KEY ABSTRACT PRESENTATIONS

THE PRECISION AND TRUE-AHF TRIALS

Recent highlights from the 2016 American Heart Association Scientific Sessions

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Keywords: acute heart failure; celecoxib; nonsteroidal anti-inflammatory drug; ularitide

THE PRECISION TRIAL

Hundreds of millions of patients with arthritis worldwide require pain-relieving therapy to maintain an acceptable quality of life. However, the ongoing uncertainty concerning the cardiovascular safety of NSAIDs, including conventional and COX-2 selective inhibitors, leaves practitioners and patients with difficult management decisions. As such, evidence from adequately powered, independently run, randomized clinical trials prospectively designed to capture cardiovascular outcomes was urgently needed. Therefore, PRECISION, a double-blind, triple-dummy, randomized, 3-arm parallel group design, multi-center, cardiovascular safety trial was designed to test the cardiovascular safety of the COX-2 selective inhibitor celecoxib in patients with osteoarthritis and rheumatoid arthritis and an overt or high risk of developing cardiovascular disease in comparison with two commonly prescribed nonselective NSAIDs—ibuprofen and naproxen. Ibuprofen is the most widely used nonselective NSAID, and naproxen is used commonly in arthritis patients, and it was hitherto believed to have the lowest cardiovascular toxicity.

Patients received celecoxib 200 to 400 mg daily (100 to 200 mg twice daily) or ibuprofen 1600 to 2400 mg daily (600 to 800 mg three times daily) or naproxen 750 to 1000 mg daily (375 to 500 mg twice daily) in addition to the usual standard of care treatment for their cardiovascular disease. The allowed doses of celecoxib, naproxen, and ibuprofen were given in accordance with approved labeling in the countries where the study was conducted. The primary end point was the first occurrence of the composite end point that consisted of cardiovascular death, nonfatal MI, or nonfatal stroke, as defined by the Antiplatelet Trialists’ Collaboration composite end point.

In the PRECISION trial, 24 081 patients were randomly assigned to celecoxib, naproxen, or ibuprofen for a mean treatment duration of 20.3±16.0 months and a mean follow-up period of 34.1±13.4 months. In the intention-to-treat analyses, a primary outcome event occurred in 188 patients in the celecoxib group, 201 patients in the naproxen group, and 218 patients in the ibuprofen group (HR for celecoxib vs naproxen, 0.93; 95% CI, 0.76-1.13; HR for celecoxib vs ibuprofen, 0.85; 95% CI, 0.70-1.04; P=0.001 for noninferiority in both comparisons). In the on-treatment analysis, a primary outcome event occurred in 134 patients in the celecoxib group, 144 patients in the naproxen group, and 155 patients in the ibuprofen group (HR for celecoxib vs naproxen, 0.90; 95% CI, 0.71-1.15; HR for celecoxib vs ibuprofen, 0.81; 95% CI, 0.65-1.02; P=0.001 for noninferiority in both comparisons). As expected, the risk of gastrointestinal events was significantly lower with celecoxib than naproxen (P=0.01) or ibuprofen (P=0.002). Intriguingly, the risk of renal events was significantly lower with celecoxib than with ibuprofen (P=0.004). Thus, PRECISION clearly demonstrates that celecoxib is noninferior to ibuprofen or naproxen regarding cardiovascular safety.

PRECISION provides further insight that the NSAIDs and COX-2 selective inhibitors are not as homogenous as previously thought, which might reflect differences in chemical structure, pharmacokinetic properties, and subsequent metabolism, resulting in clinically relevant differential effects, particularly on blood pressure.

THE TRUE-AHF TRIAL

Hospitalizations for acute heart failure syndromes account for ≈1 million admissions annually in both Europe and the US, and this value continues to increase. The high morbidity, mortality, and economic costs of acute heart failure are explicable, in part, by the lack of safe and effective therapies. Unfortunately, efforts to develop new drugs and interventions have largely been proven ineffective in changing the short-term course of the disease. Therefore, the TRUE-AHF trial was designed to delineate whether administering a vasodilator within the first 6 hours following an initial clinical evaluation and in doses sufficient to
improvement myocardial wall stress and clinical stability rapidly would reduce the long-term risk of cardiovascular death in patients hospitalized for acute heart failure.

In TRUE-AHF, 2157 patients hospitalized for acute heart failure were randomized to receive either placebo (n=1069) or the natriuretic peptide ularitide (n=1088) at a dose of 15 ng/kg/hr for 48 hours. Ularitide is a chemically synthesized analog of urodilatin. Urodilatin is synthesized in renal tubular cells, and it is secreted luminally to act downstream at distal segments of the nephron. Intravenous administration of urodilatin leads to both systemic and renal vasodilation, diuresis and natriuresis, and renin-angiotensin system inhibition in animal models of heart failure, in healthy volunteers, and in patients with heart failure. The primary outcomes of TRUE-AHF were death from cardiovascular causes during a follow-up period of up to 34 months and a hierarchical composite end point that evaluated each patient’s initial 48-hour clinical course.

While ularitide exerted the expected hemodynamic effects of reducing blood pressure and NT-proBNP levels and resulted in fewer episodes of in-hospital worsening heart failure during the infusion, no long-term benefits were demonstrated. In particular, death from cardiovascular causes occurred in 225 patients in the placebo group and 236 patients in the ularitide group (HR, 1.03; 95% CI, 0.85-1.25; P=0.75). In addition, no differences between the two groups for the hierarchical composite end point were reported.4

The TRUE-AHF findings indicate that ularitide can exert favorable short-term physiological effects, but these benefits do not appear to change the natural disease history for these patients. A definitive answer as to whether it will remain worthwhile to continue pursuing the early injury hypothesis should be provided by the eagerly awaited results of the RELAX-AHF2 trial that is testing the effects of the vasodilatory peptide hormone serelaxin on the primary end point of cardiovascular mortality.

REFERENCES


