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Better glycemic control and cardiovascular outcomes

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Abstract

Diabetics are at high risk of developing cardiovascular disease, which is correlated to the degree of hyperglycemia. However, pharmacological approaches to lowering blood glucose levels in diabetics is not always associated with a decrease in the risk of developing heart failure. In fact, some treatments actually increase the risk of cardiovascular disease. For instance, the use of thiazolidinediones (ie, rosiglitazone and pioglitazone) increases the risk of heart failure development in type 2 diabetes mellitus (T2DM) patients. Older antihyperglycemic medications, such as metformin, also seem to have a reduced risk of adverse cardiovascular outcomes compared with sulfonylureas. Newer agents, such as the glucagon-like protein 1 (GLP-1) receptor agonists, the dipeptidyl peptidase-4 (DPP-4) inhibitors, and the α-glucosidase inhibitors, appear to have neutral effects on cardiovascular outcomes. In contrast, recent trials with sodium-glucose cotransporter 2 (SGLT2) inhibitors (ie, empagliflozin) have demonstrated a dramatic decrease in adverse cardiovascular outcomes. As a result, it is clear that care must be taken in choosing the antihyperglycemic agent to be used in T2DM patients, especially if underlying cardiovascular disease is present. ■ *Heart Metab*. 2017;73:9-12

Keywords: antihyperglycemic agent; cardiovascular outcome; heart failure; type 2 diabetes mellitus

Introduction

The prevalence of diabetes worldwide has rapidly increased in the last 20 years, with the number of type 2 diabetes mellitus (T2DM) patients now exceeding 400 million.[1] These diabetic patients are at twice the risk of developing cardiovascular disease, which is the most common cause of death in diabetics.[2] The risk of developing heart failure in diabetics is also positively correlated to the degree of hyperglycemia.[3-6] As a result, this would imply that lowering blood glucose should decrease cardiovascular risk. However, there is uncertainty in this regard, and lowering glucose levels may not always result in a reduction in the risk of heart failure. It is also becoming clear that the type of pharmacological approach used for lowering blood glucose may have differential effects on cardiovascular risk in the diabetic. In fact, some antihyperglycemic therapies may actually increase the risk of developing heart failure. As a result, the European Medicines Agency and the US Food and Drug Administration implemented regulations in 2008 calling for adequately powered cardiovascular outcomes trials (CVOTs) to evaluate the efficacy and cardiovascular safety of new antihyperglycemic agents. Although many of these CVOTs

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Abbreviations

CVOT: cardiovascular outcomes trial; **DPP-4:** dipeptidyl peptidase-4; **ELIXA:** Evaluation of LIXisenatide in Acute coronary syndrome [trial]; **EMPA-REG OUTCOME:** Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes [trial]; **GLP-1:** glucagon-like protein 1; **SGLT2:** sodium-glucose cotransporter 2; **T2DM:** type 2 diabetes mellitus; **UKPDS:** United Kingdom Prospective Diabetes Study

are still ongoing, reports from a number of trials are available; in some, antihyperglycemic agents have been reported to increase the risk of developing heart failure; in others, to have neutral effects on heart failure risk or actually lessen heart failure risk. This paper reviews this clinical data.

Blood glucose and heart failure

Poor glycemic control in T2DM is associated with an increased risk of developing heart failure.[6,7] This includes poor glycemic control as assessed by increased fasting blood glucose, postprandial blood glucose, glycated hemoglobin (HbA_{1c}) levels, and/or measures of insulin resistance in T2DM patients. Trials such as UKPDS (the United Kingdom Prospective Diabetes Study) also showed a beneficial effect between lowering blood glucose and decreasing heart failure risk in T2DM patients.[4] A number of medications have been developed to improve glycemic control in T2DM patients, and these include thiazolidinediones (TZDs), insulin analogs, metformin, sulfonylureas, α-glucosidase inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like protein 1 (GLP-1) receptor agonists, and sodium-glucose cotransporter 2 (SGLT2) inhibitors. However, despite being effective antihyperglycemic agents, these medications have very different effects on heart failure risk in T2DM patients. The reasons for these differences in heart failure risk in T2DM patients taking these medications are not completely clear, although it is clear that it is not related to the degree of glycemic control. However, as the outcomes of more and more CVOTs trials are reported, it is clear that when choosing the type of antihyperglycemic agent to use in T2DM patients, the risk of heart failure development should be carefully considered.

Thiazolidinediones

TZDs are peroxisome proliferator–activated receptor-γ agonists that have insulin-sensitizing actions. Rosiglitazone and pioglitazone are two agents in this class of medications. However, despite favorable antihyperglycemic and blood pressure–lowering actions, both of these agents in CVOTs showed increased risk of heart failure in T2DM patients[8,9] (*Table I*). The reasons for this increase in heart failure risk are not clear, although plasma volume expansion due to increasing renal tubular sodium reabsorption has been proposed. The outcomes of these CVOTs suggests that the use of TZDs should be contraindicated in patients at high risk for heart failure.

Metformin

Metformin is an older antihyperglycemic agent that has not been investigated in larger CVOTs. However, UKPDS demonstrated that metformin reduced the rate of adverse cardiovascular outcomes in T2DM patients with heart failure compared with other antihyperglycemic agents.[4] This included a 20% lower death rate than with other antihyperglycemic agents.

Antihyperglycemic agent	Heart failure risk	Hypoglycemia risk
Thiazolidinediones (rosiglitazone, pioglitazone)	Increased	Low
Metformin	Decreased compared with sulfonylureas	Low
Sulfonylureas (tolbutamide, glibenclamide)	Increased compared with metformin	Higher
GLP-1 receptor agonists (lixisenatide, liraglutide)	Neutral	Low
DPP-4 inhibitors (saxagliptin, sitagliptin)	Increased with saxagliptin Neutral with sitagliptin	Low
α-Glucosidase inhibitors (acarbose)	Increased compared with DPP-4 inhibitors	Low
SGLT2 inhibitors (empagliflozin)	Decreased	Low

Table I *Classes of antihyperglycemic agents and associated risks of developing heart failure and hypoglycemia in type 2 diabetes mellitus patients.*
Abbreviations: *DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like protein-1; SGLT2, sodium-glucose cotransporter 2.*

Although data from CVOTs is missing, this clinical data has resulted in metformin not being contraindicated in T2DM patients with heart failure.[10]

Sulfonylureas

Sulfonylureas, such as tolbutamide and glibenclamide, are an older class of antihyperglycemic agent and act by increasing insulin release from the β-cells in the pancreas. Like metformin, the sulfonylureas have not been investigated in large CVOTs. However, a review of 72 randomized clinical trials showed that sulfonylureas did not increase all-cause mortality in T2DM patients.[11] In contrast, UKPDS did show that sulfonylureas were inferior to metformin in terms of overall survival of T2DM patients.[4] Although sulfonylureas are not contraindicated in T2DM patients with heart failure, it is generally recommended that metformin be preferably used in these patients.

Glucagon-like protein 1 receptor agonists

GLP-1 receptor agonists are injectable antihyperglycemic agents that mimic the actions of GLP-1, an incretin that stimulates the release of insulin and that lowers glucagon production in T2DM patients. An advantage of these newer antihyperglycemics is that they have a low risk for hypoglycemia. Two representative GLP-1 agonists are lixisenatide and liraglutide. Recently completed CVOTs with these agents did not show any increased risk of heart failure development. The long-term effects of lixisenatide in CVOTs were examined in the ELIXA trial (Evaluation of LIXisenatide in Acute coronary syndrome), which enrolled 6068 patients. Although lixisenatide did not show any cardiovascular benefit in patients with T2DM and a recent acute coronary syndrome, it also did not show any harm.[12] A 3.8-year CVOT was also recently completed with liraglutide, which examined the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke in 9340 T2DM patients at high cardiovascular risk.[13] A beneficial effect of liraglutide was seen with regard to the primary composite end point (13% vs 14.9% in placebo); a decrease in cardiovascular death was also seen (4.7% vs 6.0% in placebo). This suggests that GLP-1 receptor agonists can be used in heart failure.

Dipeptidyl peptidase-4 inhibitors

DPP-4 inhibitors are oral antihyperglycemic agents that increase incretin levels (GLP-1 and gastric inhibitory polypeptide [GIP]) by blocking their degradation by DPP-4; they therefore increase insulin secretion and inhibit glucagon release. Saxagliptin and sitagliptin are two representative DPP-4 inhibitors. The first major CVOT with DPP-4 inhibitors that was reported was with saxagliptin, which examined 16 492 patients with T2DM and a history of cardiovascular disease over a 2.1-year period.[14] Although there was no difference in cardiovascular death, myocardial infarction, or stroke seen in the saxagliptin-treated patients, a significant increase in hospitalization for heart failure was observed. In addition, an increased risk for hypoglycemic events was observed. In contrast, a recently completed CVOT (involving 14 671 patients) that examined sitagliptin in T2DM patients with cardiovascular disease showed that sitagliptin was noninferior to placebo for the primary composite cardiovascular outcomes, and no difference in hospitalization rates for heart failure was observed.[15] As a result, DDP-4 inhibitors have proven cardiovascular safety in T2DM patients, although caution should be used with saxagliptin in heart failure patients.

α-Glucosidase inhibitors

α-Glucosidase inhibitors, which include acarbose, have antihyperglycemic actions by preventing carbohydrate digestion in the small intestine. Although a large CVOT has not been performed with acarbose in T2DM patients, a meta-analysis of smaller randomized clinical trials did not show any differences in heart failure outcomes. However, a recent study comparing add-on therapy with acarbose added to a combined dual therapy with metformin and sulfonylurea showed that the risk of stroke and all-cause mortality was higher with DPP-4 inhibitor add-on therapy.[16]

Sodium-glucose cotransporter 2 inhibitors

SGLT2 inhibitors are antihyperglycemic agents that act by preventing glucose reabsorption in proximal tubules of the kidney. Three representative SGLT2 inhibitors include empagliflozin, canafligozin, and dapagliflozin. Of these, only empagliflozin has been investigated in a complete and major CVOT, the EM-

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PA-REG OUTCOME trial (Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes).[17] Empagliflozin was examined in high-risk patients with diabetes and established cardiovascular disease over a 3-year treatment period. The CVOT reported a dramatic 35% to 40% relative reduction in cardiovascular death and all-cause mortality in empagliflozin-treated patients. A dramatic decrease in hospitalization for heart failure was also observed. This has generated considerable excitement, although the mechanisms for the beneficial effects of empagliflozin have not been unequivocally determined. Possible mechanisms for this benefit include a decrease in diuresis and plasma volume, a decrease in body weight, a decrease in blood pressure, or an increased cardiac efficiency in use of fuel.[18-20] Although major CVOTs have yet to be reported for other SGLT2 inhibitors, the dramatic benefit on cardiovascular outcomes with empagliflozin and the low risk for hypoglycemic events has resulted in empagliflozin presently being evaluated for heart failure treatment even in the absence of diabetes.

Summary

Although hyperglycemia is an important contributor to increased cardiovascular risk in diabetics, not all antihyperglycemic approaches in T2DM patients have similar effects on heart failure risk. Some pharmacological approaches can actually increase heart failure risk, whereas some have neutral effects. In contrast, some approaches, such as SGLT2 inhibition, may actually significantly decrease the risk of developing heart failure in T2DM. ■

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