Dapagliflozin for Hypertension in Diabetes

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Dapagliflozin 10 mg, an investigational sodium-glucose co-transporter 2 (SGLT-2) inhibitor, effectively reduced both glycosylated hemoglobin (HbA1c) and systolic blood pressure (BP) in two studies. Participants had diabetes and hypertension, both uncontrolled even though they were taking an oral antidiabetes drug and an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARB).

Dapagliflozin (Bristol-Myers Squibb/AstraZeneca), known as Forxiga in Europe, blocks the reabsorption of glomerular-filtered glucose. Its innovative mechanism of action, Dr. Weber said, decreases glucose reabsorption in the renal tubules. At the same time, working at the SGLT receptor, it reduces sodium reabsorption. Because of the loss of glucose in the urine, osmotic diuresis accentuates the loss of sodium. Furthermore, the loss of glucose produces a significant improvement in glucose metabolism.

The analyses in Dr. Weber’s posters evaluated antihypertensive therapy in the same multicenter, randomized, double-blind, placebo-controlled phase 3 trial (NCT01137474), but they looked separately at two treatments. The first strategy included only patients receiving the renin–angiotensin system blockers (ACE inhibitors and ARBs) with (n = 302) and without (n = 311) dapagliflozin 10 mg. The second approach included patients who were taking those drugs in addition to diuretics, calcium-channel blockers, or other classes of antihypertensive drugs, also with (n = 225) and without (n = 224) dapagliflozin 10 mg.

Changes from baseline to week 12 in systolic BP and from baseline to week 12 in HbA1c were the co-primary endpoints.

In the first analysis, the adjusted difference in reduction in systolic BP compared with placebo, was 3.1 mm Hg (10 mm Hg with dapagliflozin, –7.3 mm Hg with placebo, P = 0.001). The adjusted mean change in HbA1c was –0.48% (–0.56% with dapagliflozin and –0.10% with placebo; P < 0.001).

For the analysis of the cohort with additional antihypertensive medications, the difference in change from baseline in systolic BP was –4.3 mm Hg (–7.6 mm Hg without dapagliflozin and –11.9 mm Hg with dapagliflozin; P = 0.0002).

The difference in the adjusted mean change from baseline in HbA1c was –0.61% (–0.02% without dapagliflozin, –0.63% with dapagliflozin; P < 0.0001).

Dr. Weber commented, “We saw on average a reduction in HbA1c of about 0.5%—which is really quite effective. At the same time, we see on average a fall in systolic blood pressure of somewhere between 3 and 4 mm Hg.”

The finding was confirmed not only through conventional office BP readings but also through 24-hour BP monitoring. Regarding modest but significant reductions in uric acid, Dr. Weber also said:

Now that’s interesting, because normally, with the sodium loss that’s produced by a conventional thiazide diuretic, we see, if anything, an increase in uric acid. With dapagliflozin, however, there is a decrease, which—given concerns about gout—is, again, quite a useful clinical finding. Also, as you might imagine, when we are losing glucose into the urine, there is a negative calorie balance—and that has helped us to see an average of about a 2- to 3-pound reduction in body weight.

He concluded, “In the end, the results were very similar. It didn’t seem to matter what the underlying antihypertensive therapies were, the results were roughly the same.”
Clear demonstration of significantly reduced risks in heart failure trials among patients with reduced ejection fraction who received a mineralocorticoid receptor antagonist provided a rationale for TOPCAT. The trials, which include RALES, EPHESUS, and EMPHASIS–HF, showed a risk reduction of 15% to 30%, Dr. Pfeffer said in a late-breaking clinical trial press conference.

The patient population in TOPCAT, however, consisted of those with preserved ejection fraction for whom there is no proven therapy. The six-nation, 270-center randomized, double-blind, placebo-controlled trial included 1,722 patients who received spironolactone 15 mg (titrated to 45 mg) and 1,723 patients who received placebo. Mean age for both groups was 69 years. The primary composite endpoint was cardiovascular mortality, aborted cardiac arrest, or hospitalization for heart failure.

Treatment was discontinued in 34.3% of patients in the spironolactone group and in 31.4% of the placebo group after a mean follow-up of 3.3 years.

In a first presentation of results from the trial, funded by the National Health, Lung and Blood Institute (NHLBI), the primary outcome was reported at a rate of 20.4% in the placebo group and at 18.6% in the spironolactone group (hazard ratio [HR] = 0.89; 95% confidence interval [CI], 0.77–1.04; P = 0.138). The component of heart failure hospitalization, however, was reduced with spironolactone (14.2% with placebo vs. 12.0% with spironolactone) (HR = 0.83; 95% CI, 0.69–0.99; P = 0.042). Furthermore, the occurrence of multiple hospitalizations for heart failure was also reduced with spironolactone (P = 0.005). All-cause hospitalization and death rates were similar between groups.

Although no deaths from hyperkalemia were reported, this adverse drug effect (≥5.5 mmol/L) was more common with spironolactone (9.1%) than with placebo (18.7%) (P < 0.001). Hypokalemia (<3.5 mmol/L) was more common in the placebo group (22.9% vs. 16.2%, respectively (P < 0.001).

Creatinine increases at twice the upper limit of normal (ULN) were more common with spironolactone (HR = 1.49; 95% CI, 1.18–1.87; P = 0.001), but higher creatinine levels of 3.0 mg/dL or more were not more common in the spironolactone group (HR = 1.06; 95% CI, 0.79–1.43; P = 0.697). Also, reports of the need for dialysis were not more common in the spironolactone patients (1.9% for placebo and 1.1% for spironolactone).

Regarding these higher levels, Dr. Pfeffer cautioned, “In this population, spironolactone requires careful monitoring of potassium and creatinine.”

He concluded, “Spironolactone did not alter the primary composite endpoint, but reductions in hospitalization for heart failure were observed.”

“One has to worry that the problems with renal function and hyperkalemia may be much more common in clinical practice than in the highly monitored environment of a clinical trial,” cautioned Dr. Redfield. She observed that the trends toward benefit became attenuated as the duration of follow-up became longer. Although the findings show a clear signal of benefit, she said further, that benefit appears to be strongest in the subset of patients with a higher risk.

Do Nesiritide and Dopamine Preserve Renal Function? ROSE AHF

Outcomes are worse in patients with acute heart failure who have deteriorating renal function and inadequate decongestion during treatment. Low-dose dopamine or low-dose nesiritide (Natrecor, Scios), small studies have suggested, might be able to preserve renal function and improve decongestion in acute heart failure.

An analysis conducted for the National Heart, Lung, and Blood Institute (NHLBI) Heart Failure Clinical Research Network included data from 360 hospitalized acute heart failure patients with renal dysfunction, defined as a glomerular filtration rate (GFR) of 15 to 60 mL/minute/1.73m².

In a late-breaking clinical trial press conference, Dr. Chen noted that infusions of low-dose dopamine (2 mcg/kg per minute) selectively activates dopamine receptors and promotes renal vasodilatation. According to mostly small, single-center studies, it may also enhance decongestion and preserve renal function during diuretic therapy in these patients.

Also, in a small earlier study, a dose lower than the standard for nesiritide (0.005 mcg/kg without a bolus) enhanced decongestion and preserved renal function during diuretic therapy in acute heart failure. Based on these small trials, the ROSE AHF investigators hypothesized that these lower doses of dopamine and nesiritide might improve the co-primary endpoints of change in serum cystatin-C (renal function) from baseline to 72 hours and the 72-hour cumulative urine volume (decongestion), compared with placebo in acute heart failure patients who were enrolled within 24 hours of admission.

In the ROSE AHF trial, all patients (mean age, 70 years; 73% male) received the standard diuretic dose for the first 24 hours. They were then randomly assigned to receive 72 hours of either nesiritide or dopamine, then in a 2:1 ratio, to the active drug or placebo.

Dr. Chen reported that in patients receiving dopamine, 72-hour urine volume (L) was 8.3 for placebo and 8.5 for dopamine (P = 0.58). The change in cystatin C was 0.11 for placebo and 0.12 for dopamine (P = 0.72). There were no differences between placebo and dopamine for the secondary endpoints (60-day death or heart failure readmission and 180-day mortality).

In the patients receiving nesiritide, 72-hour urine volume (L) was 8.6 for nesiritide and 8.3 for placebo (P = 0.25). The change in cystatin C was 0.11 for placebo and 0.07 for nesiritide (P = 0.35). Similarly, differences in death or heart failure readmission rates at 60 days and mortality rates at 180 days were not significant.

“In patients with acute heart failure and underlying renal dysfunction, when added to standardized diuretic dosing, neither low-dose dopamine nor low-dose nesiritide enhanced decongestion or improved renal function,” Dr. Chen concluded.
Niacin and CEPT Inhibitors and HDL Subfractions: Framingham Offspring and Jackson Heart Studies

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Clinical trial results of high-density lipoprotein (HDL)-raising agents such as niacin and cholesteryl ester transfer protein (CEPT) inhibitors have been stubbornly negative despite the substantial evidence that HDL-cholesterol (HDL-C) levels are known to be inversely proportional to risk for coronary heart disease (CHD)—related events. This study of the relationship between HDL-C subfractions (HDL₂ and HDL₃) and remnant lipoproteins and cardiovascular disease events suggests a plausible cause for the failure of those trials—the strategies are directed at the wrong target.

The Framingham Offspring Study and the Jackson Heart Study together enrolled 5,932 men and women without prevalent coronary heart disease and observed them for 8 years. Dr. Toth’s team, using vertical auto profile (VAP Lipid Panel, Atherotech) testing, subfractionated serum lipoproteins from these subjects to determine relationships between HDL and its subfractions to incident CHD events, including myocardial infarction (MI), cardiovascular mortality, and revascularization procedures. Results were adjusted for age, sex, body mass index, smoking status, blood pressure (BP), lipid treatment, and diabetes mellitus.

For the combined group, HDL (HR = 0.81; 95% CI, 0.67–0.98; P < 0.033) and HDL₂ correlated with reduced risk for cardiovascular events (HR = 0.77; 95% CI, 0.64–0.93; P < 0.007). By contrast, HDL₃ was not correlated significantly (HR = 0.92; 95% CI, 0.76–1.10; P = 0.353).

Similarly, an evaluation of CHD risk via the ratio of total atherogenic lipoprotein cholesterol to HDL and its subfractions, non-HDL/HDL and non-HDL/HDL₂, were predictive of increased risk (HR = 1.32; 95% CI, 1.13–1.53; P < 0.001; and HR = 1.36; 95% CI, 1.18–1.58; P < 0.001), whereas non-HDL/HDL₃ was not (HR = 1.12; 95% CI, 0.95–1.32; P = 0.188). Results were similar for both Caucasians and African-Americans.

“It has been suggested based on small studies,” Dr. Toth said in an interview, “that HDL₂ is protective, while HDL₃ is less protective or even harmful.”

Niacin and CEPT inhibitors, he commented further, increase HDL₂. Dr. Toth’s analysis, however, showed no correlation between HDL₂ and cardiovascular risk and benefit for HDL₃. He explained:

All the action appears to reside in the smaller, denser particles that do tend to be more lipid-avid. There is a very strong relationship in both the Jackson Heart Study and the Framingham Offspring Study in terms of baseline HDL and risk for hard cardiovascular heart disease outcomes, including nonfatal myocardial infarction and cardiovascular mortality. These findings may help explain why clinical trials performed with niacin and CEPT inhibitors are negative.

Additional research by Dr. Toth presented at the AHA meeting suggested that the risk of coronary artery disease is also conferred by very-low-density-lipoprotein (VLDL) remnants and intermediate-density lipoproteins. The research suggests potential utility for fibrate therapy because fibrates raise HDL, and facilitate clearance of lipoprotein remnant particles. Post hoc analyses of the Bezafibrate Infarction Prevention study, the Helsinki Heart Study, and FIELD all showed significant primary endpoint reductions in patients with this lipid phenotype who received fibrates. Also, in the ACCORD trial, there was a strong trend toward benefit (P = 0.06) in this population.

Determining the clinical relevance of these findings may require another fibrate trial, Dr. Toth said, one that specifically randomizes patients with hypertriglyceridemia (a marker of increased remnants in serum) and low HDL-C levels.

Dr. Toth is a member of Atherotech’s medical advisory board.

Cangrelor Decreases Ischemia-Driven Revascularization: A Meta-analysis

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Cangrelor (The Medicines Company) failed to show superiority to clopidogrel (Plavix, Bristol-Myers Squibb/Sanofi) in the CHAMPION PCI trial or to placebo in the CHAMPION PLATFORM trial. In the more recent CHAMPION PHOENIX trial, however, which used the universal definition for myocardial infarction (MI), cangrelor significantly reduced the rate of ischemic events, including stent thrombosis during percutaneous coronary intervention (PCI), with no significant increase in severe bleeding.

Cangrelor is an investigational intravenous (IV) adenosine diphosphate (ADP) P2Y₁₂ receptor inhibitor. (The FDA filing for the New Drug Application was completed in July 2013.) The drug offers very rapid onset, and with a 3- to 6-minute plasma half-life, platelet function returns in 30 to 60 minutes, unlike other available agents such as clopidogrel, prasugrel (Effient, Eli Lilly), and ticagrelor (Brilinta, AstraZeneca).

Pooling data from 25,107 patients undergoing PCI who were enrolled in the three randomized controlled trials, investigators compared the effectiveness of cangrelor with clopidogrel or placebo in controls. For both MI and all-cause mortality, respectively, cangrelor was similar for controls (risk ratio [RR] = 0.94; 95% CI, 0.78–1.13 and RR = 0.72; 95% CI, 0.36–1.43). However, cangrelor significantly reduced the risk of ischemia-driven revascularization (RR = 0.72; 95% CI, 0.52–0.98), stent thrombosis (RR = 0.60; 95% CI, 0.44–0.82), and Q-wave MI (RR = 0.53; 95% CI, 0.30–0.92) without causing an increase in severe or life-threatening GUSTO bleeding or TIMI (Thrombolysis in Myocardial Infarction) major bleeding.

“These are very encouraging results for this medicine,” Dr. Nairooz said in an interview.

He pointed out that cangrelor’s properties make it suitable when the patient arrives at the catheter laboratory and the current cardiac anatomy is unknown. On the one hand, the patient may have non–ST-segment MI (NSTEMI) suitable for stenting; on the other hand, the patient may end up needing to be sent for bypass graft surgery.

“With cangrelor you can cover yourself (and the patient) during the procedure, but then in just 36 minutes, platelet function goes back to normal, allowing surgery if required,” Dr. Nairooz said.