patients with T2D and BMI ≥27 kg/m^2.[23] Orlistat, lorcaserin, liraglutide, naltrexone/bupropion sustained release, and phentermine/topiramate are US Food and Drug Administration (FDA)-approved for weight management with demonstrated cardiovascular safety and the additional benefit of A1c lowering.[69,70] If weight loss after 3 months is <5% or safety issues arise, the medication should be discontinued and alternative medications or treatment approaches should be considered.[23] Long-term cardiovascular event reduction has not been formally tested, but notable cardiovascular risk reduction was shown for liraglutide at lower doses among those with ASCVD or high cardiovascular risk.[71] Non-weight loss–approved medications commonly used in T2D lower weight, including pramlintide, sodium-glucose cotransporter-2 inhibitors (SGLT-2Is), metformin, and other glucagon-like peptide 1 receptor agonists (GLP-1RA).[69] Further studies are ongoing to determine the combinations of these therapies that may be most beneficial for weight loss.[69,70]

The recently published STEP (Semaglutide Treatment Effect in People with Obesity) 1,[72] STEP 2,[73] STEP 3,[74] and STEP 4[75] trials demonstrate the tremendous impact of once weekly GLP-1RA treatment with semaglutide on weight loss and cardiovascular risk factors. The STEP 2 trial specifically evaluated individuals with diabetes taking ≤3 oral hypoglycemic agents at baseline with BMI of ≥27 kg/m^2.[73] Average bodyweight reductions were 9.6%, 7.0%, and 3.4% with semaglutide 2.4 mg, 1.0 mg, and placebo, respectively, over 68 weeks combined with lifestyle intervention (counseling provided every fourth week to maintain a 500 kcal per day reduction relative to the estimated total daily energy expenditure and 150 minutes per week of physical activity).[73] Cardiovascular risk factors improved significantly on semaglutide 2.4 mg daily with reductions in A1c, glucose, very-low-density lipoprotein cholesterol, free fatty acids, triglycerides, and C-reactive protein.[73] The findings of STEP 1 and STEP 3 were consistent with STEP 2 in duration but were conducted among participants without diabetes. Both trials exhibited significant weight loss on the semaglutide 2.4 mg daily (14.9% and 16.0%, respectively), [72,74] with similar cardiovascular risk factor reduction. In STEP 1, among participants with prediabetes at baseline, 84% reverted to normoglycemia on intervention versus 48% in the control.[72] STEP 4 demonstrated the importance of long-term therapy with GLP-1 RAs by evaluating semaglutide 2.4 mg for the first 20 weeks, after which participants were randomly assigned to receive either semaglutide or placebo for the remaining 48 weeks.[75] The semaglutide 2.4 mg group had sustained weight loss over the 68 weeks, whereas the placebo group experienced weight regain and worsening of cardiovascular risk factors from weeks 21 to 68.[75] Gastrointestinal side effects were common with semaglutide, but rates of discontinuation were similar to placebo. Thus, once weekly semaglutide 2.4 mg delivers impressive weight loss and cardiovascular risk factor improvement and is FDA approved for chronic weight management in adults with BMI ≥30 kg/m^2 or BMI ≥25 kg/m^2 with a comorbid condition (ie, T2D, hypertension, hyperlipidemia).

Surgical Procedures

Growing evidence supports the use of metabolic surgery for the treatment of comorbid obesity in T2D.[23,76] The extant literature from numerous randomized controlled (nonblinded) clinical trials, matched studies, and meta-analyses demonstrate that metabolic surgery achieves superior glycemic control and reduction of cardiovascular risk factors including body weight, fasting glucose, A1c, BP, HDL, and triglycerides in patients with T2D and obesity compared with various lifestyle/medical interventions.[77–79] Improvements in CVD, CVD mortality, and all-cause mortality have been observed in nonrandomized observational studies, matched cohort studies, and meta-analyses (ranging from ≈40% to 80% risk reduction in meta-analyses) with potentially greater benefits for mortality among patients with versus without diabetes.[26,79–81] It is notable that most of the current studies were performed before the increased utilization of SGLT-2Is and GLP-1RAs with proven CVD reduction in T2D. The risk of metabolic surgery includes both short-term (<30 days) and long-term (≥30 days) complications. Short-term complications include postsurgical complications (bowel obstruction, venous thromboembolism, gastrointestinal bleeding, anastomotic leaks, wound infections, etc).[79] Long-term complications include marginal ulceration, cholelithiasis, dumping syndrome, nutritional and vitamin deficiencies, malabsorption, fistulas, etc.[79] At present, perioperative mortality ranges from 0.03% to 0.20%, which continues to improve over time.[79] Thus, a balanced discussion of the procedural and long-term risks and benefits should guide a patient-informed decision.

Metabolic surgery is recommended to treat patients who have T2D with BMI ≥40 kg/m^2 and in those with BMI 35.0 to 39.9 kg/m^2 without durable weight loss and improvement in comorbidities with nonsurgical methods, and should be considered in those with T2D and BMI of 30.0 to 34.9 kg/m^2 without similar improvements.[23] In Asian individuals, these BMI cut points are reduced by 2.5 kg/m^2.[23] In addition to these 2nd Diabetes Surgery Summit (DSS-II) recommendations, the ADA recommends that (1) metabolic surgery should be performed in high-volume centers with experienced, multidisciplinary teams; (2) long-term lifestyle support and routine monitoring of micronutrient and nutritional status must be provided; and (3) people presenting for metabolic surgery should receive comprehensive readiness and mental health assessment.[23]