Cardiovascular Outcomes Using Drugs for Type 2 Diabetes

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**Cardiovascular (CV) risk of type 2 diabetes mellitus (DM):** microvascular complications closely associated with hyperglycemia, but relationship vague; probability of microvascular complications increases as hemoglobin (Hb)A1c increases; association between macrovascular complications and hyperglycemia less vague, and driven by atherosclerosis, hypertension, hyperlipidemia, smoking, and other risk factors; association between DM, hyperglycemia, and CV disease (CVD) debatable; DM trials — no significant improvement in CV outcomes early on; however, microvascular outcomes improved with intensive glycemic control; Action to Control Cardiovascular Risk in Diabetes trial — HbA1c of 6% targeted and 6.4% achieved, but worsening of mortality seen; CV mortality driven by hypoglycemia; ideal HbA1c in DM 6.5% to 7% (HbA1c >7% associated with increased microvascular and possible macrovascular complications; HbA1c <6.5% may cause more harm than good); intensive glycemic control group showed improvement in CV outcomes at 10 yr; DM mortality — associated mainly with CV outcomes; macrovascular complications primary driver of mortality; nearly 80% of deaths due to coronary artery disease (CAD) and stroke; lifestyle modification — study found that no significant CV morbidity or mortality changes achieved with lifestyle modification alone

**Sulfonylureas:** trial data showed no significant difference in CV outcomes between sulfonylureas and placebo; meta-analyses showed slight increase in CV risk; sulfonylureas associated with weight gain and hypoglycemia (especially harmful in patients with CAD or atherosclerosis), which may increase CV risk; sulfonylureas interfere with myocardial ischemic preconditioning; glyburide most often implicated in impairing myocardial ischemic preconditioning (second-generation sulfonylureas, which are not associated with significant hypoglycemia, recommended over glyburide)

**Metformin:** United Kingdom Prospective Diabetes Study looked at patients with newly diagnosed DM and found that reduction in myocardial infarction (MI), CAD, and all-cause mortality higher with metformin (30%-33%) than with sulfonylureas for duration of trial and at 10 yr; first-line drug, regardless of presence of CAD; study of patients with history of CAD found that hazard ratio for major adverse CV event outcomes lower in metformin group than in glipizide group; metformin beneficial in patients with dyslipidemia and associated with effective glycemic control, weight loss, reduction in postprandial lipemia, and stabilization of plaques and endothelial dysfunction in setting of atherosclerosis

**Meglitinides:** sulfonylurea-like agents, but shorter acting (half-life of 3-4 hr; taken before each meal); advantages — decreased risk for hypoglycemia due to shorter half-life; can be used in patients with renal dysfunction

**Thiazolidinediones (TZDs):** 30-day CV mortality study found no difference between TZDs and sulfonylureas; mechanism of action of pioglitazone slightly different from that of rosiglitazone; advantages — insulin sensitizers (beneficial in patients with atherosclerotic disease); improve endothelial dysfunction; favorable effect on CV profile; change fat deposition pattern Disadvantages of rosiglitazone: associated with increase in low-density lipoprotein cholesterol and triglycerides; increased water retention secondary to enhanced renal sodium absorption may cause congestive heart failure (CHF); side effects include fluid overload, weight gain, and possible increased CV mortality; not commonly prescribed

**Pioglitazone:** Prospective Pioglitazone Clinical Trial in Macrovascular Events looked at high-risk patients with history of CAD; showed reduction in MI and stroke; Insulin Resistance Intervention after Stroke trial looked at pioglitazone vs placebo in nondiabetic patients with history of insulin resistance, and found statistically significant reduction (0.76) in risk for stroke; pioglitazone has role in carefully selected patients (ie, no weight issues, no risk for CHF, extremely insulin resistant); not recommended routinely due to increased likelihood of weight gain, edema, and fracture, and increased risk for bladder cancer

**Dipeptidyl peptidase (DPP)-4 inhibitors:** inhibit degradation of glucagon-like peptide-1 (GLP-1; enteric gut hormone that signals presence of food); associated with increased insulin production and release from pancreas (glucose dependent; sulfonylureas glucose independent, which may result in hypoglycemia); retards stomach emptying; decreases output of hepatic glucose; Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus—Thrombolysis in Myocardial Infarction 53 trial found no increased risk for major adverse CV events, but did find statistically significant increased risk for CHF hospitalization; Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care trial found no increase in CV risk and no changes in CHF hospitalization; class as whole neutral from CV standpoint

**Educational Objectives**

The goal of this program is to improve the management of cardiovascular disease in patients with type 2 diabetes mellitus and to achieve weight loss in patients with obesity. After hearing and assimilating this program, the clinician will be better able to:

1. Counsel patients about the risk for adverse cardiac events associated with the use of medications to treat type 2 diabetes mellitus.
2. Select appropriate pharmacologic treatment for diabetic patients who have a history of cardiovascular disease.
3. List the advantages and disadvantages of thiazolidinediones.
4. Explain the mechanism of action of agents commonly prescribed to treat obesity.
5. Choose appropriate antihypertensive medication for a patient with obesity.

**Faculty Disclosure**

In adherence to ACCME Standards for Commercial Support, Audio Digest requires all faculty and members of the planning committee to disclose relevant financial relationships within the past 12 months that might create any personal conflicts of interest. Any identified conflicts were resolved to ensure that this educational activity promotes quality in health care and not a proprietary business or commercial interest. For this program, members of the faculty and planning committee reported nothing to disclose.
Sodium-glucose cotransporter-2 (SGLT2) inhibitors: Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes trial — patients with high CV risk and previous CV event randomized to empagliflozin vs placebo; empagliflozin associated with dramatic reduction in CV mortality, CHF hospitalization, and all-cause mortality; study found reduction in intravascular volume and blood pressure secondary to osmotic diuresis in patients on empagliflozin, as well as loss of calories (≤300 per day) due to excretion of glucose in urine (results in early weight loss and decreased visceral adiposity); beneficial effect on lipid profile observed in some patients

**Guidelines: American Diabetes Association** — metformin first-line agent; no preferred second-line agent; Canadian Diabetes Association — start with metformin and lifestyle modification; in patients with clinical CV disease, consider SGLT2 inhibitor (empagliflozin) with demonstrated CV benefit; recommendation — SGLT2 inhibitor as second-line therapy in patients with established CV disease, able to afford treatment, and not experiencing major side effects

**Suggested Readings**


**Guidelines for Treatment of Obesity**

**American College of Cardiology/American Heart Association**

**Task Force on Practice Guidelines and the Obesity Society Guidelines**

**Evaluation:** identify patients who need to lose weight by measuring height and weight to calculate body mass index (BMI) and waist circumference (WC); discuss BMI and its significance for risk (BMI ≥25 [overweight] associated with increased risk for cardiovascular disease [CVD]; risk for CVD and all-cause mortality higher if BMI >30); advise patients in higher BMI categories that risk for CVD, type 2 diabetes mellitus (DM), and all-cause mortality increases as BMI increases; WC — large WC associated with increased risk for DM, all-cause mortality, and CVD; in whites, cutoff for change of significant risk for CVD, all-cause mortality, and DM is 35 for women and 40 for men; actual measurement of amount of visceral fat that contributes to metabolic components of illness; also changes level of risk in certain ranges of BMI (if BMI 25-30, increases to high risk; if BMI 30-35, increases to extremely high risk); comorbidities due to weight — significant number of obese or overweight individuals already have medical problems caused by or associated with their condition; modest weight loss (3%-5%) can help lower blood glucose (BG) and serum triglycerides and prevent transition from prediabetes to diabetes; even greater weight loss can help lower blood pressure and low-density lipoprotein, increase high-density lipoprotein, and further decrease triglycerides and BG

**Diabetes goal:** 1200 to 1500 per day for women and 1500 to 1800 per day for men (or calorie deficit of 500 or 750 per day); other diets involve not calorie counting but restricting certain classes of food (eg, low-carbohydrate diet); diet, if adhered to, results in average weight loss of 8 kg (5%-10%); prescribe (not recommend) diet

**Lifestyle program:** requirements — ≥6 mo in duration; ≥14 face-to-face visits with trained interventionist (should focus restricting calories to create calorie deficit); increased physical activity and exercise

**Weight maintenance:** part of weight loss program; monthly contact or face-to-face visits for 1 yr after 6-mo weight loss program; more exercise needed than during weight loss phase, because metabolism slows down as result of weight loss; 200 to 300 min/wk of exercise required to maintain weight loss

**Bariatric surgery:** criteria — cutoff BMI of 40 or 35 with comorbidity; should be option for patients who are motivated to lose weight but have failed to respond to behavioral treatment, with or without pharmacotherapy, with sufficient weight loss to achieve targeted health outcome goals

**Pharmacotherapy:** cutoff BMI of 30, regardless of comorbidities (or ≥27 with comorbidities due to weight); discuss medications and surgery during initial evaluation, not after completion of weight loss program; medications can be prescribed at time weight loss program initiated

**Very low calorie diets:** <800 per day; effective; reserved for patients who can be medically supervised in intense lifestyle program; rapid weight loss has possible risks (eg, gallstones, electrolyte abnormalities)

**Endocrine Society Guidelines**

**Antidiabetes medications:** mostly affect signaling through hypothalamus and affect appetite and energy intake

Phentermine: dose 30 to 37.5 mg; sympathomimetic amine (acts as norepinephrine-releasing agent on dopaminergic neurons); trials showed 3.6 kg weight loss compared with placebo; approved only for short-term use due to lack of long-term studies; has stimulant effect on cardiovascular system; contraindications — untreated hyperthyroidism; inadequately treated hypertension; coronary artery disease; pregnancy and breastfeeding (contraindicated for all weight-loss drugs); acute-angle glaucoma

Orlistat: dose 120 mg three times daily; taken with meals that contain fat; lipase inhibitor, so triglycerides in lumen of gut
not broken down and absorbed in circulation; fats excreted in stool; malabsorption of fat-soluble vitamins most common side effect, and may lead to discontinuation; affects absorption and metabolism of some medications, so adjustment of dosage needed; trial—superior to placebo for weight loss (10% vs ∼5%); effective as long as drug taken
Lorcaserin (Belviq): dose 10 mg twice daily; serotonin (5-HT₄) receptor agonist (fenfluramine is nonspecific 5-HT receptor agonist and causes heart valve problems); not associated with heart valve disease; trial showed 3.6% weight loss compared with placebo; contraindicated in pregnancy; can interact with psychotropic medications (e.g., selective serotonin reuptake inhibitors); in trial, weight regained after drug stopped
Phentermine plus topiramate: dose consists of phentermine 15 mg and topiramate 92 mg; 8.6% weight loss compared with placebo; few side effects; contraindications—pregnancy; hyperthyroidism; glaucoma; topiramate is teratogenic and effects occur in early first trimester; avoid in women of childbearing age, unless reliably on 1 or 2 forms of birth control; pregnancy test recommended before starting drug and every month while on drug
Naltrexone plus bupropion: dose consists of naltrexone 32 mg and bupropion 360 mg; start with one pill daily and increase by one pill per week due to common side effect of nausea (from naltrexone component); bupropion works in same pathway as phentermine (similar side effects); superior to placebo for weight loss at 1 yr (8% vs 3%); medications more effective than placebo and effective while being taken and for 1 to 2 yr
Liraglutide: used to treat DM; injectable glucagon-like peptide (GLP)-1 receptor agonist; dose 3 mg; 5.8 kg weight loss compared with placebo; nausea and vomiting common side effects, as well as pancreatitis at higher doses; contraindications include medullary thyroid cancer and multiple endocrine neoplasia type 2 (based on mouse models); stimulates GLP-1 receptors in central nervous system; trial showed 10% to 12% weight loss at 1 yr; trial looked at efficacy for weight maintenance and found additional 8% of weight loss with liraglutide
Other measures: changing medications for comorbid condition to favor weight loss or to prevent weight gain; DM—use first- and second-line agents that are weight neutral or cause weight loss; for patients starting insulin, add another diabetes drug that induces weight loss to prevent weight gain associated with insulin; weight has set point; hypertension—use angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and calcium channel blockers instead of β-blockers; antidepressants—sertraline and fluoxetine favor weight loss; paroxetine and amitriptyline favor weight gain; antipsychotics—all atypical antipsychotics associated with weight gain; if necessary, use aripiprazole, lurasidone, or ziprasidone if weight gain not as significant; clozapine and olanzapine worst for weight gain; antiepileptics—topiramate and zonisamide induce weight loss; gabapentin and pregabalin induce weight gain

American Association of Clinical Endocrinologists Guidelines

Diet: compared with low-fat diet, low-glycemic, low-carbohydrate, and Mediterranean diets beneficial for glycemic control, for reducing hemoglobin A₁c, and for reducing need for diabetes medication
Exercise: >150 min/wk of aerobic exercise of moderate intensity and resistance training 2 to 3 times per week; prescribe exercise regimen; use exercise physiologists or fitness professionals to personalize exercise regimen and help with compliance

Suggested Readings


Acknowledgments

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Estimated time to complete the educational process:

Review Educational Objectives on page 1 5 minutes
Take pretest 10 minutes
Listen to audio program 60 minutes
Review written summary and suggested readings 35 minutes
Take posttest 10 minutes

Suggested Readings
1. Which of the following sulfonylureas is most often implicated in the impairment of myocardial ischemic preconditioning?
   (A) Tolbutamide  (B) Glyburide  (C) Glipizide  (D) Glimepiride

2. Insulin sensitizers belong to the _______ class of drugs for the treatment of type 2 diabetes mellitus.
   (A) Sulfonylurea  (B) Meglitinide  (C) Thiazolidinedione  (D) Dipeptidyl peptidase–4 inhibitor

3. Which of the following dipeptidyl peptidase–4 inhibitors was found to be associated with a statistically significant increased risk for hospitalization due to congestive heart failure?
   (A) Saxagliptin  (B) Sitagliptin  (C) Alogliptin  (D) Linagliptin

4. Glucagon-like peptide–1 receptor agonists are associated with a reduction in all the following, EXCEPT:
   (A) Appetite  (B) Blood pressure  (C) Heart rate  (D) Postprandial hyperglycemia and lipemia

5. Which of the following sodium-glucose cotransporter-2 inhibitors was found to be associated with a dramatic reduction in cardiovascular mortality, hospitalization due to congestive heart failure, and all-cause mortality?
   (A) Ipragliflozin  (B) Dapagliflozin  (C) Canagliflozin  (D) Empagliflozin

For questions 6-9, match the antiobesity medication in Column I with its corresponding class in Column II.

<table>
<thead>
<tr>
<th>Column I</th>
<th>Column II</th>
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<tbody>
<tr>
<td>6. Phentermine</td>
<td>(A) Lipase inhibitor</td>
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<tr>
<td>7. Orlistat</td>
<td>(B) Glucagon-like peptide–1 receptor agonist</td>
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<tr>
<td>8. Lorcaserin</td>
<td>(C) Serotonin (5-HT)$_{2c}$ receptor agonist</td>
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<tr>
<td>9. Liraglutide</td>
<td>(D) Sympathomimetic amine</td>
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10. All the following antihypertensive drugs favor weight loss, EXCEPT:
    (A) Angiotensin-converting enzyme inhibitors  (B) Angiotensin II receptor blockers  (C) Calcium channel blockers  (D) β-blockers

Answers to Audio Digest Internal Medicine Volume 64, Issue 09: 1-D, 2-C, 3-A, 4-C, 5-D, 6-C, 7-A, 8-C, 9-D, 10-C