

SPECIAL FOCUS ISSUE: CARDIOVASCULAR HEALTH PROMOTION

EDITORIAL COMMENT

# Prevention of Heart Failure With SGLT-2 Inhibition

## Insights From CVD-REAL\*



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It is projected that by 2045, 629 million individuals worldwide will have type 2 diabetes (1). Despite significant advances in systems of care, pharmacotherapy, and interventional/surgical approaches, cardiovascular disease continues to be the leading cause of death and disability in persons with diabetes. Not only does diabetes predispose one to an increase in the risk of cardiovascular events, long-term outcomes are worse in those with diabetes following an event or revascularization (2-4).

In addition to ischemic cardiovascular events, such as myocardial infarction and stroke, individuals with diabetes are at a markedly higher risk of developing heart failure (5). Although recent data indicate that the rates of heart failure, myocardial infarction, and stroke are declining among those with diabetes (6), heart failure persists as the leading cause of hospitalization in this group (5,7). Antiplatelet therapies (8), anticoagulant approaches (9), inflammation reduction (10,11), and intensification of lowering low-density lipoprotein cholesterol (12) are great examples of ischemic cardiovascular risk reduction,

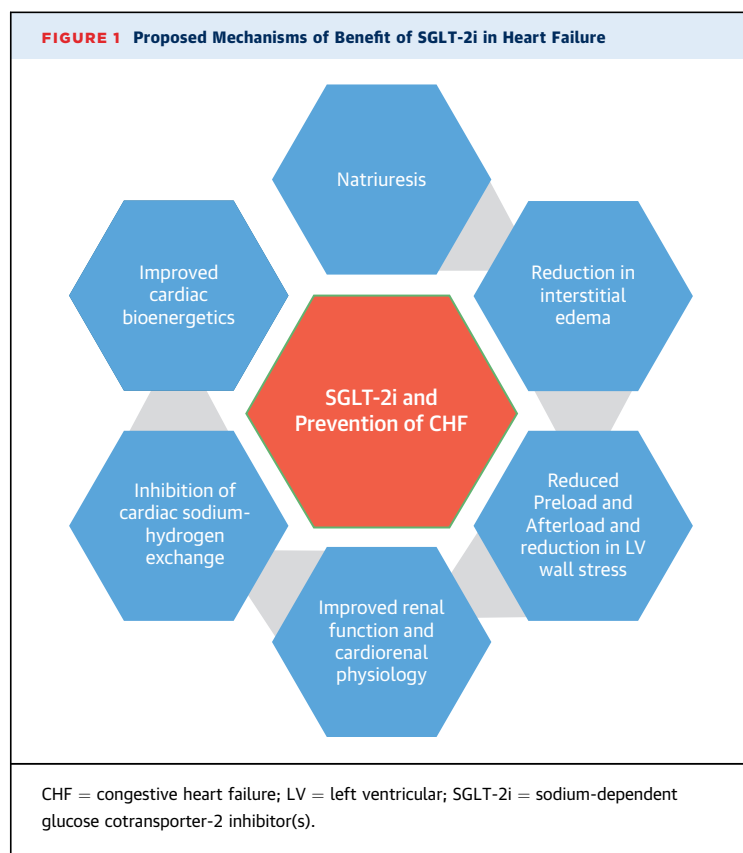
but they do not target the pathophysiological mechanisms germane to the development of diabetic cardiomyopathy.

The collective effects of hyperglycemia and insulin resistance on the cardiomyocyte represents one of the earliest derangements in diabetes, preceding and independent of macrovascular and atherosclerotic vascular disease (13,14). The concept of diabetes-related cardiomyopathy is now widely accepted, and both “heart failure with a preserved ejection fraction” (HFpEF) and “heart failure with a reduced ejection fraction” (HFrEF) phenotypes have been described. It is critical to point out that impaired ventricular relaxation and diastolic dysfunction occur early in diabetes and are seen even in asymptomatic individuals with minimal cardiovascular risk factors (13-15). Therefore, although the conventional definition of primary versus secondary prevention may hold true with respect to ischemic risk, this definition may not be best suited to define those with diabetes who are at risk of heart failure development. Most middle-age persons with type 2 diabetes will have evidence of diastolic dysfunction, even in the absence of a prior ischemic event or known vascular disease. Therefore, heart failure preventative strategies need to be implemented earlier in individuals with diabetes.

The sodium-dependent glucose cotransporter-2 inhibitor(s) (SGLT-2i) class of medications, currently marketed for persons with diabetes, improves glycemic control by promoting glycosuria. In the landmark EMPA-REG OUTCOME (EMPAgliflozin Removal of Excess of Glucose OUTCOME) trial (16), the empagliflozin group exhibited a marked 38% reduction in cardiovascular death without any significant changes in ischemic endpoints of myocardial infarction or stroke. Heart failure-associated hospitalization rates were 35% lower in the empagliflozin group (16); there

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was concomitant lowering of the incidence of worsening nephropathy by 39% among empagliflozin-treated individuals (17). In the CANVAS (CANagliflozin cardioVascular Assessment Study) program (18), a mixed group of participants with and without prior cardiovascular disease were studied. The primary endpoint was similarly reduced to that reported for the EMPA-REG OUTCOME trial, with the point estimate for heart failure-associated hospitalizations reduced by 33%. This effect was consistent in both primary and secondary prevention groups (19), whereas there appeared to be little benefit for ischemic complications in primary prevention. Although there was an increase in amputations of lower limbs associated with canagliflozin therapy in the CANVAS program (18,19), the same was not observed in the empagliflozin arms of the EMPA-REG OUTCOME trial (20,21).

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In this issue of the *Journal*, Cavender et al. (22) provide a subanalysis of the multinational observational CVD-REAL (Comparative Effectiveness of Cardiovascular Outcomes in New Users of SGLT-2 Inhibitors) study that compared outcomes with SGLT-2i therapy versus that with other glucose-lowering therapies in

patients with heart failure and cardiovascular death rates, as stratified by the presence or absence of pre-existing cardiovascular disease. In approximately 300,000 propensity-matched individuals receiving either SGLT-2i or other glucose-lowering therapies, 87% had no previous cardiovascular disease. Use of SGLT-2i was associated with a marked reduction in heart failure-associated hospitalizations and cardiovascular deaths with no heterogeneity based on the presence or absence of baseline cardiovascular disease. Of course, absolute risk of heart failure was higher in those with a history of cardiovascular disease, and therefore, the absolute risk reduction with SGLT-2i versus that with other glucose-lowering agents was greater in those individuals, but the overall relative risk reductions were identical between groups. The magnitude of benefit noted was comparable to that observed in the EMPA-REG OUTCOME and CANVAS program studies. Notably, most of the subjects in the CVD-REAL study were receiving either canagliflozin or dapagliflozin.

The analysis conducted by Cavender et al. (22) provides critical insights into how SGLT2 inhibition may prevent heart failure in a broad range of persons with and without cardiovascular disease and supports recent data from CANVAS (19). Although measurements of diastolic or systolic function are not known in this study, it would be reasonable to hypothesize that a large proportion of those without cardiovascular disease already had impaired diastolic function and were predisposed to developing heart failure. SGLT-2i, when used in such individuals, can prevent heart failure, similar to that observed in people with established cardiovascular disease. These observational data, although tantalizing and hypothesis-generating, require prospective confirmation. The ongoing DECLARE-TIMI 58 (Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events) (23), which recruited a large proportion of participants without established atherosclerotic vascular disease, will help shed light on this issue in a more definitive fashion.

The biology of SGLT2 inhibition from a cardiac standpoint is intriguing (24), and many mechanisms, including diuresis, natriuresis, ketone metabolism, and direct myocardial effects, have been put forward (25-28) (Figure 1). Natriuresis along with glycosuria lead to osmotic diuresis, which in turn, may serve to reduce preload. This condition coupled with an effect to reduce afterload may further optimize loading conditions of the myocardium. Intriguingly, the cardioprotective effects of SGLT-2i have also been observed in nondiabetic animal models of heart failure (25). Recent data also suggest that SGLT-2i may inhibit

myocardial sodium-hydrogen exchange and, through that mechanism, may alter intracellular sodium and calcium handling, which may afford benefits in heart failure. In animal models, SGLT-2i have been shown to attenuate phosphorylation of STAT3 and, through that mechanism, reduce myocardial extracellular matrix accumulation and cardiac fibrosis (29). Compared with other loop diuretics, SGLT-2i has been proposed to differentially regulate interstitial (vs. intravascular) volume status, which may be a particularly useful mechanism in heart failure (30). Preliminary studies indicate that SGLT-2i improve diastolic function in patients with type 2 diabetes (28), and more definitive studies of left ventricular mass regression are currently underway (NCT02998970).

In conclusion, we congratulate the authors for this important subanalysis, which continues to remind us of the importance of heart failure prevention in individuals with diabetes, while ushering hope that SGLT-2i may be a preferred agent of choice in the prevention of one of the deadliest complications of diabetes. Perhaps one of the most important lessons

here is that the distinction between primary and secondary prevention, although appropriate for atherosclerosis risk stratification (and therefore pertinent to antiplatelet and low-density lipoprotein-cholesterol-lowering therapies), may not be ideal for stratifying risk in persons with diabetes and the therapies that are aimed at preventing heart failure. Further insights from the CVD-REAL 2 study are also eagerly awaited. Whether SGLT-2i will be useful agents in the treatment (vs. prevention) of heart failure with and without diabetes remains an important question for which ongoing studies are currently underway (31).

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## REFERENCES

1. International Diabetes Federation. IDF Diabetes Atlas, 8th edition. Brussels, Belgium: International Diabetes Federation; 2017.
2. Donahoe SM, Stewart GC, McCabe CH, et al. Diabetes and mortality following acute coronary syndromes. *JAMA* 2007;298:765-75.
3. van Diepen S, Fuster V, Verma S, et al. Dual antiplatelet therapy versus aspirin monotherapy in diabetics with multivessel disease undergoing CABG: FREEDOM insights. *J Am Coll Cardiol* 2017; 69:119-27.
4. Verma S, Farkouh ME, Yanagawa B, et al. Comparison of coronary artery bypass surgery and percutaneous coronary intervention in patients with diabetes: a meta-analysis of randomised controlled trials. *Lancet Diabetes Endocrinol* 2013; 1:317-28.
5. McMurray JJ, Gerstein HC, Holman RR, Pfeffer MA. Heart failure: a cardiovascular outcome in diabetes that can no longer be ignored. *Lancet Diabetes Endocrinol* 2014;2:843-51.
6. Gregg EW, Li Y, Wang J, et al. Changes in diabetes-related complications in the United States, 1990-2010. *N Engl J Med* 2014;370: 1514-23.
7. Burrows NR, Li Y, Gregg EW, Geiss LS. Declining rates of hospitalization for selected cardiovascular disease conditions among adults aged ≥35 years with diagnosed diabetes, U.S., 1998-2014. *Diabetes Care* 2018;41:293-302.
8. Bhatt DL, Bonaca MP, Bansilal S, et al. Reduction in ischemic events with ticagrelor in diabetic patients with prior myocardial infarction in PEGASUS-TIMI 54. *J Am Coll Cardiol* 2016;67: 2732-40.
9. Eikelboom JW, Connolly SJ, Bosch J, et al. Rivaroxaban with or without aspirin in stable cardiovascular disease. *N Engl J Med* 2017;377: 1319-30.
10. Ridker PM, Everett BM, Thuren T, et al. Anti-inflammatory therapy with canakinumab for atherosclerotic disease. *N Engl J Med* 2017;377: 1119-31.
11. Verma S, Leiter LA, Bhatt DL. CANTOS ushers in a new calculus of inflammasome targeting for vascular protection—and maybe more. *Cell Metab* 2017;26:703-5.
12. Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med* 2017;376: 1713-22.
13. Seferovic PM, Paulus WJ. Clinical diabetic cardiomyopathy: a two-faced disease with restrictive and dilated phenotypes. *Eur Heart J* 2015;36: 1718-27. 1727a-7c.
14. Loncarevic B, Trifunovic D, Soldatovic I, Vujic-Tesic B. Silent diabetic cardiomyopathy in everyday practice: a clinical and echocardiographic study. *BMC Cardiovasc Disord* 2016;16:242.
15. Ernande L, Audureau E, Jellis CL, et al. Clinical implications of echocardiographic phenotypes of patients with diabetes mellitus. *J Am Coll Cardiol* 2017;70:1704-16.
16. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015;373: 2117-28.
17. Wanner C, Inzucchi SE, Lachin JM, et al. Empagliflozin and progression of kidney disease in type 2 diabetes. *N Engl J Med* 2016;375:323-34.
18. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med* 2017;377: 644-57.
19. Mahaffey KW, Neal B, Perkovic V, et al. Canagliflozin for primary and secondary prevention of cardiovascular events: results from the CANVAS program (Canagliflozin Cardiovascular Assessment Study). *Circulation* 2018;137:323-34.
20. Inzucchi SE, Iliev H, Pfarr E, Zinman B. Empagliflozin and assessment of lower-limb amputations in the EMPA-REG OUTCOME trial. *Diabetes Care* 2018;41:e4-5.
21. Verma S, Mazer CD, Al-Omran M, et al. Cardiovascular outcomes and safety of empagliflozin in patients with type 2 diabetes mellitus and peripheral artery disease: a subanalysis of EMPA-REG OUTCOME. *Circulation* 2018;137:405-7.
22. Cavender MA, Norhammar A, Birkeland KI, et al. SGLT-2 inhibitors and cardiovascular risk: an analysis of CVD-REAL. *J Am Coll Cardiol* 2018;71: 2497-506.
23. Raz I, Bonaca MP, Mosezon O, et al. DECLARE-TIMI 58: design and baseline characteristics. Paper presented at: The 77th Scientific Sessions of the American Diabetes Association, June 11, 2017, San Diego, CA.
24. Verma S, McMurray JJV, Cherney DZI. The metabolodiuretic promise of sodium-dependent glucose cotransporter 2 inhibition: the search for the sweet spot in heart failure. *JAMA Cardiol* 2017; 2:939-40.
25. Byrne NJ, Parajuli N, Levasseur JL, et al. Empagliflozin prevents worsening of cardiac function in an experimental model of pressure

overload-induced heart failure. *J Am Coll Cardiol Basic Transl Sci* 2017;1:347-54.

26. Lopaschuk GD, Verma S. Empagliflozin's fuel hypothesis: not so soon. *Cell Metab* 2016;24:200-2.

27. Shi X, Verma S, Yun J, et al. Effect of empagliflozin on cardiac biomarkers in a zebrafish model of heart failure: clues to the EMPA-REG OUTCOME trial? *Mol Cell Biochem* 2017;433:97-102.

28. Verma S, Garg A, Yan AT, et al. Effect of empagliflozin on left ventricular mass and

diastolic function in individuals with diabetes: an important clue to the EMPA-REG OUTCOME trial? *Diabetes Care* 2016;39:e212-3.

29. Lee TM, Chang NC, Lin SZ. Dapagliflozin, a selective SGLT2 inhibitor, attenuated cardiac fibrosis by regulating the macrophage polarization via STAT3 signaling in infarcted rat hearts. *Free Radic Biol Med* 2017;104:298-310.

30. Hallow KM, Helmlinger G, Greasley PJ, et al. Why do SGLT2 inhibitors reduce heart failure hospitalization? A differential volume

regulation hypothesis. *Diabetes Obes Metab* 2018;20:479-87.

31. Butler J, Hamo CE, Filippatos G, et al. The potential role and rationale for treatment of heart failure with sodium-glucose co-transporter 2 inhibitors. *Eur J Heart Fail* 2017;19:1390-400.

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