University, Melbourne, Australia, presented the results of a composite analysis of 3 randomized trials: the WHICH? trial [Stewart S et al. *Int J Cardiol.* 2014], the SAFETY trial [Stewart S et al. *Lancet.* 2015], and the NIL-CHF study [Stewart S et al. *Eur J Heart Fail.* 2015]. The hypothesis was that HBI would be superior to high levels of SC in the prevention of repeated hospitalizations and premature mortality and that the effectiveness of HBI would increase as the complexity of the clinical cases increased.

The 3 trials enrolled patients across the spectrum of cardiac disease. The WHICH? trial enrolled patients with heart failure (HF) with reduced ejection fraction and preserved ejection fraction, the SAFETY trial enrolled patients with chronic atrial fibrillation without HF, and the NIL-CHF study enrolled cardiac patients, most with acute coronary syndrome, without HF. In all of the studies, patients were recruited during acute hospitalization before returning home. All 3 trials were compliant with the Consolidated Standards of Reporting Trials, had independent data management and statistical analysis, and had blinded end point acquisition and adjudication. Follow-up ranged from 2 years (SAFETY) to 3 years (WHICH? and NIL-CHF).

A total of 1226 patients were analyzed, of which 612 received HBI and 614 received SC. The demographics of the study cohort were well matched across interventions. Patients were older (approximately 70 years), had multiple comorbidities and high clinical complexity, and had received appropriate levels of treatment. Thirty percent of patients were women.

Several aspects of recurrent hospital stays significantly favored HBI, including the median length of stay per patient in unplanned admission days ($P=.011$), CV admission days ($P=.039$), and all admissions (days in the hospital; $P=.017$). Further, all-cause mortality was lower with HBI vs SC (15.4% vs 20.2%; adjusted HR, 0.56; 95% CI, 0.41 to 0.78; $P=.001$). Patients in the HBI group also achieved a mean of 1210 ± 463 days alive and out of the hospital (90.1%; 95% CI, 88.2 to 92.0) compared with 1184 ± 494 days event free in the SC group (87.2%; 95% CI, 85.1 to 89.3; $P=.02$).

HBI was associated with worse event-free survival in lower clinical complexity cases, and Dr Stewart noted that HBI worked best when the clinical complexity was increased. Accordingly, to reduce the chance for harm, HBI should be reserved for cases that are more clinically complex.

Limitations of this study include that it was a post hoc analysis of studies in which the participants were not blinded. The mechanisms through which HBI increases events at low clinical complexity and benefits cases of high clinical complexity need to be further explored.

TECOS Finds Sitagliptin Does Not Increase Heart Failure Risk

Written by Muriel Cunningham

The TECOS study [Green JB et al. *New Eng J Med.* 2015] was a large randomized placebo-controlled trial conducted in patients with type 2 diabetes mellitus (T2DM) and prevalent cardiovascular (CV) disease. Frans Van de Werf, MD, PhD, University of Leuven, Leuven, Belgium, presented the results of a prespecified secondary analysis from this trial.

The objective of the TECOS study was to evaluate CV risk with sitagliptin added to usual care. For the primary composite end point of CV death, nonfatal myocardial infarction, nonfatal stroke, and hospitalization for unstable angina, sitagliptin was noninferior to placebo for CV risk (HR, 0.98; 95% CI, 0.88 to 1.09; $P<.001$).

Patients with T2DM and atherosclerosis are at an increased risk of hospitalization for heart failure (HF). Two large clinical trials have suggested that dipeptidyl peptidase-44 inhibitors could increase HF hospitalizations: saxagliptin in the SAVOR-TIMI 53 trial [Scirica BM et al. *New Eng J Med.* 2013] and alogliptin in the EXAMINE trial [White WB et al. *New Eng J Med.* 2013]. A prespecified secondary analysis of TECOS investigated the potential effects of sitagliptin on hospitalization for HF and associated outcomes in the study population and selected subgroups.

Of the 14 671 patients enrolled in TECOS, 457 (3.1%) had a hospitalization for HF during the study. Baseline characteristics for these 2 groups are presented in Table 1. There

Table 1. Baseline Characteristics by Hospitalization for HF

Characteristic	With Hospitalization for HF (n = 457)	No Hospitalization for HF (n = 14 214)
Age, y	68.5 ± 7.6	65.4 ± 8.0
Women	25.2	29.4
Duration of diabetes, y	12.3 ± 8.7	11.6 ± 8.1
Percentage HbA$_{1c}$	7.3 ± 0.5	7.2 ± 0.5
eGFR, mL/min/1.73 m^2	66.5 ± 20.9	75.2 ± 21.1
Prior vascular disease		
Coronary artery disease	85.3	73.7
Cerebrovascular disease	29.1	24.3
Peripheral artery disease	17.3	16.6
Prior myocardial infarction	58.2	42.1
Prior HF	41.8	17.3

Values are presented as mean ± SD or percentage.

eGFR, estimate glomerular filtration rate; HF, heart failure.

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was no significant difference between sitagliptin and placebo in the time to first hospitalization for HF (HR, 1.00; 95% CI, 0.84 to 1.20; *P* = .95). In addition, no significant risk was noted in selected subgroups of age, sex, body mass index, diabetes duration, HbA$_{1c}$, insulin use, renal function, prior coronary artery disease, prior HF, and HF severity.

There were also no significant differences in other HF-related outcomes, such as hospitalization for HF or CV death (HR, 1.02; 95% CI, 0.90 to 1.14; *P* = .81), hospitalization for HF or all-cause death (HR, 1.00; 95% CI, 0.90 to 1.11; *P* = .93), and total hospitalization for HF events (first plus recurrent; HR, 1.00; 95% CI, 0.80 to 1.25; *P* = .996). In terms of HF-related outcomes in patients with prior HF at baseline (sitagliptin, n = 1303; placebo, n = 1340), there were no significant differences between treatment groups in hospitalization for HF (HR, 1.03; 95% CI, 0.77 to 1.36; *P* = .86), CV death (HR, 0.91; 95% CI, 0.71 to 1.17; *P* = .46), hospitalization for HF or CV death (HR, 0.96; 95% CI, 0.79 to 1.18; *P* = .71), or all-cause death (HR, 0.92; 95% CI, 0.75 to 1.14; *P* = .46).

Dr Van de Werf concluded that this prespecified analysis of the TECOS database does not suggest an increased risk of HF or related adverse events with sitagliptin in patients with T2DM and prevalent CV disease. These findings support the use of sitagliptin in these patients without concerns of worsening HF.

ARTS-HF Study: Finerenone Is Safe and Effective for Patients With HFrEF

Written by Alla Zarifyan

Gerasimos Filippatos, MD, Athens University Hospital Attikon, Athens, Greece, presented results of the ARTS-HF study [Pitt B et al. *Eur J Heart Fail.* 2015], demonstrating that finerenone was well tolerated and had a comparable efficacy with eplerenone in reducing N-terminal pro-brain natriuretic peptide (NT-proBNP) and a greater efficacy in reducing the incidence of the clinical composite end point of all-cause death, cardiovascular (CV) hospitalization, or emergency presentation for worsening chronic heart failure (CHF) in patients with heart failure with reduced ejection fraction (HFrEF).

Mineralocorticoid receptor antagonists (MRA) such as spironolactone and eplerenone are recommended by treatment guidelines [Yancy CW et al. *Circulation.* 2013; McMurray JJ et al. *Eur Heart J.* 2012], as they reduce mortality and hospitalizations in patients with HFrEF. However, they may be underused because of the fear of inducing hyperkalemia or worsening renal function in high-risk patients, and despite the current treatments, mortality and morbidity remains high, especially after hospitalization for worsening heart failure. Finerenone is a novel nonsteroidal MRA that has greater receptor selectivity than spironolactone and better receptor affinity than eplerenone in vitro.

ARTS-HF was a randomized, double-blind, active-comparator-controlled, multicenter, phase 2b dose-finding study with an objective to compare the safety and efficacy of different once-daily oral doses of finerenone with eplerenone in patients with worsening chronic HFrEF and type 2 diabetes or chronic kidney disease (CKD). The primary end point was the proportion of patients with a relative decrease in NT-proBNP of > 30% from baseline to day 90. The exploratory end points included the clinical composite end point of death from any cause, CV hospitalization, or emergency presentation for worsening CHF.

A total of 1055 patients were enrolled and randomized to eplerenone (n = 221) or to 5 different finerenone doses: 2.5 to 5 mg (n = 172), 5 to 10 mg (n = 163), 7.5 to 15 mg (n = 167), 10 to 20 mg (n = 169), and 15 to 20 mg (n = 163). The percentage of patients who had an NT-proBNP decrease of > 30% at day 90 compared with baseline did not differ substantially between each treatment group, with reductions ranging from 30.9% to 38.8%.

The incidence of the exploratory clinical composite at day 90 was lower with all finerenone doses (except 2.5–5 mg) than with eplerenone, with the lowest incidence observed in the group treated with finerenone 10–20 mg. The risk of all-cause death was reduced more by finerenone 10–20 mg vs eplerenone (HR, 0.14; 95% CI, 0.02 to 1.07), and the risk of CV hospitalization was also lowered more significantly by finerenone 10–20 mg (HR, 0.56; 95% CI, 0.34 to 0.93). Health-related quality of life was improved comparably in all treatment groups.

The incidence of any adverse event (AE), serious AEs, and AEs of special interest was similar in all treatment groups. The mean change in the potassium levels from baseline was statistically significantly lower with the 3 lowest finerenone doses compared with eplerenone.

Prof Filippatos concluded that in patients with HFrEF, finerenone had a comparable efficacy to eplerenone in reducing NT-proBNP and a greater efficacy in reducing the incidence of the clinical composite end point of all-cause death, CV hospitalization, or emergency presentation for worsening CHF.

Bayer says it plans to move ahead with phase 3 trials with finerenone, including a study called FINESSE-HF in more than 3000 HF patients with reduced ejection fraction and type 2 diabetes and/or chronic kidney disease. It also plans to conduct the FIGARO-DKD and FIDELIO-DKD trials in patients with diabetic kidney disease.

Reviewer comment: We need to be cautious in our interpretation of this underpowered exploratory trial. The overall dose response of finerenone is somewhat inconsistent.