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EDITORIAL COMMENT

Glucose-Lowering Therapies in Patients With Concomitant Diabetes Mellitus and Heart Failure

Finding the "Sweet Spot"*

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Since the U.S. Food and Drug Administration guidance in 2008 required the specific cardiovascular safety evaluation of novel glucose-lowering therapies, over 150,000 patients with type 2 diabetes mellitus (T2DM), at high cardiovascular risk, have been rigorously studied in dedicated cardiovascular outcome trials. These trials have studied treatment effects with respect to cardiovascular events, using several different therapies thus far, prompting the Food and Drug Administration to expand the regulatory labeling of empagliflozin (reduction of cardiovascular mortality) and liraglutide (reduction of major adverse cardiovascular events) for T2DM patients at heightened cardiovascular risk. Despite these accumulating data and broadened indications for use, the safety and efficacy of these emerging glucose-lowering therapies in patients at risk for or with prevalent heart failure (HF) are presently not entirely certain.

RATIONALE FOR STUDYING HF WITH NOVEL GLUCOSE-LOWERING THERAPIES

There is a clear rationale and an unmet clinical need to study the intersection between T2DM and HF better. Patients with T2DM are at risk for developing HF over time, and incident HF is associated with a uniquely poor prognosis in this cohort. In addition, the treatment risks and benefits on HF-specific outcomes may vary by the specific drug, therapeutic class, and baseline HF status. Few glucose-lowering therapies increase risk of HF without modifying other cardiovascular outcomes (e.g., thiazolidinediones). Certain drugs increase risk for hospitalization for HF (e.g., dipeptidyl peptidase [DPP]-4 inhibitors, saxagliptin, and, to a lesser extent, alogliptin), whereas other drugs in the same therapeutic class do not appear to have these adverse treatment effects (e.g., sitagliptin). Other glucose-lowering therapies reduce risk of overall cardiovascular events, a treatment benefit that appears to be driven by their benefits in HF risk, even in patients without prevalent HF at baseline (e.g., the sodium-glucose cotransporter-2 inhibitors) (1). Finally, some drugs may have important cardiovascular benefits in an overall high-risk cohort of patients with T2DM but may have limited (or even adverse) effects on clinical stability in patients with established HF (e.g., liraglutide).

DIABETES MELLITUS AND HF: A COMPLEX DEADLY COMBINATION

In the setting of these mixed therapeutic effects and as novel glucose-lowering therapies become incorporated into the general cardiometabolic armamentarium, 2 articles in this issue of *JACC: Heart Failure* (2,3) further our understanding of the complex interplay between T2DM and HF. Lawson et al. (2) conducted a broad-scale, nested-case control study from 2002 to 2014 of ~49,000 patients with incident HF and evaluated subsequent clinical events based on T2DM status, glycemic control, and background

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T2DM therapies. The study was conducted within the U.K. Clinical Practice Research Datalink, a governmental, nonprofit research database containing anonymized ambulatory records capturing data from ~10% of the general U.K. population. The authors found a U-shaped relationship between glycated hemoglobin (HbA_{1c}) levels and all-cause hospitalization and death, such that poorly controlled glycemic status of >9.5% and very tight glycemic control of <5.5% were associated with excess risk. Furthermore, short-term interval change in HbA_{1c} (either increase or decrease of >1%) was associated with worse prognosis (2). These data are subject to a number of limitations inherent in the study design, including identification of HF based on electronic administrative records (which is known to be subject to variable accuracy [4]), lack of characterization of HF, and use of all-cause rather than cardiovascular or HF-specific outcomes (2).

SEE PAGES 8 AND 18

Despite these limitations, this large, representative study highlights several important findings. Patients with incident HF, especially those with pre-existing T2DM diagnosed prior to development of HF, face a malignant course with >50% mortality during a median follow-up of 2.6 years. Consistent with temporal changes in other cardiometabolic parameters (5), fluctuation of glycemic status may be deleterious, although the causality of such association is uncertain. Indeed, patients with established HF at high-risk for clinical events may be prone to hypoglycemic events. The safe development of therapies targeting T2DM in patients with prevalent HF must be achieved while limiting untoward effects of glucose lowering. Finally, short-term decreases in HbA_{1c} and de-escalation of glucose-lowering therapies, likely reflecting progressive systemic illness and clinical worsening, were unsurprisingly associated with adverse outcomes. This disconnect between glycemic indices and clinical outcomes in high-risk patients emphasizes the role of exploring therapeutic pathways beyond optimizing glycemic status alone in this population.

EXPANDING CARDIOVASCULAR SAFETY ASSESSMENT TO INCLUDE HF

Also featured in this issue, McMurray et al. (3) present the placebo-controlled, double-blind, early-phase VIVIDD (Vildagliptin in Ventricular Dysfunction Diabetes) trial evaluating the DPP-4 inhibitor vildagliptin in patients with T2DM and HF with reduced ejection fraction. The trial enrolled 254 patients from 67 global sites over more than 3 years. Echocardiographic assessment was conducted by a blinded team in a dedicated core laboratory. The investigators demonstrated noninferiority with respect to the primary endpoint of change in left ventricular ejection fraction after 1 year of treatment with vildagliptin compared with placebo. Patients randomized to vildagliptin did however experience increased left ventricular volumes over time. There were also numerically higher deaths (8.6% vs. 3.2%, respectively), cardiovascular hospitalizations (14.8% vs. 11.2%, respectively), and hospitalizations for HF (10.2% vs. 8.0%, respectively) in the vildagliptin arm compared with the placebo arm, but the overall number of these clinical events was low, and the study was not powered to assess cardiovascular safety. The drug improved glycemic control (reduction in HbA_{1c} of ~0.4% over 1 year compared with placebo) without other major side effects (3).

Despite its modest size, this study rigorously and uniquely collected granular details regarding HF functional class, ventricular function, and baseline HF therapies that have been previously poorly characterized regarding this class of glucose-lowering therapies. In fact, large cardiovascular outcome trials of saxagliptin, alogliptin, and sitagliptin have enrolled only a fraction of patients with HF at baseline and poorly define these elements. It is however important to recognize that VIVIDD was not a conventional cardiovascular safety trial; it focused instead on ventricular function. Given uncertain risks of HF with the use of DPP-4 inhibitors, this trial provides initial data regarding the stability of left ventricular ejection fraction but also raises concerns regarding increased left ventricular volumes and potentially higher clinical event rates with vildagliptin. The clinical significance of these signals will need to be further clarified in larger studies of DPP-4 inhibitors in patients with T2DM and established HF.

LOOKING BACK BEFORE MOVING FORWARD

Novel glucose-lowering therapies offer great promise to improve cardiovascular health in patients with or at risk for HF. Prior to widespread adoption, especially in older, higher risk, and more medically comorbid patients, we must ensure complete understanding of the therapeutic effects of these drugs. Multiple studies are now underway to define the safety and efficacy profile of glucose-lowering therapies in patients with established HF, including in the significant and clinically important subset with HF with preserved ejection fraction (6). In the interim, greater

mechanistic data similar to VIVIDD should focus on in-depth patient profiling with cardiovascular biomarkers, myocardial structural and functional parameters, hemodynamics, and cardiometabolic indices to understand the pathobiology underlying T2DM and HF and the beneficial and harmful therapeutic effects. Finally, effective implementation programs are needed for these therapies to be integrated into routine clinical care, while balancing polypharmacy and minimizing treatment-related adverse events, including hypoglycemia. These studies represent important steps to further efforts to characterize this high-risk subset with T2DM and HF and to optimize their cardiometabolic health.

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