Heart Failure, Diabetes Mellitus, and Chronic Kidney Disease
A Clinical Conundrum

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Type 2 diabetes mellitus and heart failure (HF) commonly coexist, with diabetes mellitus occurring in ≈25% of patients with chronic HF and ~40% in those hospitalized with acute HF. Importantly, the presence of diabetes mellitus in HF is associated with reduced survival and increased rates of hospitalization compared with HF patients without diabetes mellitus. Despite the common and dangerous coexistence of diabetes mellitus and HF, the optimal management of diabetes mellitus in patients with established HF is not well defined, and the presence of HF complicates the pharmacological treatment of hyperglycemia. For example, thiazolidinediones are associated with greater rates of HF hospitalization and should be avoided in symptomatic HF patients. Additionally, the risk of hypoglycemia with sulfonylureas and insulin may be particularly relevant.

See Article by Patel et al

The presence of chronic kidney disease (CKD) further complicates the treatment of diabetes mellitus in HF patients. Approximately 40% to 50% of HF patients have CKD, and the severity of renal dysfunction is associated with a graded increased risk of death. Similar to HF, pharmacological treatment of hyperglycemia in patients with CKD is challenging, with few studies to guide treatment in this population. As CKD progresses, most of the oral antihyperglycemic medications must be reduced or discontinued depending on renal clearance. Metformin is contraindicated in patients with advanced CKD (eGFR <30 mL/min per 1.73 m²), although the absolute renal threshold for discontinuation of metformin varies per guidelines. With moderate or severe CKD, most sulfonylureas should be avoided because of decreased renal clearance and risk of hypoglycemia. Further challenging the cardiologist is the growing number of available antihyperglycemic medications. These newer medications include the incretin-based therapies, such as dipeptidyl peptidase-4 inhibitors and glucagon-like peptide 1 receptor agonists and the sodium–glucose co-transporter 2 inhibitors. Medications within each of these classes may require dose adjustment or discontinuation in patients with worsening CKD.

In this issue of Circulation: Heart Failure, Patel et al bring much needed attention to the complicated conundrum regarding the treatment of hyperglycemia in older patients with HF, diabetes mellitus, and CKD. Using the Get With the Guidelines-Heart Failure (GWTG-HF) program and linking the program to Medicare Part D Claims data, the authors describe the pattern of antihyperglycemic medication use in diabetic patients discharged with HF and CKD. The GWTG-HF patients with diabetes mellitus selected for the analysis were older (median age, 77 years) and had a high prevalence of CKD (17.2% with eGFR<30 mL/min per 1.73 m² and 49.1% with eGFR 30–60 mL/min per 1.73 m²), findings that confirm the common existence of advanced renal dysfunction in older HF patients with diabetes mellitus. Multiple observations of the study highlight treatment challenges in this population. Despite being discharged with HF, 6.6% of patients were treated with thiazolidinediones. Moreover, the use of antihyperglycemic medications that may be contraindicated occurred in 35% of patients with advanced CKD (eGFR<30 mL/min per 1.73 m²). Temporal trends demonstrated improvements in prescribing patterns over the study (2006–2011), with reductions in the use of thiazolidinediones and potentially renal contraindicated antihyperglycemic medications, but the use of other medications that should be cautiously used or avoided, such as dipeptidyl peptidase-4 inhibitors, increased.

The challenges of treating diabetes mellitus in HF patients, particularly in the presence of CKD, highlighted in the study by Patel et al reflect a historical gap in knowledge and data regarding the optimal treatment of these high-risk patients. Indeed, this need for further safety data regarding antihyperglycemic therapy in high cardiovascular-risk patients was reflected in the US Food and Drug Administration requirements, which has led to multiple large-scale cardiovascular outcome studies of new antihyperglycemic medications. Several of these cardiovascular outcome trials of antihyperglycemic medications have now been completed (Table) and provide observations relevant to the population studied by Patel et al. As demonstrated in Table, the cardiovascular outcome studies have included larger number of patients with established HF and baseline CKD, although several studies excluded patients with an eGFR <30 mL/min per 1.73 m² if the medication was contraindicated. Studies also required treatment dose reductions based on renal function.

The outcomes of these studies have also provided important data. By meeting their primary noninferiority major adverse cardiovascular event outcome, the studies have provided reassuring safety data in high-risk cardiovascular patients. Even

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more promising, recent studies with liraglutide and empagliflozin have demonstrated cardiovascular benefit when compared with placebo. Importantly, the cardiovascular outcome studies have demonstrated no heterogeneity in the primary outcome in those with and without HF at baseline. Although most studies have also not demonstrated heterogeneity for the primary outcome in patients with baseline CKD, thiazolidinediones, and nearly 20% of patients with an eGFR <60 mL/min per 1.73 m² (hazard ratio 0.69, 95% confidence interval 0.57–0.85) compared with those with eGFR ≥60 mL/min per 1.73 m² (hazard ratio 0.94, 95% confidence interval 0.83–1.07; P interaction =0.01). On the contrary, alogliptin was associated with nominally increased rates of major adverse cardiovascular events in those with eGFR <60 mL/min per 1.73 m² (hazard ratio 1.15, 95% confidence interval 0.91–1.46) compared with those with eGFR ≥60 mL/min per 1.73 m² (hazard ratio 0.84, 95% confidence interval 0.68–1.04; P interaction =0.046). Finally, although most studies have shown no difference in HF hospitalization with active therapy, HF hospitalization was increased with saxagliptin and reduced with empagliflozin.

In aggregate, these cardiovascular trials provide welcome data regarding the treatment of hyperglycemia in diabetic patients with high cardiovascular risk, including patients with HF and CKD. Nonetheless, more information is needed regarding the treatment of diabetic patients who have both HF and CKD. In the Saxagliptin Assessment of Vascular Outcomes Recorded in Myocardial Infarction 53 trial (SAVOR-TIMI 53), 56.5% of patients with HF at baseline had an eGFR <60 mL/min per 1.73 m², and despite being in a clinical trial, 3.5% of these HF patients were treated with thiazolidinediones, and nearly 20% of patients with an eGFR <30 mL/min per 1.73 m² at baseline were treated with metformin. These findings, coupled with GWTG-HF data, highlight the need for increasing awareness regarding the use of antihyperglycemic medications in patients with HF and CKD, implementing appropriate dose reductions based on renal function and avoiding medications that are potentially harmful.

Disclosures
Dr Aguilar has received consulting fees from Bristol-Myers Squibb and is a researcher in the Exenatide Study of Cardiovascular Event Lowering Trial (EXSCEL) trial.

Table. Key Characteristics and Outcomes of Cardiovascular Outcome Trials Evaluating Antihyperglycemic Medications

<table>
<thead>
<tr>
<th>CV Outcome Trial</th>
<th>Intervention</th>
<th>Number of Patients</th>
<th>Patients With HF at Baseline, %</th>
<th>Renal Dysfunction at Baseline, %</th>
<th>Hazard Ratio for Primary MACE Outcome (95% CI)*</th>
<th>Hazard Ratio for HF Hospitalization (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAVOR-TIMI 53</td>
<td>Saxagliptin</td>
<td>16492</td>
<td>12.8%</td>
<td>eGFR 30–50: 13.6%</td>
<td>1.00 (0.89–1.12)</td>
<td>1.27 (1.07–1.51)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>eGFR&lt;30: 2.0%</td>
<td></td>
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</tr>
<tr>
<td>EXAMINE 10</td>
<td>Alogliptin</td>
<td>5380</td>
<td>28.5%</td>
<td>eGFR&lt;60: 29.1%</td>
<td>0.96 (upper 95% CI 1.16)</td>
<td>1.07 (0.79–1.46)</td>
</tr>
<tr>
<td>TECOS 14</td>
<td>Sitagliptin</td>
<td>1487</td>
<td>18.0%</td>
<td>eGFR&lt;60: 22.7%</td>
<td>0.98 (0.88–1.09)†</td>
<td>1.00 (0.83–1.20)</td>
</tr>
<tr>
<td>ELIXA 15</td>
<td>Lixisenatide</td>
<td>6068</td>
<td>22.4%</td>
<td>eGFR&lt;60: 23.2%‡</td>
<td>1.02 (0.89–1.17)†</td>
<td>0.96 (0.75–1.23)</td>
</tr>
<tr>
<td>LEADER 16</td>
<td>Liraglutide</td>
<td>9340</td>
<td>14.0%</td>
<td>eGFR 30–59: 20.7%</td>
<td>0.87 (0.78–0.97)</td>
<td>0.87 (0.73–1.05)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>eGFR &lt;30: 2.4%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EMPA-REG Outcome 17</td>
<td>Empagliflozin</td>
<td>7020</td>
<td>10.0%</td>
<td>eGFR&lt;60: 25.6§</td>
<td>0.86 (0.74–0.99)</td>
<td>0.65 (0.50–0.85)</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate (mL/min per 1.73 m²); ELIXA, The Evaluation of Lixisenatide in Acute Coronary Syndrome trial; EXAMINE, the Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care trial; HF, heart failure; LEADER, Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results trial; MACE, major adverse cardiovascular events; SAVOR-TIMI 53, the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus-Thrombolysis in Myocardial Infarction 53 trial; and TECOS, Trial Evaluating Cardiovascular Outcomes with Sitagliptin trial.

* MACE outcome = CV death, MI, and stroke.
† MACE included unstable angina hospitalization.
‡ Excluded patients with eGFR<30 mL/min per 1.73 m².

References
Aguilar Heart Failure, Diabetes, and CKD


Key Words: Editorials ■ chronic kidney disease ■ diabetes mellitus ■ heart failure ■ hyperglycemia ■ insulin