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Diabetic Agents, From Metformin to SGLT2 Inhibitors and GLP1 Receptor Agonists

JACC Focus Seminar

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ABSTRACT

Given the intersection between diabetes mellitus and cardiovascular disease (CVD), pharmacologic agents used to treat type 2 diabetes mellitus must show cardiovascular safety. Comorbid conditions, including heart failure and chronic kidney disease, are increasingly prevalent in patients with diabetes; therefore, they also play a large role in drug safety. Although biguanides, sulfonylurea, glitazones, and dipeptidyl peptidase 4 inhibitors have variable effects on cardiovascular events, sodium glucose cotransporter 2 inhibitors and glucagon-like peptide 1 receptor agonists have consistently shown safety and reduction in cardiovascular events in patients with established CVD. These medications are becoming essential tools for cardioprotection for patients with diabetes and CVD. They may also have roles in primary prevention and renal protection. This paper will review the cardiovascular impact, adverse effects, and possible mechanisms of action of pharmacologic agents used to treat patients with type 2 diabetes. (J Am Coll Cardiol 2020;75:1956–74)

Type 2 diabetes mellitus (T2DM) is a well-established risk factor for cardiovascular disease (CVD), and CVD is the leading cause of death in adults with T2DM. Compared with an individual without T2DM, the life expectancy of a 50-year-old with T2DM is on average 6 years shorter. The lifespan of an individual with T2DM and a prior myocardial infarction (MI) is shortened further still by 12 years. Sixty percent of the difference in survival is attributable to excess CVD mortality (1). As previously characterized (2), heart failure (HF) is also under-recognized among T2DM patients and increases mortality (3). In recent years, the scope of diabetes treatment has broadened to reversal of known pathophysiologic defects and not simply on improving dysglycemia. Glycemic control, a traditional mainstay of T2DM management, overall does not correlate with reduced burden of CVD or mortality, particularly in the near-term (4,5). Insulin resistance in liver and muscle and eventual β-cell failure constitute the core pathophysiologic defects in T2DM. Additional mechanisms of disease include hyperglucagonemia, incretin deficiency or resistance, and maladaptive increases in renal glucose reabsorption. Defects in the fat cells, such as

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HIGHLIGHTS

- Historically, glycemic control was the primary focus in reducing cardiovascular risk in patients with diabetes mellitus.
- Although historic agents effectively lower blood sugar, evidence for cardiovascular benefit was lacking.
- Newer glucose-lowering medications target numerous novel pathways to reduce cardiovascular and renal events in patients with type 2 diabetes.
- These medications should be considered in patients with diabetes and CVD and may play a role in primary prevention of cardiovascular and renal disease.

increased lipolysis, and impaired hypothalamic appetite regulation have also been implicated (6). Because of the progressive and multifaceted pathophysiology of type 2 diabetes, pharmacologic agents with distinct yet complementary actions are needed. Obesity, hypoglycemia, and CVD risk are important considerations in the treatment of T2DM, and interventions aimed at reducing chronic micro- and macrovascular complications and improving cardiorenal outcomes are of paramount importance (7).

The perceived cardiovascular risk with certain glucose-lowering agents and evidence that hemoglobin a1c (HbA1c) lowering per se did not significantly reduce cardiovascular risk or mortality led to the regulatory requirement for cardiovascular safety trials for new agents beginning in 2009. Before the EMPA-REG OUTCOME (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 diabetes Mellitus Patients) trial, antihyperglycemic agents were believed to prevent or delay the development of microvascular complications, but were not able to reduce major adverse cardiovascular events. Since December 2008, the U.S. Food and Drug Administration (FDA) regulatory guidance for industry mandated cardiovascular outcome trials (CVOTs) for cardiovascular safety of novel antidiabetic agents to ensure their cardiovascular safety. This statute is met by blinding central adjudication of CVD events and inclusion of high-risk subjects such as those with advanced age, advanced CVD, and kidney disease. Medications must also be studied for 2 years or approximately 15,000 patient-years. In this setting, studies that evaluate novel medications for T2DM are well-positioned to evaluate cardiovascular risk, resulting in a surge of data on

the FDA mandate, 21 CVOT studies are on track to be completed by 2020, first in predominantly high-risk T2DM patients with established CVD (secondary prevention) and later in broader populations with multiple CVD risk factors (primary prevention) (8). After the success of many of these trials, the FDA commissioned additional labels specifically evaluating CVD risk reduction for empagliflozin, canagliflozin, and liraglutide.

The advent of CVOTs has led to a paradigm shift in the clinical practice recommendations for the management of T2DM. Until 2008, the approval of novel antidiabetic agents was based on their glucose-lowering potential (9). In 2012, guidelines proposed that HbA1c targets should be individualized according to patient's risk profile, in the context of potential risks associated with hypoglycemia and other adverse drug effects, disease duration, life expectancy, comorbidities, vascular complications, patient attitude, and expected treatment efforts and resources (10). The strategy for the management of type 2 diabetes was updated in 2018 in response to the abundance of new cardiovascular outcome data from the CVOTs published since 2015, which showed safety, tolerability, and cardiovascular and renoprotection with 2 classes of agents, sodium glucose cotransporter 2 inhibitors (SGLT2i) and glucagon-like peptide receptor agonists (GLP1RA) in patients with established CVD (11). In response to these findings, in 2018 European Association for the Study of Diabetes (EASD) and the American Diabetes Association (ADA) consensus guidance provides a decision cycle for patient-centered management of T2DM, taking into account not only key patient characteristics (age, weight, CVD, and renal history), but also specific factors such as HbA1c lowering effect, hypoglycemic risk, effect on weight, side effects, complexity, costs, and cardiorenal effects. These guidelines integrate these data for recommendations on choice of treatment and a shared decision-making strategy to create a management plan. In this plan, the focus has shifted from a pure glucocentric approach towards a holistic approach, with a preferred use of agents with proven cardiorenal superiority (11).

To synthesize this wealth of new data, we will provide an updated overview of pharmacologic agents for cardiovascular care in T2DM from metformin, sulfonylureas, and glitazones to dipeptidyl peptidase 4 inhibitors (DPP4i), SGLT2i, and GLP1RA, discussing mechanism of action, metabolic and cardiorenal effects, and benefits and limitations of current design.

ABBREVIATIONS AND ACRONYMS

CKD = chronic kidney disease
CVD = cardiovascular disease
CVOT = cardiovascular outcome trials
DPP4i = dipeptidyl peptidase 4 inhibitors
GLP1RA = glucagon-like peptide 1 receptor agonist
HbA1c = hemoglobin A1c
HF = heart failure
MI = myocardial infarction
SGLT2i = sodium glucose transporter 2 inhibitor
T2DM = type 2 diabetes mellitus
TZD = thiazolidinediones

TABLE 1 SGLT2i Cardiovascular Outcome Trials

	EMPA-REG Empagliflozin (n = 7,020)	CANVAS Program Canagliflozin (n = 10,142)	DECLARE Dapagliflozin (n = 17,160)	CREDENCE Canagliflozin (n = 4,401)	DAPA-HF Dapagliflozin (n = 4744)
Median follow-up, yrs	3.1	2.4	4.2	2.6	1.5
Mean age, yrs	63	63	64	63	66
Female, %	29	36	37	34	23
Mean BMI, kg/m^2	30.6	32.0	32.1	31.3	28.2
HbA1c, %	8.1	8.3	8.3	8.3	NR
Baseline metformin, %*	73	77	82	66	73
Baseline eGFR†	74	77	85	56	65
eGFR† <60 ml/min/1.73 m^2, %	26	20	7	59	40
Prior CVD, %	99	66	41	50	
Prior HF, %	10	14	10	15	
3P-MACE	**0.86 (0.74–0.99)**	**0.86 (0.75–0.97)**	0.93 (0.84–1.03)	**0.80 (0.67–0.95)**	NR
CV death	**0.62 (0.49–0.77)**	0.87 (0.72–1.06)	0.98 (0.82–1.17)	0.78 (0.61–1.00)	0.82 (0.69–0.98)
MI	0.87 (0.70–1.09)‖	0.89 (0.73–1.09)‖	0.89 (0.77–1.01)	NR	NR
Stroke	1.18 (0.89–1.56)‖	0.87 (0.69–1.09)‖	1.01 (0.84–1.21)	NR	NR
CV death or HHF	**0.66 (0.55–0.79)**	**0.78 (0.67–0.91)**	**0.83 (0.73–0.95)**	**0.69 (0.57–0.83)**	**0.75 (0.65–0.85)**
All-cause mortality	**0.68 (0.57–0.82)**	0.87 (0.74–1.01)	0.93 (0.82–1.04)	0.83 (0.68–1.02)	0.83 (0.71–0.97)
HHF	**0.65 (0.50–0.85)**	**0.67 (0.52–0.87)**	0.73 (0.61–0.88)	**0.61 (0.47–0.80)**	0.70 (0.59–0.83)
Renal events‡	**0.61 (0.53–0.70)** (103)	**0.60 (0.47–0.77)**	0.53 (0.43–0.66)	0.66 (0.53–0.81)	0.71 (0.44–1.16)
Other primary outcome§	NR	NR	NR	**0.70 (0.59–0.82)**	**0.74 (0.65–0.85)**

Values are hazard ratio (confidence interval) unless otherwise indicated. *Average of entire study group (treatment and control). †eGFR units ml/min/1.73 m^2. ‡Definition varied across trials. §Primary outcome DAPA-HF: heart failure hospitalization or urgent visit for heart failure resulting in intravenous therapy, cardiovascular death. Primary outcome CREDENCE: ESRD (dialysis, transplantation, or a sustained estimated GFR of < 15 ml/min), doubling serum creatinine, death from renal or CV causes. ||Fatal or nonfatal outcome. Bold as follows: Bold indicates outcomes meeting prespecified significance of P <0.05.

3P-MACE = 3-point major adverse cardiac events; BMI = body mass index; CANVAS = Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes; CREDENCE = Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy; CV = cardiovascular; CVD = cardiovascular disease; DAPA-HF = Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction; DECLARE = Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes; eGFR = estimated glomerular filtration rate; EMPA-REG = Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes; HbA1c = hemoglobin A1c; HF = heart failure; HHF = hospitalization for heart failure; NR = not reported; SGLT21 = sodium glucose cotransporter 2 inhibitor.

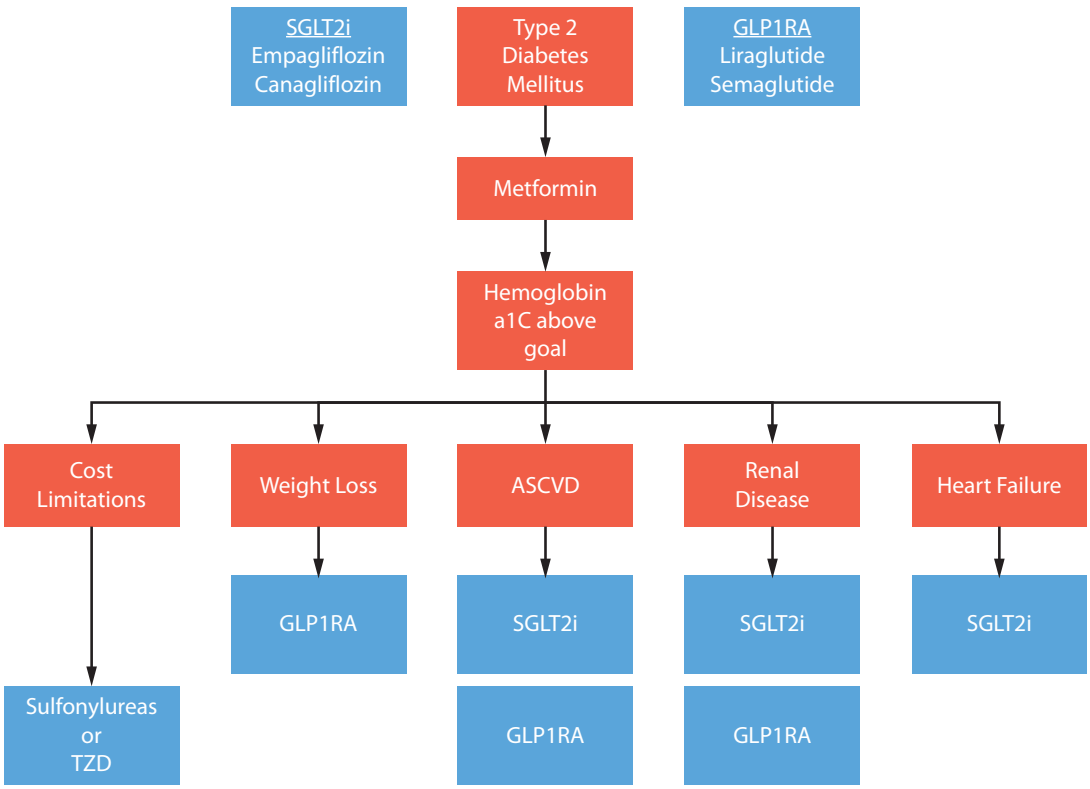
GLP1RA has rightfully prompted the diabetes and cardiovascular communities to incorporate these new classes of agents into clinical management guidance.

BIGUANIDES

Metformin has remained first-line treatment for T2DM due to its efficacy, safety, duration of evidence, affordability, and limited side-effect profile. The biguanide was developed in the 1920s, before the era of target-specific drug development; therefore, exact cellular mechanisms of metformin remain ill-defined. Metformin has been used in Europe since the 1950s whereas phenformin, another biguanide, was primarily used in the United States until metformin was approved in 1990 (12). Metformin lowers blood glucose by increasing peripheral uptake of glucose and decreasing hepatic glucose production, likely via inhibition of mitochondrial enzymes. Metformin's role in inflammatory pathways may also underpin the non-metabolic benefits of the drug (13). In the last decade, our understanding of metformin's mechanism has expanded from alterations in liver metabolism leading [illegible] complex picture reflecting its multiple modes of action, including a key role in the gut (13).

Data on the cardiovascular impact of metformin rely heavily on the United Kingdom Prospective Diabetes Study (UKPDS). In the 1970s, the study group assigned a total of 1,704 overweight adults with T2DM aged 25 to 65 years to a number of glucose control strategies: diet only versus intensive control with metformin only. The metformin control group was then compared to chlorpropramide, glibenclamide, or insulin, and followed for changes in metabolic, renal, and cardiovascular outcomes over 10 years (14). Compared to diet alone, in the group of 342 newly diagnosed overweight patients with T2DM treated with metformin, MI was reduced by 39%, coronary deaths by 50%, stroke by 41%, and all-cause mortality by 36% after a median 10.7 years (14). These reductions in major CVD events with diet plus metformin were greater than diet with either a sulfonylurea or insulin. Additional follow-up for 8 to 10 years when all patients received intensive therapy found that the reduced risk of MI and mortality with initial metformin therapy persisted over time compared with early [illegible]

FIGURE 1 Algorithm for Choosing Pharmacologic Therapy for Type 2 Diabetes



In patients with type 2 diabetes on metformin with hemoglobin a1c above goal, second-line therapy depends on cost limitations, comorbid disease, and desire for weight loss. ASCVD = atherosclerotic cardiovascular disease; GLP1RA = glucagon-like peptide 1 receptor agonist; SGLT2i = sodium glucose cotransporter 2 inhibitor; TZD = thiazolidinedione.

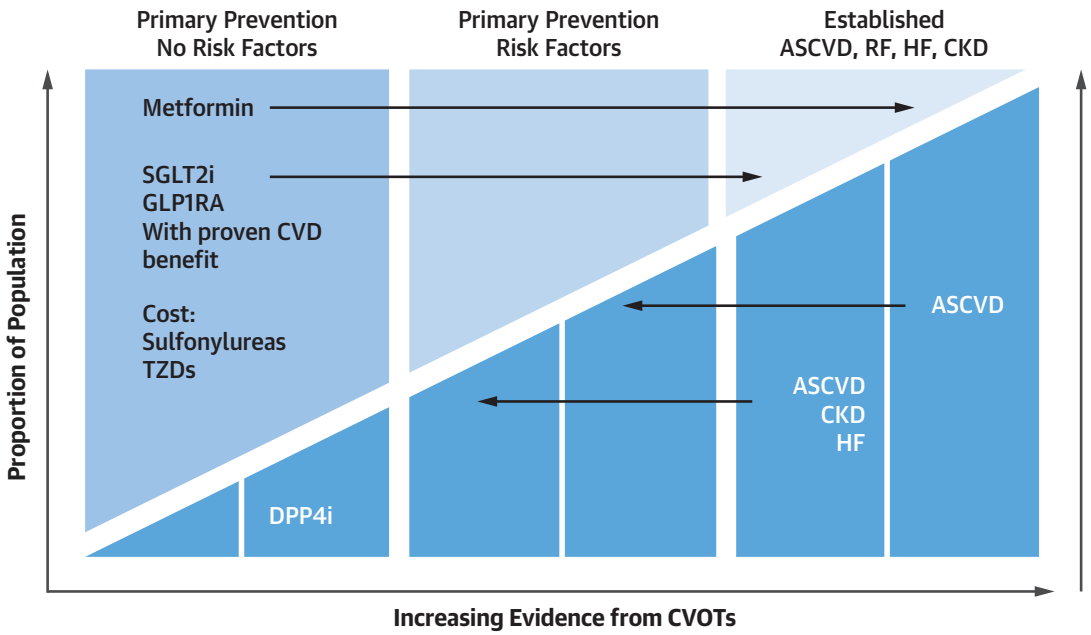
Metformin use was also associated with fewer hypoglycemic episodes and less weight gain.

However, any conclusions drawn from the UKPDS data is tempered by major limitations in study design. For example, the study population was low risk and excluded recent acute coronary syndrome, HF, or microvascular disease events and was performed in the absence of contemporary lipid-lowering therapy with statins. Moreover, compared to recent CVOTs, the UKPDS study population was small, incompletely blinded, and lacked placebo-control. Additional data on the cardiovascular benefits of metformin relative to placebo remain sparse, limited to meta-analyses with wide confidence intervals (CIs) for most cardiovascular endpoints (16). The VA-IMPACT trial is attempting to fill this gap by evaluating cardiovascular outcomes in patients with pre-diabetes and established CVD treated with metformin versus placebo (NCT02915198).

Patients with chronic kidney disease (CKD) are also

use for CVD risk reduction in T2MD. Per current FDA guidelines, metformin is contraindicated at an estimated glomerular filtration rate (eGFR) <30 ml/min/1.73 kg/m^2, and initiation is not recommended at an eGFR between 30 and 45 ml/min/1.73 kg/m^2 (17). For patients tolerating the drug who experience a decreases in glomerular filtration rate (GFR), new guidelines state reduced renal dosing is a safe option (17,18). This was supported in a post hoc analysis of SAVOR-TIMI 53 (Saxagliptin and Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus-Thrombolysis In Myocardial Infarction 53) participants showing that exposure to metformin did not significantly affect cardiovascular outcomes in patients with severe CKD (19). Metformin's major adverse effect is a type B lactic acidosis that may develop at the upper therapeutic limit of drug dosing, which current evidence indicates is rare in contemporary practice (20). Withholding metformin during "sick days" may miti-

FIGURE 2 Selecting Pharmacologic Therapy for Patients With Type 2 Diabetes



The evidence base for selecting pharmacologic therapy for patients with type 2 diabetes depends on presence of risk factors, comorbid heart failure, atherosclerotic disease, and renal disease. CKD = chronic kidney disease; CVD = cardiovascular disease; CVOT = cardiovascular outcome trial; DPP4i = dipeptidyl peptidase 4 inhibitor; HF = heart failure; RF = risk factor; other abbreviations as in Figure 1.

approach is lacking. Metformin was background medical therapy for most patients in recent CVOTs, further enshrining its use as first-line therapy for most patients with T2DM. Given the duration of evidence, low cost, favorable safety profile, and background use in recent CVOTs, metformin has, until now, remained first-line therapy onto which additional agents can be considered for cardiovascular risk reduction in T2DM (Figure 1). However, new European Society of Cardiology (ESC)/EASD guidelines recommend initiating SGLT2i or GLP1RA monotherapy in drug-naive patients with T2DM with established or high risk for CVD (21). This recommendation is made despite high prevalence (51% to 83%) of baseline metformin use in these trials (Table 1).

SULFONYLUREAS

Sulfonylureas have historically been considered second-line treatment for T2DM for patients with uncontrolled hyperglycemia on metformin. In contrast to metformin, sulfonylureas increase blood insulin concentration via stimulation of pancreatic beta cells. Augmented insulin secretion and sensi-

weight gain (22). Although sulfonylureas are associated with slightly greater upfront reductions in glycosylated hemoglobin levels (HbA1c, 1% to 1.25% reduction) relative to metformin (0.5% to 1.25%) (23) in the UKPDS study, after 6 months, reduction in a1c levels were similar between groups on either therapy. Over 6 years, 54% of patients allocated sulfonylureas alone required the addition of insulin to achieve the prespecified target of a fasting glucose under 106 mg/dl (24).

The UKPDS and ADVANCE trials have shown microvascular benefits of sulfonylureas, including a reduction in the incidence or worsening of nephropathy and retinopathy, and no increase in all-cause mortality. However, whether these benefits were due to sulfonylurea therapy versus an overall glucose-lowering effect could not be confirmed (4).

Since the 1960s, sulfonylureas have been implicated with increased risk of adverse cardiovascular outcomes. The University Group Diabetes Program observed increased risk of all cause and cardiovascular mortality in those treated with the first-generation sulfonylurea tolbutamide versus placebo (25). The UKPDS study randomized patients to either

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