The global burden of diabetes has risen dramatically over the last two decades, and it is expected to affect over 500 million adults worldwide by 2030, with the majority having type 2 diabetes mellitus (T2DM). People with T2DM have a shorter life expectancy, primarily due to cardiovascular disease (CVD).

The FDA has approved a new indication for the diabetes drug empagliflozan to reduce the risk of death from CVD in adult patients with T2DM and CVD. The Centers for Disease Control and Prevention has reported that CVD deaths are about 70% higher among adults with diabetes compared to those without it.

**Guidelines**

There are 12 drugs approved for treating patients with T2DM. They all lower glucose, but outcomes data to guide selection of agents is sparse. To fill this gap, the American College of Physicians (ACP) has updated its 2012 guideline on the comparative effectiveness and safety of oral medications for T2DM in adults. Recommendations are based on a systematic review of randomized trials and observational studies published through December 2015. Evaluated medications were metformin, thiazolidinediones, sulfonylureas, dipeptidyl peptidase (DPP)-4 inhibitors and sodium-glucose cotransporter (SGLT)-2 inhibitors.

**Key Points**

**Lowering glycosylated hemoglobin levels:** Most drugs were similarly effective in lowering HbA1c levels, although DPP-4 inhibitors were inferior to metformin and sulfonylureas. All combination therapies with metformin were superior to metformin monotherapy.

**Lowering risk for weight gain:** Metformin was better for weight reduction than thiazolidinediones, sulfonylureas or DPP-4 inhibitors. Combination therapies with metformin and an SGLT-2 inhibitor were superior to metformin monotherapy for weight reduction. DPP-4 inhibitors are considered weight neutral. Thiazolidinediones and sulfonylureas were associated with more weight gain.

**Harms of antidiabetic therapies:** Sulfonylureas conferred greater risk for hypoglycemia than did other agents. Relatively little is known about the CV effects of diabetes drugs, and there are concerns that some, including sulfonylureas, might increase risk. The thiazolidinediones, rosiglitazone (Avandia) and pioglitazone (Actos) were associated with excess risk for HF and are contraindicated in Class III and IV HF.
SGLT-2 inhibitors, alone or combined with metformin, heightened risk for genital mycotic infections compared with other therapies. The FDA now considers metformin to be safe for patients with mild renal impairment and for some patients with moderate renal impairment; metformin is contraindicated in patients with glomerular filtration rates (GFR) ≤ 30 mL/minute/1.73 m² and shouldn’t be started with GFR ≤ 45 mL/minute/1.73 m². The DPP-4 inhibitors—(sitagliptin (Januvia), saxagliptin (Onglyza), linagliptin (Tradjenta) and alogliptin (Nesina)—might confer risk for HF, particularly in patients with cardiac or renal disease.

**Recommendations**

Therapeutic lifestyle changes (TLC)—what we like to call “tender loving care” for the body—including diet and exercise and tobacco cessation are recommended for all patients (outlined in previous Heartbeats on our website (www.sjhg.org).

Prescribe metformin as first-line therapy (strong recommendation, moderate-quality evidence—metformin monotherapy was associated with lower CVD-related death than was sulfonylurea monotherapy).⁷

After discussing benefits, adverse effects and costs with the patient, consider adding a sulfonylurea, a thiazolidinedione, an SGLT-2 inhibitor, or a DPP-4 inhibitor to metformin when glycemic control is inadequate (weak recommendation, moderate-quality evidence). The ACP guideline does not address use of injected antidiabetes drugs (insulin and glucagon-like peptide-1 receptor agonists). The American Association of Clinical Endocrinology does address injectables and they are considered second-line dual therapy with metformin, as are alpha-glycosidase inhibitors, colesevelam and bromocriptine.⁸

This guideline provides us with comparative effectiveness of the drugs, but doesn’t give us any direction on which add-on therapy might be best. Add-on therapy will depend on goals of therapy, desire for weight-neutral and weight-loss medications weighed against risk of hypoglycemia, cost and side effects. Minimizing weight gain is a priority.

The American Diabetes Association’s (ADA) 2017 Standards of Medical Care in Diabetes are similar, except the ADA also invites clinicians to “consider” prescribing the SGLT-2 inhibitor empagliflozin (Jardiance) for patients with established CV disease, as this drug was associated with lower incidence of adverse CV events.⁹

**Empagliflozin first antidiabetes drug to gain cardioprotective indication:** The 48-month, open-label EMPA-REG trial enrolled more than 7,000 patients who had T2DM and a high risk of CVD.¹⁰ The study’s big surprise was not empagliflozin’s safety, but its striking cardioprotective qualities. It reduced the risk of the primary endpoint, the first occurrence of the three-point major adverse cardiac event (MACE) components: cardiovascular death, nonfatal myocardial infarction (MI) or nonfatal stroke, by 14%. Results show reduction in CV death, but no significant between group difference in nonfatal MI or nonfatal stroke; therefore reduction in CV death drove the primary endpoint. When examined as individual outcomes in a secondary analysis, empagliflozin significantly reduced the risk of CV death by 38% (32% reduction in all-cause mortality), which was linked closely with a reduction in HF hospitalizations. Risk reductions on other endpoints were not significant. Experts called empagliflozin’s CV benefit a potential game-changer for the clinical challenge of managing patients with both disorders.

Recently, the EMPA-REG OUTCOME investigators reported on the impact of empagliflozin on overall HF burden by analyzing its effects on various HF outcomes. The idea was to explore the relationship between HF and CV death in subgroups of patients with prevalent and incident heart failure. Overall, there was a surprisingly high relative risk reduction of 35% in the rate of hospitalization for HF, which likely means fewer cases of new-onset HF developed over time.¹¹ Empagliflozin does have diuretic and BP lowering effects along with possible neuroendocrine and
vasodilatory effects. Recent European guidelines for HF recommend it in T2DM for HF prevention.\textsuperscript{12} The recently presented CVD-REAL study, which was retrospective and observational, suggests that these benefits may indeed be a class effect. Canagliflozin (Invokana) and dapagliflozin (Farxiga) were the predominant SGLT2 inhibitors used in the study, which showed those patients had a 50% lower rate of hospitalization for HF and all-cause mortality after up to four years than those newly prescribed other glucose-lowering drugs.\textsuperscript{13} These predominantly preventative benefits of SGLT-2 inhibitors appear to extend to lower-risk, real-world patients.

Another antidiabetes drug improves outcomes:

LEADER followed 9,340 high-risk adults with T2DM for 3.5 to five years, who were randomly assigned to receive either a subcutaneous injection of the (GLP)-1 analogue liraglutide (Victoza) 1.8 mg once daily (or the maximum tolerated dose) or placebo along with standard treatment. The primary end point MACE was reduced 13% (occurring in 608 of 4,668 patients taking liraglutide) vs 14.9% (in 694 of 4672 taking placebo) (P = .01 for superiority), including a 22% lower rate of CVD (4.7 vs 6.0%, P = .007).\textsuperscript{14} The number of patients needed to treat to prevent one event in three years was 66 for the MACE composite, and 98 for death from any cause. Liraglutide also reduced HbA1c, body weight and hypoglycemia, and its safety profile was similar to what has been seen in previous trials, with gastrointestinal adverse events and increases in heart rate being the most common.

New Trials Inform Clinical Choice of Second Drug for T2DM

We have to gravitate toward treatments that improve CV outcomes instead of focusing entirely on HbA1c. With more than one drug now showing clear CV benefit, it is critically important for cardiologists to collaborate with endocrinologists, as well as primary care physicians, to give care based on the best available data to improve outcomes.

**High Price of Newer Diabetes Drugs May Restrict Their Use**

Having an approved antidiabetes therapy that can help people live longer by reducing the risk of CV death is an important advance for adults with T2DM. But the newer diabetes medications are now priced at around $10 a day, at least in the United States, and the cost of such agents has been creeping up over the past few years.

The situation is frustrating because we want to use these drugs, but the payers won’t pay for them and the patients can’t afford them. Cost of almost $4,000 a year has to be balanced against the benefits.

**Conclusions:**

In younger, healthy, newly diagnosed patients, a HbA1c level less than 6.5% should be the goal; in older individuals with comorbidities and higher risk for hypoglycemia, less stringent goals (HbA1C > 6.5 %) with a focus on safety and avoidance of hypoglycemia are critical. Antihyperglycemic therapy should be combined with evidence-based treatment of cholesterol and blood pressure (BP) for CV risk reduction. Although the CV benefits of SGLT2 and GLP1 agents merit consideration, these medications are not replacements for TLC, statin therapy and BP management for reducing CV risk.

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