**BACKGROUND**

- Fibroblast growth factor (FGF)-23 is a hormone regulator of mineral metabolism and is elevated in early stages of chronic kidney disease.
- Associations of FGF-23 with adverse CV and kidney outcomes have not been evaluated in large cohorts of patients with type 2 diabetes mellitus (T2DM).
- Sodium-glucose co-transporter-2 inhibitors (SGLT2i) have pleiotropic CV and kidney benefits in patients with and without T2DM, but their effects in relation to circulating FGF-23 are unknown.

**METHODS**

- DECLARE-TIMI 58 was a randomized trial of the SGLT2i dapagliflozin in patients with T2DM (median follow-up = 4.2 years).
- Biomarker substudy: FGF-23 (EliA, ProteinSimple) measured at baseline in 14,330 patients.
- Key cardiovascular endpoints included:
  - CV death (CVD) or hospitalization for HF (HHF)
  - Renal-specific composite (≥40% decline in eGFR to <60 ml/min/1.73 m², new ESRD, or renal death)
  - Slope of change in eGFR from baseline
  - Hazard ratios adjusted for age, sex, prior HF, CAD, AF, urine albumin-creatinine ratio, eGFR, and BMI
- Comparative effects with dapagliflozin vs. placebo assessed by quartiles of baseline FGF-23

**RESULTS**

- Median baseline FGF-23 was 129 (IQR, 99–178) RU/ml. Table 1. Baseline characteristics by FGF-23 quartile.

<table>
<thead>
<tr>
<th>Quartiles</th>
<th>Median FGF-23 (IQR)</th>
<th>N</th>
<th>%</th>
<th>Male sex, %*</th>
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<tbody>
<tr>
<td>Q1</td>
<td>30 (22, 49)</td>
<td>867</td>
<td>-</td>
<td>68</td>
<td>52</td>
<td>44</td>
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</tr>
<tr>
<td>Q2</td>
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<td>Q4</td>
<td>112 (89, 129)</td>
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</table>

Demographics

- Age (y), mean (SD) | 60 (5.7) | 62 (5.7) | 64 (6.0) | 64 (6.0) | 65 (6.0) | 65 (6.0) |
- Male sex, %* | 73 | 73 | 77 | 77 | 73 | 73 |
- White race, %* | 77 | 77 | 82 | 82 | 78 | 78 |
- BMI (kg/m²), median (IQR) | 27 (23, 31) | 31 (23, 31) | 32 (28, 36) | 34 (30, 38) |

Diabetes History

- Duration of DM (y), median (IQR) | 10 (10, 15) | 9 (9, 15) | 8 (8, 13) | 9 (9, 13) |
- HbA1c (%), median (IQR) | 7.3 (7.1, 8.0) | 7.2 (7.0, 8.0) | 7.6 (7.1, 8.1) | 7.6 (7.1, 8.1) |
- Baseline insulin use, %* | 34 | 34 | 39 | 39 | 42 | 42 |

Comorbidities, LBD, Vital Signs

- Established ASCVD, %* | 37 | 37 | 41 | 41 | 48 | 48 |
- Heart failure, %* | 7 | 7 | 10 | 10 | 14 | 14 |
- eGFR, median (IQR) | 94 (85, 100) | 91 (79, 97) | 86 (73, 95) | 80 (65, 92) |

SBP (mmHg), median (IQR) | 135 (125, 145) | 136 (125, 145) | 137 (124, 145) | 136 (124, 145) |

- Patients with higher FGF-23 were older, more likely to be female, and more likely to have higher BMI, lower eGFR, and pre-existing ASCVD and HF (Table 1). Figure 1. FGF-23 & cardiac endpoints (adjusted associations).

**RESULTS**

- FGF-23 more strongly associated with risk of mortality and adverse heart failure and kidney events than with atherothrombotic events (Figure 1).
- There was a stepwise gradient of higher risk for CVD/HF and the renal-specific composite across higher quartiles of baseline FGF-23 (Figure 2).

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- The reductions in CVD/HF and the renal-specific composite with dapagliflozin were consistent across quartiles of FGF-23 (Figure 3).

**CONCLUSIONS**

- Higher baseline FGF-23 is independently associated with higher risk of adverse HF and kidney outcomes in patients with T2DM, independent of age, CV history, and baseline kidney function.
- Dapagliflozin consistently reduced risk of these outcomes irrespective of FGF-23.