Ivabradine (Procoralan) for Chronic Heart Failure (The SHIFT Trial)

- Michael Komajda, MD, Groupe Hospitalier Pitie-Salpetriere, Paris, France
- Inder Anand, MD, DPhil, Discussant; Director of Heart Failure Program, Minneapolis Veterans Affairs Medical Center; and Professor of Medicine, University of Minnesota, Minneapolis, Minn.

Earlier presentations of results from SHIFT (Systolic Heart Failure treatment with the $I_f$ inhibitor Ivabradine Trial) showed an elevated heart rate to be a risk factor for cardiovascular (CV) events in patients with chronic heart failure. The study also demonstrated that lowering heart-rate profiles with ivabradine (Procoralan, Servier) reduced CV events. The current analysis tested whether baseline resting heart rate increased the risk of further events.

Dr. Komajda noted that ivabradine slows the heart by selective $I_f$ inhibition in the sinoatrial node without other known CV effects.

SHIFT included 6,505 patients in sinus rhythm with New York Heart Association (NYHA) Class II to IV heart failure. All patients had heart rates of at least 70 beats per minute (bpm) and a left ventricular ejection fraction (LVEF) of 35% or less; these patients had also been hospitalized within the previous year for worsening heart failure. Mean age was about 60 years, and about two-thirds of patients had ischemic heart failure. Mean heart rate was 80 bpm, and mean LVEF was 29%.

All patients received ivabradine 5 mg twice daily initially or matching placebo, titrated by 28 days to ivabradine 7.5, 5, or 2.5 mg twice daily, according to heart rate and tolerability. The actual mean ivabradine dose was 6.4 mg twice daily at one month and 6.5 mg at one year. The mean study duration was 22.9 months.

The primary endpoint for this analysis was the composite of CV death or hospitalization for worsening heart failure, with populations divided into quintiles of baseline heart rates. The primary composite endpoint was reduced significantly ($P < 0.0001$) by 18% in the ivabradine group (17.7% with placebo, 14.5% with ivabradine). Hospitalization rates were reduced by 0.0001) by 18% in the ivabradine group (17.7% with placebo, 14.5% with ivabradine). The risk of primary composite endpoint events increased by 3% with every heartbeat increase from the baseline heart rate and by 16% for every increase of 5 bpm. Rates for the endpoint components of hospital admission and CV death were significantly higher ($P < 0.001$) for the highest quintile heart rate.

In the ivabradine group, there was a direct association between heart rates achieved at 28 days and subsequent cardiac outcomes. For patients with heart rates lower than 60 bpm at 28 days, the CV event rate was 17.4%, compared with 32.4% for those at 75 bpm. When the investigators adjusted for changes in heartbeat, a high heart rate as a risk factor in heart failure was confirmed, Dr. Komajda said. Patients who tolerated ivabradine dosages sufficient to reduce heart rate to 60 bpm or less had the best outcomes. Adverse events were similar for the ivabradine and placebo groups of patients.

Dr. Komajda concluded, “Heart rate is an important target for therapy in heart failure.”

The take-home message from SHIFT, according to discussant Dr. Anand, “is that among patients in this population receiving usual clinical care who are unable to tolerate higher doses of beta blockers, the addition of the pure heart rate-reducing agent ivabradine is likely to improve heart failure outcomes.”

Apixaban or Aspirin in Decreasing Stroke Risk (The AVERROES Trial)

- Stuart Connolly, MD, Director, Division of Cardiology, Department of Medicine, McMaster University, Ontario, Canada
- Harald Arnesen, MD, Discussant, Oslo University Hospital Ulleval, Oslo, Norway

In what discussant Dr. Arnesen termed a landmark study, the AVERROES trial (Apixaban versus Aspirin to Reduce the Risk of Stroke) showed that the anticoagulant apixaban (Bristol-Myers Squibb/Pfizer) lowered the incidence of stroke by more than 50%, compared with aspirin (ASA) in patients with atrial fibrillation (AF) who were not candidates for therapy with a vitamin K antagonist.

Apixaban is an oral, selective direct factor Xa inhibitor with a 12-hour half-life and multiple excretion pathways (25% renal). No routine coagulation monitoring is required. In earlier
research, it was shown to be safe and effective for preventing venous thromboembolism in orthopedic surgery, said AVERROES lead investigator Dr. Connolly. He also noted that stroke risk is high in AF patients and that although vitamin K agonist therapy is effective against stroke, it is unsuitable for up to 50% of patients because of the difficulty in controlling the International Normalized Ratio (INR) and bleeding.

AVERROES, a double-blind study, included 5,600 patients with AF and one or more risk factors for stroke. These patients, from 522 centers in 36 countries, had been found to be or were expected to be unsuitable subjects for a vitamin K agonist. They were randomly assigned to receive 5 mg of apixaban or 81 to 324 mg of ASA for up to 36 months or until the end of the study.

The primary efficacy outcome was the time from the first dose of the study drug to the first occurrence of ischemic stroke, hemorrhagic stroke, or systemic embolism.

Mean age was 70 years; 60% of the patients were men. In the ASA group, most patients received 162 mg or less daily. Median follow-up was one year. The Data Monitoring Committee terminated the trial early because of the clear superiority of apixaban.

The risk of stroke or a systemic embolic event was reduced by 54% with apixaban, compared with ASA, for a risk ratio (RR) of 0.46 and a 95% confidence interval (CI) of 0.33–0.64 ($P < 0.001$). The annual rate of events for the apixaban patients was 1.6%, and the rate for the ASA group was 3.6%.

The annual rates of the apixaban advantage were seen for both stroke (1.5% vs. 3.3%) and systemic embolic events (below 0.1% vs. 0.4%). Although stroke severity also favored apixaban, the apixaban advantage for fatal stroke did not reach statistical significance ($P = 0.18$). Major bleeding was similar between groups. Minor bleeding, however, was more frequent in the apixaban patients (an annual rate of 5.2% vs. 4.1% with ASA; $P = 0.04$). The study drug rate of permanent discontinuation, though, was higher for ASA ($RR = 0.88; P = 0.04$).

Dr. Connolly concluded that if 1,000 patients were treated with apixaban instead of ASA for one year, 18 strokes, 10 deaths, and 31 cardiovascular hospitalizations could be prevented.

Dr. Arnesen commented, “The results from AVERROES will obviously have [an] impact on guidelines in atrial fibrillation, and the use of ASA will probably be drastically reduced.”

He noted further that apixaban’s twice-daily dosing would be a challenge.

**Atopaxar (E5555) for Acute Coronary Syndrome and Coronary Artery Disease in Japanese Patients (The J-LANCELOT Trial)**

- Shinya Goto, MD, on behalf of the J-LANCELOT investigators
- Jean-Pierre Bassand, MD, Professor of Cardiology and Cardiovascular Medicine, University of Besançon, France

Among patients with ACS or high-risk coronary artery disease (CAD) whose platelets remain activated despite treatment with current standard therapies, a novel protease-activated receptor 1 (PAR-1) inhibitor, atopaxar (E5555, Eisai), might be a valuable add-on therapy.

Dr. Goto, lead investigator for two phase 2 studies of atopaxar—both part of J-LANCELOT (Japanese–Lesson from Antagonizing the Cellular Effect of Thrombin)—noted that thrombin plays a critical role in the development and propagation of thrombus via both blood coagulation and platelet aggregation. Atopaxar inhibited platelet aggregation induced by thrombin without affecting blood coagulation, fibrinolysis, or bleeding time in early-phase trials among healthy volunteers.

In an interview, Dr. Bassand commented that all previous advances in platelet inhibition with agents such as aspirin, clopidogrel (Plavix, Bristol-Myers Squibb/Sanofi-Aventis), prasugrel (Effient, Eli Lilly/Daiichi-Sankyo), and ticagrelor (Brilinta, AstraZeneca) have lengthened bleeding time and produced at least some increase in bleeding risk. PAR-1 inhibition, however, prevents platelet function activation without prolonging bleeding time.

For patients with CAD who were included in J-LANCELOT, high risk was defined by one or more of the following: diabetes mellitus (under treatment), a history of peripheral artery disease or of thromboembolic transient ischemic attack (TIA), or stroke within the previous year: J-LANCELOT was conducted among 241 ACS and 263 high-risk CAD patients. Mean age was 65 years for the ACS patients and 67 years for the CAD patients. About 81% and 89% of patients in the ACS and CAD groups, respectively, were men.

The primary safety endpoint was bleeding events, and the secondary endpoint was major adverse cardiac events (MACE, comprising cardiovascular death, myocardial infarction [MI], stroke, recurrent ischemia) and inhibition of platelet aggregation induced by thrombin receptor activation peptide (TRAP). The incidence of thrombolyis in MI (TIMI) major, minor, and minimal bleeding requiring medical attention was similar. Enrollees were randomly assigned, in a 1:1:1:1 ratio, to receive atopaxar 50, 100, or 200 mg or placebo once daily for 12 weeks (ACS patients) or for 24 weeks (CAD patients). ACS patients received 400 mg of apixaban or placebo on day 1, and CAD patients received aspirin at a dose of 75 to 325 mg daily.

More than 90% platelet inhibition was achieved with both atopaxar 100 mg and 200 mg, and 20% to 60% platelet inhibition was achieved with atopaxar 50 mg. The incidence of thrombolyis in MI (TIMI) major, minor, and minimal bleeding requiring medical attention was similar for the placebo and combined atopaxar groups (ACS, 6.6% for placebo vs. 5% for atopaxar; CAD, 1.5% for placebo vs. 1.5% for atopaxar).

Clinically significant bleeding events were not increased in patients with ACS and CAD. There was a dose-related trend toward increased “nuisance” bleeding events not requiring medical attention with atopaxar. The rate of MACE was lower in the combined atopaxar group than in the placebo group: ACS, 6.6% for placebo vs. 5% for atopaxar ($P = 0.73$) and CAD, 4.5% for placebo vs. 1% for atopaxar ($P = 0.066$). However, the differences were not significant.

Dr. Goto stated that significant dose-dependent liver function test abnormalities and increases in the corrected QT interval (QTcP) with atopaxar call for further study.

Dr. Bassand concluded, “If phase 3 trials confirm these results for atopaxar and those of vorapaxar, that will be a major splash.”

He noted that phase 2 results for a thrombin receptor antagonist, vorapaxar (SCH 530348, Schering/Merckc), on top of aspirin and clopidogrel, also revealed no increase in bleeding as well as a trend toward better efficacy than standard treatment. There were no safety concerns, Dr. Bassand said.
The genetic polymorphisms cytochrome P450 2C19 (CYP 2C19) and ABCB1 are known to adversely affect clopidogrel (Plavix) metabolism in patients with ACS, requiring genetic testing prior to dual antiplatelet therapy. A substudy of PLATO (A Study of Platelet Inhibition and Patient Outcomes) showed that ticagrelor (Brilinta) was superior to clopidogrel for preventing cardiovascular (CV) death, MI, and stroke regardless of CYP 2C19 and ABCB1 genotypes.

To evaluate the effects of CYP 2C19 and ABCB1 genes on the efficacy and safety of ticagrelor and clopidogrel, PLATO researchers randomly assigned 18,624 patients with ACS to receive a loading dose of ticagrelor 180 mg and a twice-daily maintenance dose of 90 mg versus a clopidogrel loading dose of 300 to 600 mg and a 75-mg daily maintenance dose for six to 12 months (median, nine months). All patients received background therapy with aspirin.

For this PLATO substudy, investigators genotyped 10,285 DNA samples from subjects for CYP 2C19 loss-of-function and gain-of-function alleles and for the ABCB1 nucleotide polymorphism. Subjects were then stratified according to the presence or absence of any loss-of-function CYP 2C19 allele and for predicted high, medium, or low gene expression of ABCB1.

The combined primary efficacy endpoint—CV death, MI, or stroke after up to 12 months of treatment with ticagrelor or clopidogrel—occurred less often with ticagrelor than with clopidogrel, irrespective of CYP 2C19 genotype, as follows:

- 8.6% vs. 11.2% of patients with any loss-of-function genetic CYP 2C19 variation (P = 0.038)
- 8.8% vs. 10% of patients without any genetic variation (P = 0.0608).

For ABCB1 low, intermediate, and high genetic expression groups, primary outcome event rates with ticagrelor (8.1%–9% per year) were lower than with clopidogrel for low expression (9.9% per year), intermediate expression (9.3% per year), and high expression (11.5% per year). Furthermore, ischemic event benefits with ticagrelor appear earlier in carriers of any CYP 2C10 loss-of-function allele.

Dr. Wallentin also reported that in subjects with any gain-of function CYP 2C19 alleles, there was a nonsignificant increased risk of bleeding for those taking clopidogrel. There was no effect on bleeding for ticagrelor patients with regard to CYP 2C19 and ABCB1 genotypes.

“Our findings indicate that the use of ticagrelor, instead of clopidogrel, eliminates the need for presently recommended genetic testing before dual antiplatelet treatment,” he said.

Dr. Wallentin concluded, “In a broad, global population with acute coronary syndrome, ticagrelor was superior to clopidogrel for preventing CV death, MI, and stroke, regardless of CYP 2C19 and ABCB1 genotype.”

After an advisory committee voted to recommend approval of ticagrelor, the FDA announced on September 16 that it would extend its review for another three months.