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# Antihyperglycemic drugs that improve cardiovascular outcomes and a model of diabetic cardiomyopathy

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**Abstract:** Recent cardiovascular outcome trials (CVOTs) have transformed the landscape for the management of type 2 diabetes mellitus. In a remarkably short period of time, national and international guidelines have been overhauled to reflect the remarkable cardiovascular benefits of sodium/glucose linked transporter-2 inhibitors (SGLT2is) and glucagon-like peptide-1 receptor analogues (GLP-1RA) in mitigating cardiovascular risk. Both SGLT2is and GLP-1RAs remain second-line to metformin, reflecting the historical importance of this biguanide antihyperglycemic. In this review, these three very different antihyperglycemics are discussed in the light of CVOT data and of the preclinical data revealing remarkable pleiotropic signaling effects of these drugs. A model of diabetic cardiomyopathy is discussed, and the points of contact that these therapeutic interventions have upon this model may of help in understanding how each can be best targeted in this complex pathophysiological disease process. ■ *Heart Metab*. 2019;80:18-22

**Keywords:** cardioprotection; diabetic cardiomyopathy; GLP-1 receptor agonist; metformin; SGLT2 inhibitor; type 2 diabetes mellitus

## Introduction

Since the late 19th century, diabetes mellitus has been recognized as an important cardiovascular risk factor in the development of atherosclerosis.[1,2] Because elevated blood sugar is a principal diagnostic feature of this complex disease, unsurprisingly it was hoped that the control of circulating glucose would improve cardiovascular outcomes in diabetic patients. However, the reality of this approach has not been as rewarding as might have been wished, with generally neutral, or even adverse, cardiovascular outcomes observed. However, cardiovascular outcome trials (CVOTs), mandated by medicine regulators in both the United States and in Europe, have recently revealed two disparate classes of therapies for the use in type 2 diabetes (T2DM) with a significant and unexpected cardiovascular benefit: the sodium-glucose linked transporter inhibitors (SGLT2is) and the glucagon-like peptide-1 receptor agonists (GLP-1RA).

## Metformin: the bedrock of contemporary diabetic management

The cornerstone of current T2DM management is the biguanide, metformin, an insulin sensitizer. In many respects, metformin could be regarded as the prototyp-

ical cardioprotective antihyperglycemic medication. In the UKPDS 34 study,[3] metformin was compared with both the then standard of care (predominantly diet control) and an "intensive blood-glucose control" group in overweight patients with T2DM. This latter drug-control group used either sulfonylureas or insulin to more effectively lower circulating glucose levels. Interestingly, while reductions in blood sugar were not maintained by any of the drug therapy regimens over the duration of 10-year follow-up, metformin, nonetheless, significantly improved cardiovascular outcomes. The incident rate of nonfatal and fatal myocardial infarction/sudden cardiac deaths separated from the control group after approximately 1 year, and by 10 years, patients on metformin had a significant 39% risk reduction (*P*=0.010) compared with patients in the control group[3] *(Figure 1).* In contrast, this composite end point was not significantly improved by "intensive medical therapy" with sulfonylurea or insulin (*P*=0.11).[3]

Recent meta-analyses (encompassing 40 trials and 1 million patients) suggest that the extent of the cardiovascular benefits of metformin seen in the UKPDS study is greater than that seen in contemporary practice; however, the protection appears robust and significant: comparison of metformin versus non-metformin revealed a significant reduction of cardiovascular mortality with an adjusted hazard ratio of 0.81 (95% CI of 0.79-0.84, *P*<0.00001).[4]

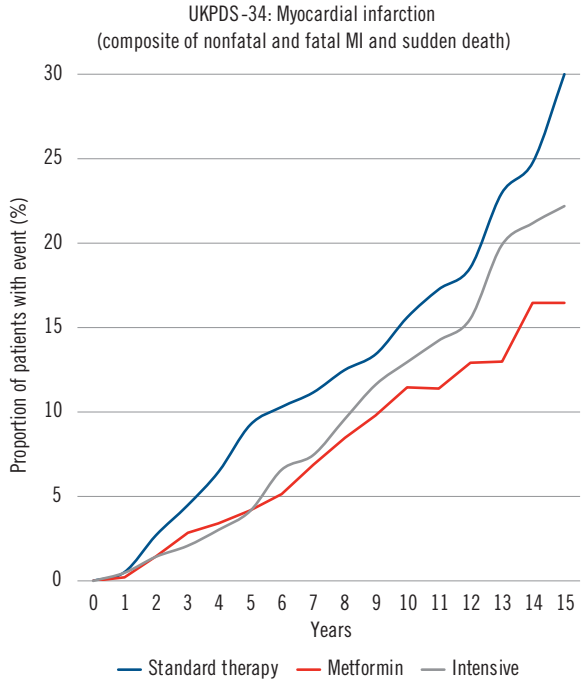


***Figure 1*** *Positive cardiovascular impact of metformin monotherapy upon myocardial infarction (a composite of nonfatal and fatal and sudden death) in the UKPDS 34 study. Compared with diet control (standard therapy), metformin led to a significant reduction of myocardial infarction, whereas there was no significant benefit with intensive therapy with either sulfonylureas and/or insulin, after median 10 year follow-up. Figure adapted from UKPDS 34.*[3]

The mechanism of this cardioprotective benefit has been extensively studied, with well-supported literature demonstrating the pleotropic effects that metformin has upon cell survival signaling (for example, 5' adenosine monophosphate-activated protein kinase (AMPK)[5] and endothelial nitric oxide synthase (eNOS) activation, see ref 6.

Metformin has thus been shown to have direct cardioprotective properties and, in historical and contemporary practice, to attenuate cardiovascular mortality.

## SGLT2 inhibitors

The SGLT2is ameliorate hyperglycemia by inhibiting renal reabsorption of glucose via the renal SGLT2 transporter, which are responsible for 90% of normal reabsorption in the proximal tubule, thus promoting glucosuria and reduction of circulating glucose. Concomitant with glucosuria are natriuresis, osmotic diuresis, weight reduction (significant calorific loss) and mild ketosis. Empagliflozin, in the EMPA-REG OUTCOME study,[7] revealed a significant cardiovascular outcome benefit in patients with high-risk and established cardiovascular disease. Particularly impressive are their ability to reduce hospital admissions with heart failure, an observation that has been also been seen in other drugs within this class, canagliflozin and dapagliflozin (CANVAS[8] and DECLARE-TIMI 58[9]) and most recently confirmed in the prospective dapagliflozin heart failure study (DAPA-HF).[10] What is particularly remarkable regarding these therapies is the rapidity of the divergence of the survival curves – evident within just weeks of initiation of therapy. Thus, cardiovascular outcome benefits are unlikely to be related to attenuation of arterial atherosclerosis. Moreover, there is no difference in the rates of myocardial infarction during the relatively short duration of follow-up of these investigations. The cardiovascular mortality benefit therefore appears to be through benefits derived through heart failure and perhaps also improved survival from myocardial ischemia.

The mechanism of the cardioprotection stemming from SGLT2 inhibition has been the subject

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of intense research, and currently remains unclear. The reduction in the rates of hospitalization for heart failure may well have its foundation upon the diuretic and natriuretic effects of these drugs with concomitant benefits upon ventricular pre- and afterload. However, the evolution of the diabetic cardiomyopathy (DMCM) through left ventricular hypertrophy and heart failure with preserved ejection fraction (HFpEF) and concluding with a dilated cardiomyopathy and heart failure with reduced ejection fraction (HFrEF, *Figure 2)* is a complex pathophysiological process,[11,12] one in which SGLT2is may interact. Indeed, SGLT2is appear to have a positive impact upon left ventricular mass in the earlier phases of DMCM and improved ventricular performance (reviewed in ref 13). The ventricular remodeling and progression from HFpEF to HFrEF appear to be characterized by ischemic heart disease and ischemia/reperfusion injury,[11,12] and this too represents a target for SGLT2is.

EMPA-REG, CANVAS, and DECLARE were not studies designed to look at myocardial infarction (the number of fatal myocardial infarcts were very low, even within the high-risk population recruited into EMPA-REG). However, preclinical studies have revealed that SGLT2 inhibition does significantly reduce myocardial infarct size.[14-16] This is surprising: SGLT2 is not widely expressed in man, and there is negligible SGLT2 expression in the heart.[17] Remarkably, SGLT2i cardioprotection is independent of diabetic or glycemic status, and mediated through cytoprotective signaling: explanted hearts remain protected when perfused, ex vivo, following oral SGLTi administration.[14] This memory effect may be through the recruitment of cell-survival kinases, through Jak-STAT[15] or AMPK signaling[16] and the bolstering of cellular antioxidant defences.[16] In contrast, cardioprotection against heart failure may be mediated through preferential metabolism of β-hydroxybutyrate (augmented by SGLT2i therapy)[18] or through sodium/calcium exchange inhibition,[19] to attenuate adverse calcium accumulation.

With emerging evidence to suggest that SGLT2is may have benefits in all patients, irrespective of diabetic status,[10] the restriction of SGLT2i to patients with diabetes may change. DAPA-HF is the first heart failure study to demonstrate that SGLT2i is equally beneficial in both diabetic and nondiabetic patients, and this study will be joined by a number of heart failure trials that are due to report in the near future, including the EMPEROR-Reduced and EMEROR-Preserved studies.[20]

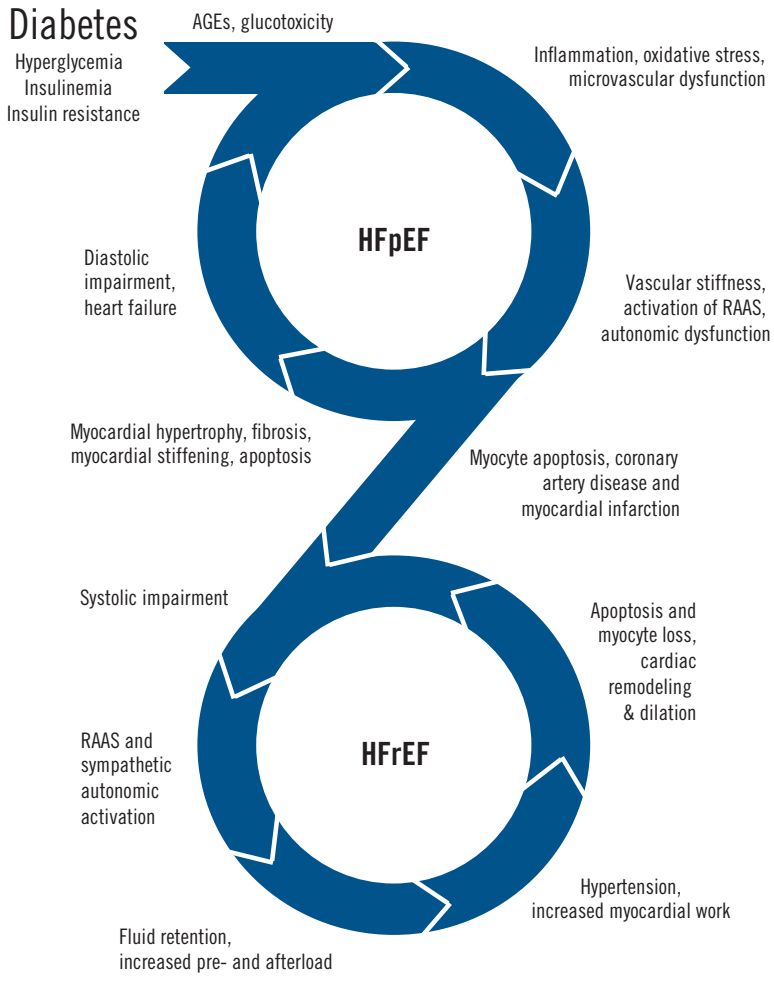


***Figure 2*** *A proposed model of diabetic cardiomyopathy. Diabetes and its consequences of hyper-insulinemia and insulin resistance leads to the initial insult upon the cardiovascular system. This initiates a self-sustaining loop of injury, characterized by vascular injury, hypertension, increased afterload, and myocardial hypertrophy and subsequent diastolic impairment and myocardial fibrosis. As this becomes symptomatic, these features characterize heart failure with preserved ejection fraction (HFpEF). Over time, the sustained strain and injury upon the left ventricle leads to myocyte loss through apoptotic cell death, which, in combination with the development of coronary atherosclerosis and ischemic heart disease and the initiation of a second self-sustaining loop of heart failure with reduced ejection fraction (HFrEF) and the characteristic late-phase dilated cardiomyopathy. AGE, advanced glycation end products; RAAS, renin-angiotensin-aldosterone system*

## Glucagon-like peptide-1 receptor agonists

Synthetic analogues of the incretin hormone, GLP-1, glucagon-like peptide receptor agonists (GLP-1RAs) are predominantly injectable antihyperglycemics, although oral formulations of this class of drug are now emerging. GLP-1RAs stimulate insulin release from pancreatic islet cells to regulate glucose concentration, reduce glucagon secretion, alter gut motility, satiety, and lipid metabolism, and thus can lead to reduction of body weight.[21] These properties alone should have a positive impact upon the cardiovascular risk profile, but their benefit is likely to extend beyond their impact upon their canonical role.

The GLP-1RAs are either GLP-1- or Exendin-based (with modification to promote half-life), and it is interesting to note that GLP-1RAs based upon native GLP-1 (liraglutide, semaglutide, and albiglutide) have an advantageous impact upon cardiovascular outcomes. LEADER,[22] SUSTAIN-6,[23] and HARMONY[24] respectively revealed significant reductions in MACCE in patient populations at high risk of developing cardiovascular complications. In contrast to the SGLT2 inhibitors, the time to separation of the survival curves was longer and there was no positive signal in terms of heart failure (noninferior to placebo); indeed the benefits of GLP-1RAs appear to be mediated by the reduction of atherosclerosis-related cardiovascular events (myocardial infarction and stroke).[25]

Unlike SGLT2, GLP-1 receptors are widely expressed in man, including the heart.[26] Exogenously administered GLP-1 reduces infarct size in rodent models through cytoprotective signaling, involving post-receptor cAMP and cGMP activation,[27] Akt, Erk1/2, p70S6K, and AMPK signaling and inhibition of proapoptotic signaling.[28,29] The atherosclerosis benefits of these drugs may be mediated through a beneficial impact upon lipid profiles[30] and augmented endothelial nitric oxide.[31]

Thus, the characteristics of GLP-1-based receptor agonists are different from those seen with SGLT2i, which raises the intriguing possibility that the two classes of therapy may have additive benefits, particularly in patients with established coronary or cardiovascular disease.

## An emerging paradigm of cardiovascular disease management in diabetes

Cardioprotection in T2DM has many facets, but evolution and progression of DMCM is a central feature *(Figure 2).* In the model presented, almost any intervention designed to mitigate hyperglycemia should slow the progression of HFpEF that characterizes early and intermediate phases of DMCM. Drugs with pleiotropic effects upon pro-survival cell signaling (eg, metformin, SGLT2i, GLP-1-based GLP-1RAs) may help prevent progression into late-phase DMCM, HFrEF, through attenuating apoptotic myocyte loss and abrogating ischemia/reperfusion injury from ischemic heart disease. Moreover, GLP-1RAs may have help ameliorate atherosclerotic progression to reduce ischemic events whereas SGLT2is may help offload and diurese, thus mitigating excess pre- and afterload and injurious cardiac decompensation. This model may be helpful in developing new therapeutic strategies in diabetes and supports triple therapy with metformin, SGLT2i, and GLP-1RA – a combination that deserves further investigation.

In summary therefore, building on the foundations of metformin therapy, there are two new classes of glucose-controlling therapies, SGLT2i and GLP-1RA, that each possess remarkable cardiovascular benefits. SGLT2is are clearly beneficial in mitigating heart failure, whereas GLP-1RA may help attenuate atherosclerosis. In clinical practice, the combination of these therapies that appear to have disparate targets may provide the optimum outcomes for diabetic and potentially also for nondiabetic patients, an effect that may have little to do with glucose levels, but through metabolic modulation and recruitment of cellular signaling to promote cellular survival. ■

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