may be obtained at lower than full dose treatment, therefore full dose escalation may not always be necessary.

The positive effects on weight reduction can lead not only to a reduction in adiposity, but to overall weight reduction, including loss in skeletal muscle mass. For example, data from the SURMOUNT-1 tirzepatide study showed that fat mass dropped between 33% and 36% and lean mass by 10% to 11%, depending on the age group. In other words, roughly one-quarter of the weight lost in that study was lean mass. For context, some degree of lean muscle mass loss is normal in most weight loss scenarios, as the body tends to shed both fat and some lean tissue when losing weight.[2] This extreme weight loss, coupled with the benefits outlined above on DM, may also result in a reduced need for other medications, including medications for diabetes and hypertension. If not recognized early and managed with medication adjustments, this can result in hypoglycemia and/or hypotension. Again, slow and careful dose titration is indicated, with concomitant evaluation for reducing or eliminating other anti-diabetic and antihypertensive medications.

Drug cost must be considered when prescribing and may necessitate exploring alternative guideline-directed medical therapies. For example, an article summarized in this issue of the Forum demonstrates the cost of GLP-1RA therapy to avoid one major adverse cardiac event (MACE) over a 3-year period in someone who is obese and with cardiovascular disease is $3.2 million.[13] As a primary CV prevention strategy, this is clearly not feasible and sustainable from a population perspective. However, there is some evidence that for high-risk individuals such as those with DM and cardiovascular disease, drug costs may be offset by reductions in hospitalization costs.[14] Unfortunately, both Novo Nordisc (semaglutide) and Lilly (tirzepatide) priced all doses of their drugs the same, such that dose reduction cannot be used as a strategy to reduce drug costs.

Semaglutide can reduce cardiovascular risk, but at a cost

Glucagon-like peptide-1 (GLP-1) agonists have been shown to reduce major adverse cardiovascular events (MACE) in patients with type 2 diabetes mellitus and obesity.[15] A recent study published in the *New England Journal of Medicine* demonstrates the benefit of the GLP-1 agonist semaglutide in reducing MACE in obese patients with known cardiovascular disease, even in the absence of diabetes.[16] Based on study findings and the dose prescribed, at the list price of $16,000 per year, the number needed to treat is 66 over 3 years to avoid one event, yielding an approximate price tag of $3.2 million to prevent one event over the 3-year period. If this analysis was extended to a population of patients without preexisting CVD, the costs would be even much higher. From the societal perspective, this is not cost-effective. The study included over 17,000 patients with obesity and evidence of cardiovascular disease, excluding those with diabetes, end-stage renal disease, or advanced heart failure. Half were assigned to the semaglutide group and half to placebo. Primary endpoints examined included death from cardiovascular causes, nonfatal myocardial infarction, and nonfatal stroke, and favored the semaglutide group (hazard ratio, 0.80; 95% confidence interval [CI], 0.72 to 0.90; P<0.001). Additional endpoints included heart failure and death from any cause, both also significantly better in the semaglutide group. Serious adverse events were reported in 33.4% in the semaglutide group and 36.4% in the placebo group. Mean change in body weight at 104 weeks after randomization was -9.39% in the semaglutide group and -0.88% in the placebo group.

Although not used in the study, tirzepatide, another GLP-1 agonist with similar properties to semaglutide, is priced about 25% less.[17] If the findings of the study could be replicated with this medication, the cost to avoid one event would drop to roughly $2.4M, still quite high and not meeting accepted criteria for cost-effectiveness.

This drug class shows great promise in safely managing obesity with cardiovascular disease. At present, however, it is priced in a manner to preclude widespread use for the indication of reducing MACE.

DM2 failing metformin – prescription and discontinuation patterns of the non-insulin drug classes

Little is known about the prescribing and discontinuation rates of the various non-insulin drug classes used as second-line therapy in patients with type 2 diabetes mellitus (T2DM) failing metformin monotherapy. Although there are evidence-based recommendations around both improved outcomes and cost-effectiveness for the use the SGLT2i category for patients with heart failure, CAD, and CKD, for other patients the choice of second-line therapy should be a shared decision-making approach with patients including the relative costs and benefits of each drug class. With respect to sulfonylurea use, we know from the CAROLINA trial,[18] that after over 6 years of follow-up, compared to the DPP-IV class which is weight neutral and does not impact MACE, that the short acting sulfonylureas (glimepiride in this case) also had no increase in MACE compared to the DPP-IVs. Moreover, the weight gain at the end of the 6 years was minor at 3.4 pounds. Severe hypoglycemia occurred in approximately 1:200 patient years in the sulfonylurea group.

Added to this body of literature is a new retrospective cohort study that examined claims from over 82,000 patients with T2DM who had failed or didn't tolerate metformin therapy and were initiated on non-insulin therapies between 2013 and 2017.[19] 43% of patients were in commercial health plans and 57% were in Medicare. In terms of which drugs were started as second-line treatment, 52% were sulfonylureas, 24% were DPP-IV, 11.6% were SGLT2i, 8% were GLP-1RA, and 5% were TZD.

38.6% of patients discontinued their secondary drug. With respect to discontinuation by the specific drug class, the highest rate of discontinuation was with the GLP1-RAs, where over half were stopped. The discontinuation rates were fairly uniform for the other drug classes in the range of 35%. The high rate of DPP-IV use is hard to understand given that they are priced at about $5,500 yearly, they are of relatively low efficacy, are not associated with improvements in cardiac or renal outcomes, and don't promote weight loss. On the other hand, given the prevalence of CKD, CHF and CAD in the population of patients with T2DM, it is likely that the SGLT2is were under-prescribed. In the absence of heart failure, ≥ 3 CV risk factors, or CKD, the cost effectiveness of the sulfonylureas supports their high utilization in this study.

Dual antiplatelet therapy for TIA/Stroke

Patients with acute mild ischemic stroke or transient ischemic attack (TIA) have a risk of recurrent stroke of approximately 5% to 10% within 90 days after the onset of the initial event. The timing of initiation of dual antiplatelet therapy (DAPT) is critical as the highest risk of recurrence is immediately following the index event. Prior studies have shown that when aspirin and clopidogrel are initiated within 24 hours, there is a significant reduction in the progression to completed stroke without an increase in severe bleeding.[20] A recent study looked at whether increasing that time window to 72 hours would still result in a reduction of the completed stroke rate.[21] As DAPT is likely to be most effective in those patients with unstable plaque in large vessels, the patient population was those patients with at least 50% stenosis of a major intracranial or extracranial artery, as confirmed by carotid duplex ultrasonography or vascular imaging, that was likely to have accounted for the clinical presentation and cerebral infarction; or acute new multiple infarctions (documented by computed tomography or magnetic resonance imaging of the head) of presumed large-artery atherosclerosis origin, including those with non-stenotic, unstable plaque ipsilateral to the infarction.

6100 eligible patients were randomly assigned in a 1:1 ratio within 72 hours after symptom onset to receive combined clopidogrel plus aspirin or matching clopidogrel placebo plus aspirin. Patients were studied for the incidence of any new stroke, MACE, or significant bleeding occurring within 90 days of randomization. 87% of the patients presented with stroke and 13% with TIA. A new stroke within 90 days occurred in 222 patients (7.3%) in the clopidogrel–aspirin group and in 279 patients (9.2%) in the aspirin group (hazard ratio, 0.79; 95% confidence interval [CI], 0.66 to 0.94; P=0.008). Stroke and/or MACE occurred in 229 patients (7.5%) in the clopidogrel–aspirin group and in 282 patients (9.3%) in the aspirin group (hazard ratio, 0.80; 95% CI, 0.67 to 0.96). Moderate-to-severe bleeding occurred in 27 patients (0.9%) in the clopidogrel–aspirin group and in 13 patients (0.4%) in the aspirin group (hazard ratio, 2.08; 95% CI, 1.07 to 4.04; P=0.03).

These data support extending the window of a beneficial effect to DAPT for TIA or mild ischemic stroke to 72 hours, and in the absence of contraindications to DAPT, this should be considered the standard of care for patients presenting with these conditions.

Arthroscopy for meniscal tears (still) rarely indicated

Previous articles in this Forum for Evidence-Based Medicine as well as the Optimal Care Measure Brief addressing knee arthroscopy in people >35 years have summarized the robust evidence in support of non-operative treatment for knee pain from meniscal injury or degenerative joint disease.[22] Two recent studies extend the evidence in favor of conservative therapies over arthroscopic surgery to include younger patients with traumatic and non-traumatic meniscal tears. The first examined both objective evidence of structural damage as well as subjective evidence of benefit at two years after the index MRI and diagnosis of meniscal tear. This prospective randomized study compared surgery or exercise for meniscal tears in patients aged 18–40 years old.[23] Exclusion criteria were prior surgery of the affected knee, fracture of that knee in the preceding year, complete knee ligament rupture, or participation in supervised exercise within the preceding 3 months. Additionally, patients were excluded if they had MRI-confirmed congenital discoid meniscus or clinical suspicion of displaced bucket handle tear. All other types of tears were included.

The 121 patients were randomized to receive knee surgery (either arthroscopic partial meniscectomy [APM] or meniscal repair, with choice left to the discretion of the surgeon) or to receive supervised exercise therapy two times per week and patient education over a 12-week program. Those randomized to the exercise group had the option to undergo knee surgery later, with 16 of the 61 patients (26%) ultimately having surgery. All patients received an online questionnaire that included KOOS[4] and WOMET (two validated patient-reported outcome measure instruments for knee pain and function[24,25]) at 3, 6, 12 and 24 months. They also had a repeat MRI at 24 months with findings graded based on a validated semiquantitative scoring system (ACLOAS[26]), appropriate blinding, and robust inter-rater agreement of the radiologists. Anatomically, the groups did not appear to differ. Baseline and 2-year MRI findings were essentially the same in both groups with no evidence of worsening cartilage damage or osteochondral damage in the exercise therapy group. There was a trend towards increased osteoarthritis progression in the surgical group (osteophytes present in 17% of surgical patients compared to none in the exercise group), which did not quite meet statistical significance. Patient-reported outcomes also were essentially the same between groups.

The second study demonstrated that physical therapy for traumatic meniscal tears in patients aged 45 and younger was more cost-effective than APM.[27] This study was also of patients with MRI-verified meniscal injury, also with a 24-month follow-up period. It examined costs per quality-adjusted life years (QALY) gained using a healthcare system and societal perspective. Of the 100 patients, roughly half were randomized to undergo APM and half to receive physical therapy, with an option for APM after 3 months. Twenty-one (41%) of the patients randomized to physical therapy eventually underwent surgery during the study period. There was no significant difference in quality of life at 24 months between the two groups, indicating the additional costs of surgery do not add any health benefit.

Two phase 3 trials of gantenerumab in early Alzheimer's Disease

Monoclonal antibody therapy for early Alzheimer's Disease and mild cognitive impairment (MCI) continues to be highly controversial. Multiple phase III trials of candidate drugs have failed to show improvement despite substantial clearing of amyloid plaque on PET/CT. Aducanumab and lecanemab have received FDA approval despite only slight improvements on research cognitive scales, and it is uncertain whether this will translate to meaningful real-world slowing of cognitive decline and clinical improvements. Donanemab is expected to soon be the third drug to receive FDA approval. Amyloid-related imaging abnormalities with edema (ARIA-E) are common, and serious related adverse events have occurred with all drugs in this class.

Recently, two phase III trials of gantenerumab were reported, studying in total close to 2,000 patients with early Alzheimer's Disease or MCI.[28] The results indicated that this was another failed molecule with no significant improvement in cognitive scores despite 27.5% of patients achieving complete amyloid clearance on PET/CT. ARIA-E was seen on imaging in 25% of patients.

Going forward with the approved medications in this drug class, it will be critical to assess whether there is a significant real-world benefit of the small observed reductions in cognitive decline. This along with other measures of effectiveness to include the ability to function independently in the home, assessment of benefits according to caregivers, quality of life, and frequency and severity of side effects needs to be studied. Lilly has planned a phase IV trial of donanemab to address all of the above and many of our neurology practices, in partnership with OCRI, will be participating in this important trial.

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