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Primary Prevention of Heart Failure in Patients With Type 2 Diabetes Mellitus:

Lost in Translation Between Clinical Trial Design, Regulatory Standards, and Practice Guidelines

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In 2008, the US Food and Drug Administration issued an industry guidance that all new therapies for type 2 diabetes mellitus (T2DM) undergo rigorous assessment of cardiovascular safety through large-scale cardiovascular outcome trials (CVOTs) reporting major adverse cardiovascular events, including cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke. Although heart failure (HF) was not specifically mentioned in the Food and Drug Administration regulatory guidance and relegated to a secondary outcome, multiple CVOTs have shown various glucose-lowering therapies to variably increase or decrease the risk of HF events. In the case of the sodium-glucose cotransporter 2 (SGLT-2) inhibitors, positive results on HF outcomes have sparked enthusiasm for these agents as a potential HF therapy, and multiple large-scale clinical trials are underway testing these medications in HF populations, irrespective of T2DM status. However, the vast majority of patients in CVOTs of SGLT-2 inhibitors did not have HF at baseline. It is therefore important to recognize that, by impressive reductions in HF events, these randomized trials provide strong evidence for the primary prevention of new-onset HF among patients with T2DM.

IMPORTANCE OF HF PREVENTION IN T2DM

Among patients with T2DM, HF is the second most common initial presentation of cardiovascular disease after peripheral artery disease, and more frequent than other atherosclerotic complications like myocardial infarction and stroke. A recent large observational study of >270 000 patients with T2DM suggests that optimal management of cardiovascular risk factors may neutralize excess risk of myocardial infarction and stroke;

but such a relationship was not seen with respect to HF, where even patients with T2DM and no additional risk factors faced a 45% excess risk of HF hospitalization in comparison with individuals without T2DM.[1] Overall risk for mortality after HF diagnosis remains «50% at 5 years, a risk worse than many forms of cancer. These data emphasize the prevention of HF as an important unmet need requiring evidence-based strategies.

CURRENT GUIDELINES FOR PRIMARY PREVENTION OF HF

HF guidelines have long recommended the prevention of HF through optimal management of risk factors and comorbidities. In 2017, for the first time, the American College of Cardiology/American Heart Association/Heart Failure Society of America HF management guidelines issued a class IIA recommendation for using natriuretic peptide screening for those at risk of developing HF, followed by team-based care to prevent the development of new-onset HF.[2] These recommendations were based on 2 trials (Table).[2] In aggregate, these programs enrolled 1674 patients without baseline HF and captured a total of 29 subsequent HF hospitalization events.[2]

SGLT-2 INHIBITORS FOR PRIMARY PREVENTION OF HF IN T2DM

The EMPA-REG OUTCOME (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients–Removing Excess Glucose) and CANVAS (Canagliflozin Cardiovascular Assessment Study) trials collectively randomly assigned 17 162 patients with T2DM at high cardiovascular risk and found treatment with empagliflozin and canagliflozin to decrease the risk of HF hospitalization by 35% and 33%, respectively.[3,4] The proportion of patients with baseline HF was low (ie, combined 12.6%), and thus these studies effectively tested the role of SGLT-2 inhibition in the primary prevention of HF. For example, based on the random assignment of 6314 patients and 143 HF hospitalization events, empagliflozin significantly reduced the risk of HF hospitalization among patients without existing HF by 31%. The collective trial data are further validated by real-world evidence from the CVD-REAL (Comparative Effectiveness of Cardiovascular Outcomes in New Users of SGLT-2 Inhibitors) study. This observational program compared >300 000 patients with T2DM newly initiated on any SGLT-2 inhibitor versus any other glucose-lowering agent across 6 countries.[5] Despite the inherent limitations of an observational analysis, CVD-REAL included 961 HF events and demonstrated a 39% relative reduction in HF hospitalization, suggesting that the benefits of SGLT-2 inhibitors for prevention of HF in clinical practice are remarkably similar to those appreciated in randomized trials.

RECOMMENDATION AND INDICATION

With nearly 15 000 patients at risk for new-onset HF randomly assigned within the EMPA-REG OUTCOME and CANVAS trials, along with large-scale real-world comparative effectiveness data from >300 000 patients in the CVD-REAL analysis, SGLT-2 inhibitor studies have offered robust data for primary prevention of HF among the high-risk T2DM population. However, despite the high risk for development of HF among patients with T2DM and high risk for mortality and morbidity subsequent to a HF diagnosis, these drugs do not carry an indication for HF prevention either from regulatory authorities or

cardiovascular or T2DM practice guidelines, largely because HF was not the primary end point in these studies.

Limitations will always exist with regard to HF being a secondary trial end point (eg, EMPA-REG OUTCOME did not use the standardized definition of HF hospitalization developed by the Standardized Data Collection for Clinical Trials Initiative). Nonetheless, this should be taken in perspective with historical guidance from the Food and Drug Administration for CVOT design. In general, it is best practice to base regulatory and guideline decisions on dedicated trials and results on prespecified primary end points. However, given the now established role of SGLT-2 inhibitors in reducing major adverse cardiovascular events in high-risk patients with T2DM, it will not be feasible or ethical to conduct trials in similar populations with these agents with HF prevention as the primary end point.

We believe that the existing evidence for SGLT-2 inhibitors in the prevention of incident HF compares favorably with evidence prompting the introduction of natriuretic peptide screening to HF guidelines, and to the evidence underlying many long-standing primary prevention strategies in other disease states (eg, aspirin for primary prevention of atherosclerotic cardiovascular disease; Table). The supporting evidence is based on (1) consistent benefit across 2 randomized, controlled trials, (2) robust statistical significance in large randomized populations, (3) confirmation with real-world data, and (4) pharmacodynamic effects that can explain the observed benefits. Optimization of conventional cardiovascular risk factors in T2DM may adequately control risk of atherosclerotic disease, but be ineffective in curtailing the high risk of HE.[1] Given the robust data from recent SGLT-2 CVOT trials and the unmet clinical need, we recommend a paradigm shift in HF preventive strategy and recognition of these agents as an effective means to prevent new-onset HF among patients with T2DM, irrespective of glycemic control or atherosclerotic risk management.

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REFERENCES

1. Rawshani A, Rawshani A, Franzén S, Sattar N, Eliasson B, Svensson AM, Zethelius B, Miftaraj M, McGuire DK, Rosengren A, Gudbjörnsdottir S. Risk Factors, mortality, and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med. 2018;379:633–644. doi: 10.1056/NEJMoa1800256 [PubMed: 30110583]
2. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Colvin MM, Drazner MH, Filippatos GS, Fonarow GC, Givertz MM, Hollenberg SM, Lindenfeld J, Masoudi FA, McBride PE, Peterson PN, Stevenson LW, Westlake C. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA

guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. Circulation. 2017;136:e137–e161. doi: 10.1161/CIR.0000000000000509 [PubMed: 28455343]

3. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, Mattheus M, Devins T, Johansen OE, Woerle HJ, Broedl UC, Inzucchi SE; EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med. 2015;373:2117–2128. doi: 10.1056/NEJMoa1504720 [PubMed: 26378978]
4. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, Shaw W, Law G, Desai M, Matthews DR; CANVAS Program Collaborative Group. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med. 2017;377:644–657. doi: 10.1056/NEJMoa1611925 [PubMed: 28605608]
5. Kosiborod M, Cavender MA, Fu AZ, Wilding JP, Khunti K, Holl RW, Norhammar A, Birkeland KI, Jørgensen ME, Thuresson M, Arya N, Bodegård J, Hammar N, Fenici P; CVD-REAL Investigators and Study Group*. Lower risk of heart failure and death in patients initiated on sodiumglucose cotransporter-2 inhibitors versus other glucose-lowering drugs: the CVD-REAL Study (Comparative Effectiveness of Cardiovascular Outcomes in New Users of Sodium-Glucose Cotransporter-2 Inhibitors). Circulation. 2017;136:249–259. doi: 10.1161/CIRCULATIONAHA.117.029190 [PubMed: 28522450]

Table.

Key Studies Relevant to the Primary Prevention of HF in Patients With Type 2 Diabetes Mellitus

Study Name (Trial Registration Number)	Study Design and Intervention	Overall Trial Population	N (%) Without Baseline HF	HF Hospitalization Events During Follow-Up Among Patients Without Baseline HF	Effect on HF Hospitalization Among Patients Without Baseline HF*
Studies of natriuretic peptide screening					
STOP-HF ()	Randomized, controlled trial of BNP screening versus usual primary care	Age >40 y and history of CV disease or CV risk factors	1374 (100)	21	OR, 0.48 (95% CI, 0.20–1.20)
PONTIAC ()	Randomized, controlled trial of treatment in cardiac outpatient clinic for up-titration of RAAS inhibitors and β-blockers plus care in a diabetes mellitus care unit versus care in diabetes mellitus care unit alone	T2DM, NT-proBNP >125 pg/mL, and no known CV disease	300 (100)	8	HR, 0.14 (95% CI, 0.02–1.14)
Studies of SGLT-2 inhibitors					
EMPA-REG OUTCOME ()	Randomized, controlled trial of empagliflozin versus placebo	T2DM and established CV disease	6314 (89.9)	143	HR, 0.59 (95% CI, 0.43–0.82)
CANVAS (;)	Randomized, controlled trial of canagliflozin versus placebo	T2DM and history of symptomatic CV disease or age ≥50 y with CV risk factors	8681 (85.6)	243 (overall trial population)	Overall trial population: HR, 0.67 (95% CI, 0.52–0.87) *P* for interaction by baseline HF status=0.47 (non-HF subgroup; HR, 0.79 [95% CI, 0.57–1.09])
CVD-REAL ()	Observational propensity-matched study of initiation of SGLT-2 inhibitor versus initiation of other glucose-lowering therapy	T2DM	299 583 (96.9)	961 (overall trial population)	Overall trial population: HR, 0.61 (95% CI, 0.51–0.73)

BNP indicates B-type natriuretic peptide; CANVAS, Canagliflozin Cardiovascular Assessment Study; CV, cardiovascular; CVD-REAL, Comparative Effectiveness of Cardiovascular Outcomes in New Users of SGLT-2 Inhibitors; EMPA-REG OUTCOME, Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients–Removing Excess Glucose; HF, heart failure; HR, hazard ratio; NT-proBNP, N-terminal pro–B-type natriuretic peptide; OR, odds ratio; PONTIAC, NT-proBNP Guided Primary Prevention of CV Events in Diabetic Patients; RAAS, renin-angiotensin-aldosterone system; SGLT-2, sodium-glucose cotransporter 2; STOP-HF, St. Vincent's Screening to Prevent Heart Failure; and T2DM, type 2 diabetes mellitus.

*Data reflect risk of HF hospitalization among patients without baseline HF, unless otherwise specified.