Sodium-Glucose Cotransporter-2 Inhibitors in Heart Failure with Mildly Reduced or Preserved Ejection Fraction: A Systematic Review and Meta-Analysis

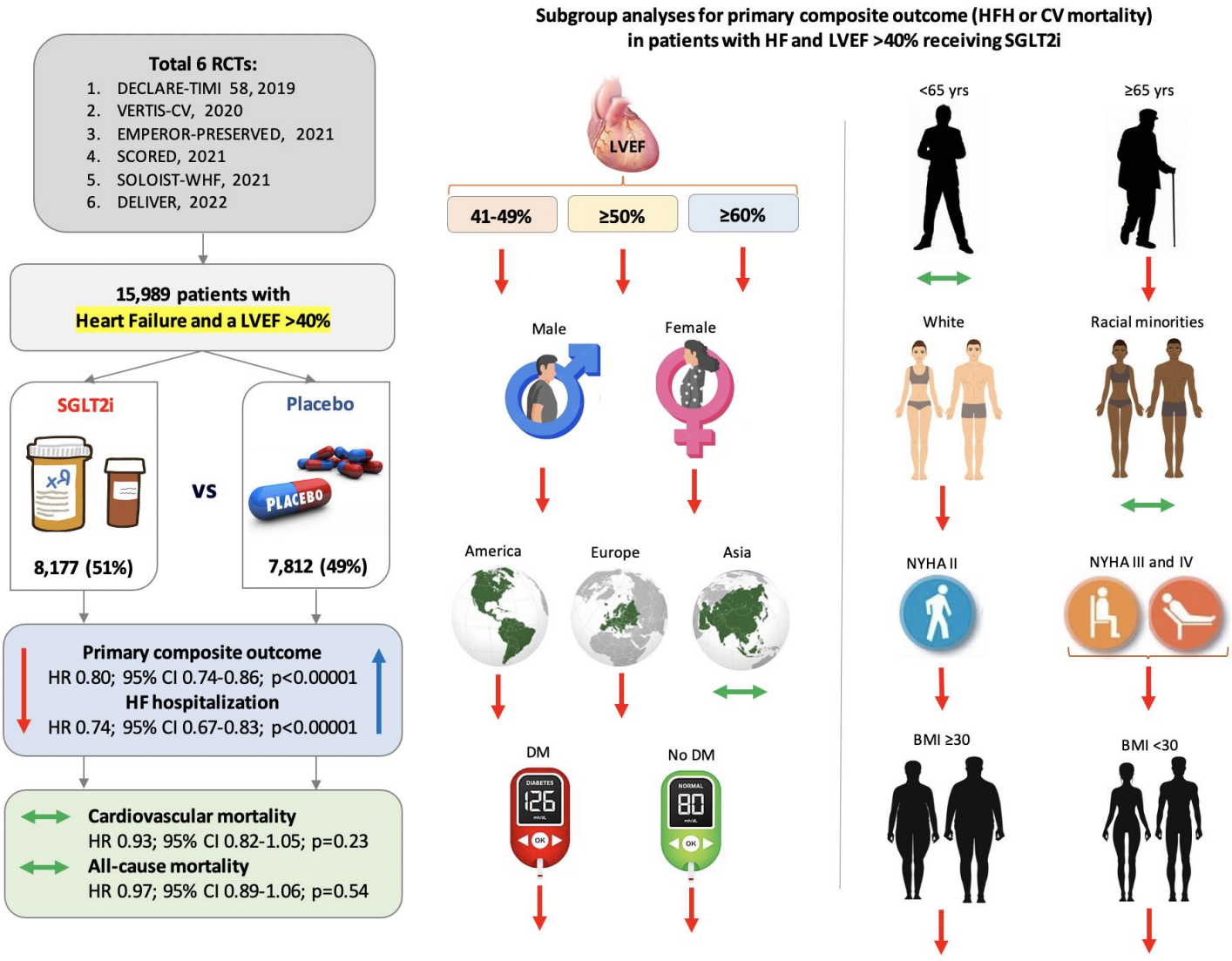
Background: Sodium-glucose cotransporter-2 inhibitors (SGLT2i) reduce the risk of heart failure hospitalizations (HFH) and cardiovascular mortality among patients with chronic heart failure and left ventricular ejection fraction (LVEF) ≤40%. There is emerging evidence of the benefits of SGLT2i in heart failure patients with a higher LVEF (>40%).

Methods: We searched multiple databases for randomized controlled trials (RCTs) comparing outcomes of SGLT2i vs. placebo in patients with heart failure (HF) and LVEF >40%. The hazard ratios (HRs) and 95% confidence intervals (CIs) in each study were used for the meta-analysis. The primary composite outcome (PCO) was HFH or cardiovascular mortality. Secondary outcomes included HFH, cardiovascular mortality, and all-cause mortality.

Results: Six RCTs with 15,989 patients were included (median follow-up=27.3 months, 40.8% females). In patients with HF and LVEF >40%, SGLT2i were associated with significantly lower PCO compared to placebo (HR 0.80; 95% CI 0.74-0.86; p<0.00001). This was consistent across 10/13 subgroups examined, including LVEF. SGLT2i also reduced HFH but not cardiovascular or all-cause mortality. Patients <65 years old, from racial minorities, or from Asia receiving SGLT2i did not demonstrate a significant reduction in PCO (Figure 1).

Conclusion: SGLT2i significantly reduce the combined risk of HFH or cardiovascular mortality among patients with HF and LVEF >40%. However, younger patients, racial minorities, and patients from Asia did not demonstrate such a reduction. Guidelines should adopt SGLT2 for HF and LVEF >40%. Further research is necessary to identify the reasons for age, racial, and geographic disparities in SGLT2i benefits in patients with HF and LVEF >40%.

Figure 1


Total 6 RCTs:
1. DECLARE-TIMI 58, 2019
2. VERTIS-CV, 2020
3. EMPEROR-PRESERVED, 2021
4. SCORED, 2021
5. SOLOIST-WHF, 2021
6. DELIVER, 2022
15,989 patients with
Heart Failure and a LVEF >40%
SGLT2i
Placebo
vs
PLACEBO
8,177 (51%)
7,812 (49%)
Primary composite outcome
HR 0.80; 95% CI 0.74-0.86; p<0.00001
HF hospitalization
HR 0.74; 95% CI 0.67-0.83; p<0.00001
Cardiovascular mortality
HR 0.93; 95% CI 0.82-1.05; p=0.23
All-cause mortality
HR 0.97; 95% CI 0.89-1.06; p=0.54
Subgroup analyses for primary composite outcome (HFH or CV mortality)
in patients with HF and LVEF >40% receiving SGLT2i
LVEF
41-49%
≥50%
≥60%
Male
Female
America
Europe
Asia
DM
No DM
<65 yrs
≥65 yrs
White
Racial minorities
NYHA II
NYHA III and IV
BMI ≥30
BMI <30