Results of the PROTECT Trial

Results from the PROTECT (A Placebo-controlled Randomized study of the selective A_1 adenosine receptor antagonist KW-3902 for patients hospitalized with acute heart failure and volume Overload to assess Treatment Effect on Congestion and renal function Trial) trial, presented at the European Society of Cardiology's annual meeting in Barcelona, Spain, by Professor Marco Metra, MD, University of Brescia, Brescia, Italy, failed to meet both the primary and secondary endpoints of the study.

The objectives of PROTECT were to assess the efficacy and safety of the adenosine A_1 receptor antagonist rolofylline versus placebo on symptoms, renal function, and short-term morbidity and mortality in 2033 patients who were hospitalized with heart failure (HF) within 24 hours with signs of fluid overload, impaired renal function (estimated GFR 20-80 ml/min), and high serum levels of B-type natriuretic peptide (BNP >500 pg/mL) or N-terminal fragment of B-type natriuretic peptide (NT-proBNP >2000 pg/mL). Rolofylline 30 mg/day or placebo (2:1 ratio) was administered in a double-blind fashion as a 4-hour daily infusion that was repeated for 3 days. Subjects were predominantly male (67%) who had a mean age of 70 years, mean creatinine clearance ~50 mL/min, and mean serum creatinine (SCr) 1.5 mg/dL. Most subjects were receiving multiple HF medications within the 2 weeks prior to study enrollment, including ACE inhibitor or ARB (75%), beta-blocker (76%), aldosterone inhibitor (43%), and digoxin (28%).

The primary study outcome was a three-category ordered outcome: treatment success (moderate to marked improvement of dyspnea at 24 and 48 hours with no evidence of treatment failure); subject unchanged; or treatment failure (death or readmission for HF through Day 7, or worsening signs/symptoms of HF occurring >24 hours after the start of the study through Day 7 or discharge, or persistent renal impairment [SCr increase ≥0.3 mg/dL at Days 7 and 14, or the initiation of hemofiltration or dialysis through Day 7]). Secondary outcomes included time to death or rehospitalization for renal or cardiovascular causes through Day 60 and the proportion of subjects with renal impairment, as defined in the primary endpoint.

There was no significant difference in the primary endpoint, wherein 40.6% of rolofylline subjects versus 36% of placebo subjects achieved treatment success, 37.5% versus 44.2% remained unchanged, and 21.8% versus 19.8% were classified as treatment failures (OR, 0.92; 95% CI, 0.78 to 1.09; p=0.35), nor was a difference observed in the secondary endpoint of persistent renal impairment (15.0% vs 13.7%, OR, 1.11; 95% CI, 0.85 to1.46; p=0.44). Furthermore, rolofylline appeared to increase neurological complications, including seizures (11 subjects [0.8%] vs no subjects on placebo), stroke (16 [1.2%] vs 3 [0.5%]), and serious adverse events that involved the nervous system (1.5% vs 0.6%).

Although the smaller PROTECT Pilot trial had shown promise for rolofylline in preventing dyspnea and renal failure, due to the lack of efficacy and apparent increase in nervous system disorders in this larger trial, further study of rolofylline in HF has been halted. Additional studies with alternative selective adenosine A_1-receptor antagonists are ongoing.

Irbesartan Fails to Prevent Most Vascular Events in Patients with AF

In the Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE-I; NCT00249795), treatment with irbesartan failed to lower the risk of stroke, myocardial infarction (MI), and vascular death compared with placebo in patients with atrial fibrillation (AF). However, irbesartan may have a role in preventing heart failure (HF), recurrent embolic events, and cardiovascular (CV) hospitalizations in patients with AF.

The ACTIVE program comprised three clinical trials that enrolled patients with documented AF and at least one additional risk factor for stroke, including ACTIVE-W (clopidogrel plus aspirin vs warfarin), ACTIVE-A (clopidogrel plus aspirin vs aspirin monotherapy), and ACTIVE-I. Salim Yusuf, MD, DPhil, McMaster University, Ontario, Canada, presented preliminary results from the ACTIVE-I trial, which was designed to evaluate the effect of additional blood pressure (BP) reduction with an angiotensin receptor blocker (ARB) on common complications of AF, including HF, stroke, and other embolic events.

In ACTIVE-I, patients who had a systolic BP >110 mm Hg and were not being treated with an ARB were randomly assigned to irbesartan at a target dose of 300 mg/day (n=4518) or placebo (n=4498). At baseline, patients generally were treated with multiple CV medications, including angiotensin-converting enzyme (ACE) inhibitors (60%), aspirin (59%), beta-blockers (54%), diuretic therapy (54%), vitamin K antagonists (38%), digoxin (35%), calcium channel blockers (27%), and antiarrhythmics (23%).

On top of this extensive background therapy, irbesartan provided an additional reduction in BP (6.8/4.5 mm Hg)

compared with placebo (3.9/2.6 mm Hg). However, ACTIVE-I failed to reach either of its two primary endpoints. The composite endpoint of stroke, MI, and vascular death occurred with equal frequency in the irbesartan and placebo groups (HR, 0.99; p=0.85), and a similar proportion reached the composite co-primary endpoint of the above plus HF hospitalization (HR, 0.94; p=0.12). Only one component of the primary endpoint, HF hospitalization, occurred less frequently in the irbesartan group (HR, 0.86; p=0.018).

Compared with placebo, irbesartan was associated with a similar frequency of total strokes (2.3% vs 2.1%; p=0.21) but fewer hemorrhagic strokes (0.2% vs 0.4%; p=0.010). Irbesartan also reduced the composite endpoint of stroke, transient ischemic attacks, and noncentral nervous system embolism (HR, 0.87; p=0.024). In particular, the reduction of recurrent embolic events in the irbesartan group (39.6% vs 44.3%; p=0.016) contributed to significantly fewer CV hospitalizations (3817 vs 4509 admissions; p=0.003) and fewer total days of hospitalization (36,440 vs 39,971 days; p<0.001) compared with placebo.

Findings from ACTIVE-I illustrate the limited benefit of a modest reduction in BP with irbesartan in the setting of AF, in which the prevalence of hypertension is high and HF is more common than stroke, Dr. Yusuf said. More aggressive BP lowering with multiple antihypertensive agents may result in an even greater clinical benefit, he concluded.

GRACE Registry Study

In a study that was reported at the 2009 European Society of Cardiology Annual Meeting by Professor Gilles Montalescot, MD, Institut de Cardiologie, Hôpital Pitié-Salpétrière, Paris, France, in-hospital death and cardiac arrest, as well as death and myocardial infarction (MI) up to 6 months following hospital discharge, were less frequent in patients with unprotected left main coronary disease (ULMCD) who presented with acute coronary syndrome (ACS) and were revascularized with coronary artery bypass grafting (CABG) compared with a group who did not undergo revascularization. Percutaneous coronary intervention (PCI) was also significantly and positively associated with improved survival over the same period, although the benefit was less than with CABG.

This study analyzed 6-month posthospital discharge data from the Global Registry of Acute Coronary Events (GRACE) registry for 1799 high-risk patients (eg, age >75 years [40%], prior MI [26%], prior STEMI [35%], heart failure [23%], or prior stroke and renal insufficiency [9%]) with ACS and ULMCD who were treated with PCI, CABG, or conservative treatment. In patients who presented with acute MI, 48% of PCI patients underwent revascularization on the day of admission versus 5.1% in the CABG group. Patients who received PCI were the more serious cases—older patients with higher GRACE scores, more frequently with STEMI or shock. Mortality was 7.7% in the hospital and 14% at 6 months, demonstrating the overall high risk of the cohort.

After adjustment, revascularization was associated with an early hazard of in-hospital death compared with no revascularization that was statistically significant for PCI (HR, 2.60; 95% CI, 1.62 to 4.18) but not for CABG (HR, 1.26; 95% CI, 0.72 to 2.22). Mortality from hospital discharge to 6 months was 10% for the conservatively treated group and 5.4% and 1.6% for patients who were revascularized with PCI and CABG, respectively. In-hospital cardiac complications (cardiac arrest, sustained ventricular tachycardia, new cardiogenic shock, rehospitalization for cardiovascular reasons, and MI) were significantly (p≤0.001) higher for PCI.

After multivariate adjustment, PCI (HR, 0.45; 95% CI, 0.23 to 0.85) and CABG (HR, 0.11; 95% CI, 0.04 to 0.28) were significantly associated with improved survival from discharge to 6 months in comparison with an initial strategy of no revascularization. However, CABG was associated with a 5-fold increase in stroke compared with PCI and no revascularization. There was no difference between the PCI and CABG groups for the triple ischemic endpoint of death, reinfarction, or stroke.

In 2000, the rate of CABG for ULMCD was 2.5-fold higher than the rate of PCI. Between 2000 and 2007 (the time period of this study), PCI had become the most common strategy of revascularization in emergent/serious cases but was associated with more frequent repeat revascularization in the 6 months after discharge. CABG was associated with good survival in lower-risk patients but resulted in more frequent incidents of acute stroke. Prof. Montalescot noted that while PCI is the most commonly used strategy in this population, "PCI and CABG appear complementary, and both types of revascularization improve 6-month survival in comparison with an initially conservative medical strategy for this rare but serious situation."

Primary PCI Versus Fibrinolysis in Very Elderly Patients with AMI

Primary percutaneous coronary intervention (PCI) was not found to provide an advantage over fibrinolytic therapy for very elderly patients with acute myocardial infarction