World Congress of Cardiology 2006: Targeting the Renin–Angiotensin System and Oral Anticoagulation in Peripheral Artery Disease

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At four-year intervals, the European Society of Cardiology and the World Heart Federation hold a combined meeting, known as the World Congress of Cardiology. This year, 12,000 clinicians chose from among thousands of presentations from September 2 to 5, in Barcelona, Spain. Among the key sessions were several on agents targeting the renin–angiotensin system and one evaluating potential benefits of adding oral anticoagulation to antiplatelet therapy for patients with peripheral artery disease.

ACE-Inhibitors

An overview of clinical trials, including approximately 42,000 patients, led researchers to conclude that angiotensin-converting enzyme (ACE)–inhibitors should be considered for all patients with evidence of vascular atherosclerotic disease.

The meta-analysis, conducted by Gilles R. Dagenais, MD, at Laval University Heart and Lung Institute, Laval Hospital, in Quebec, Canada, looked at three trials of ACE-inhibitors among patients with stable vascular disease without left ventricular systolic dysfunction or heart failure:

- HOPE–ramipril (Altace): Heart Outcomes Prevention Evaluation
- EUROPA–perindopril (Aceon): European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease
- PEACE–trandolapril (Mavik): Prevention of Events with ACE Inhibition

Dr. Dagenais then evaluated five other studies of ACE-inhibitors in patients with heart failure and left ventricular systolic dysfunction (LVSD):

- SOLVD-T: Studies Of Left Ventricular Dysfunction Treatment
- SOLVD-P: Studies Of Left Ventricular Dysfunction Prevention
- SAVE: Survival and Ventricular Enlargement
- AIRE: Acute Infarction Ramipril Efficacy
- TRACE: Trandolapril Cardiac Evaluation

Among the first three trials, only PEACE did not meet its primary outcome: a 4% relative risk reduction in death from cardiovascular disease, nonfatal myocardial infarction (MI), or coronary revascularization \((P = .043)\).

Patient populations in the HOPE, EUROPA and PEACE trials, which together included nearly 30,000 patients, were generally similar, except for age, blood pressure (BP), and diabetes rates, which were higher in HOPE. More patients in the PEACE trial received lipid-lowering agents, but more patients in PEACE also had undergone percutaneous coronary intervention or coronary artery bypass graft surgery.

In EUROPA, PEACE, and HOPE, all-cause mortality rates for ACE-inhibitors, compared with placebo, were 6.1% versus 6.9%, 7.2% versus 8.1%, and 10.4% versus 12.2%, respectively. Results across all eight trials were consistent in revealing reduced all-cause mortality for ACE-inhibitors compared with placebo.

The overall all-cause mortality odds ratio (OR) for ACE-inhibitors in the three trials without heart failure or LVSD was 0.86; the odds ratio for those with heart failure was 0.80.

Among the 12 trials, only PEACE did not show a reduction in nonfatal MI. Stroke was reduced in the EUROPA, PEACE and HOPE trials (OR, 0.77) but not in the other trials (OR, 0.96).

Dr. Dagenais concluded that in patients without known heart failure or LVSD, ACE-inhibitors demonstrated consistent and clear benefits for various outcomes. In the 12,000 patients with heart failure or LVSD, there was also consistency, with a four-fold risk reduction throughout a broad range of outcomes except for stroke.

He also suggested that in patients with coronary artery disease, it was unlikely that the benefits of ACE-inhibitors differed among patients with varying levels of risks or according to ancillary treatments. He recommended that ACE-inhibitors be considered in patients with any evidence of vascular atherosclerotic disease.

A discussant at the meeting, Nicholas Danchin, MD, of Canada, said, “The difference in PEACE results from those in HOPE and EUROPA is possibly accounted for by lower risk in the PEACE population but [is] more likely due to insufficient doses of trandolapril.”

Angiotensin-Receptor Blockers

Varied responses to pharmacological agents among different populations are not uncommon. Doses of antihypertensive agents for Asians are generally about half those prescribed for Western populations. Inhibitors of the renin–angiotensin system
system, such as angiotensin-receptor blockers (ARBs), have shown clinical benefits in patients at risk for, or with, existing cardiovascular disease, stated professor Björn Dahlöf, MD, of Sahlgrenska University Hospital in Göteborg, Sweden. However, evidence for such a benefit in Asian populations has been largely absent, said Dr. Dahlöf, lead investigator for the Jikei Heart study.

This study enrolled 3,081 Japanese patients (mean age, 65 years; 66% male) with high BP, coronary heart disease, and/or heart failure that was being conventionally treated. The patients had well-treated hypertension at baseline, and the mean BP was approximately 139/81 mm Hg. Baseline medications were similar between groups, with about 67% of the patients receiving calcium-channel blockers, 35% receiving ACE-inhibitors, and 32.5% receiving beta blockers.

Patients were divided into two treatment groups: one group received an ARB, and the other group received non-ARB agents. Both groups were treated to the same BP levels. The only difference, according to Dr. Dahlöf, was the presence or absence of the ARB.

The ARB group started with a dose of valsartan 80 mg (Diovan, Novartis), which was titrated up or down to a dose of 40–160 mg over 16 weeks. The BP target, 130/80 mm Hg, was achieved in both groups (131/77 mm Hg with valsartan; 132/78 mm Hg with non-ARBs). BP was lowered by 8.2/4.7 mm Hg in the valsartan arm and by 7.2/3.7 mm Hg in the non-ARB arm.

The primary endpoint, a composite of cardiovascular mortality and morbidity, was reduced by 39% in the valsartan group (hazard ratio [HR], 0.61; P = .00021), with 92 events in the valsartan group and 149 events in the non-ARB groups.

New or recurrent stroke was reduced by 40%, with 29 and 48 events in the same groups (HR, 0.60; P = .028). Furthermore, the rate of hospitalization for angina pectoris was reduced by 65% in the valsartan patients, with 19 events versus 53 events in the non-ARB arm (HR, 0.35; P = .00007). There were no differences between groups for MI, cardiovascular mortality, or all-cause mortality.

Dr. Dahlöf called the benefit “quite substantial,” in view of the short term of the trial. The Data Safety and Monitoring Board terminated the trial prematurely after more than three years because of the unequivocal benefit in reduced cardiovascular endpoints with valsartan.

“We have to consider not only aggressive blood pressure control but also which blood pressure drug is the best choice to prevent [adverse] outcomes,” Dr. Dahlöf said.

Another discussant, Xavier Girerd, MD, from Hôpital Pitié Salpêtrière in Paris, France, noted that the 39% stroke reduction with the ARB-containing regimen was more substantial than that seen in trials among Western populations, but this figure was consistent with data obtained in trials of ACE-inhibitors in an Asian population. He also mentioned that the BP reductions in the Jikei Heart Study, which were smaller than those in the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial, which also included valsartan, were attributable to the fact that patients were already being treated at the baseline evaluation in the Jikei study. He concluded:

“An antihypertensive regimen consisting of valsartan added to conventional therapies improves morbidity and mortality in Japanese patients with hypertension and CV disease.”

He recommended that similar trials be conducted in European populations.

**Oral Anticoagulants plus Antiplatelets**

Patients with peripheral artery disease (PAD), compared with other vascular patients, experience a three-fold excess rate of death from cardiovascular disease, MI, and ischemic stroke. Although antiplatelet therapy reduces cardiovascular events in vascular patients, and combining it with oral anticoagulant agents is promising in coronary artery disease, information about oral anticoagulants and antiplatelet therapy in PAD is limited, stated Sonia Anand, MD, of McMaster University in Hamilton, Ontario, Canada.

A study called WAVE (Warfarin Antiplatelet Vascular Evaluation) was conducted:

- to determine whether moderate-intensity oral anticoagulants (with an International Normalized Ratio [INR] of 2 to 3), in combination with antiplatelet therapy, was superior to antiplatelet therapy alone in preventing cardiovascular death, MI, or stroke, or severe ischemia of the coronary or peripheral arterial circulation.
- to precisely quantify the risk of bleeding.

The trial was conducted at 80 centers in seven countries. After a two-week run-in period with antiplatelets and an anticoagulant (warfarin [Coumadin], target INR of 1.8–3.5), 2,161 patients were randomly assigned either to antiplatelet therapy alone or to antiplatelets in combination with an oral anticoagulant. Antiplatelet therapy consisted of aspirin 81–325 mg daily.

The co-primary endpoints were (1) combined cardiovascular death, MI, or stroke or (2) cardiovascular death, MI, stroke, or severe ischemia of the coronary or peripheral arterial circulation. The safety endpoints were life-threatening bleeding or moderate bleeding requiring 3 or more units of blood products.

Enrolled in WAVE were 2,161 men and women between 35 and 85 years of age (mean age, 64) with at least one or more of the following criteria:

- intermittent claudication with objective evidence of PAD (ankle brachial index [ABI] of less than 0.9)
- prior vascular reconstruction (including amputation) or angioplasty of a peripheral artery
- asymptomatic PAD (other vascular disease plus an ABI of less than 0.9 or asymptomatic carotid stenosis above 50%)

The following patients were excluded from the study:

- patients with active bleeding or with a high risk of bleeding
- patients with a clear indication for long-term oral anticoagulation
- patients with a clear indication for long-term (more than three months) daily nonsteroidal anti-inflammatory agents
- patients who had experienced a recent stroke (less than six months earlier)
The analysis revealed that adding oral anticoagulation to antiplatelet therapy conferred no advantage but did carry additional bleeding risks. Reporting these results, Dr. Anand said that the first primary endpoint (cardiovascular death, MI, or stroke) occurred in 12.2% of the anticoagulant/antiplatelet group of patients and in 13.3% of the antiplatelet group ($P = .49$).

The second endpoint (severe ischemia) was met by 15.9% of the patients in the anticoagulant/antiplatelet group and in 17.4% of the patients in the antiplatelet group ($P = .38$). No significant differences were found among the separate components of the combined endpoints. Life-threatening bleeding occurred at a significant rate ($P < .001$) more often in the anticoagulant/antiplatelet group (4%) than in the antiplatelet group (1.2%). Dr. Anand concluded:

“Oral anticoagulants (targeting INR, 2–3), added to antiplatelet therapy, do not lower the rate of cardiovascular events, and they increase life-threatening bleeding, compared with antiplatelet therapy alone in patients with PAD.”

Freek Verheught, MD, from University Hospital of Nijmegen in The Netherlands, commented:

“More studies with better antithrombotic agents are needed in PAD: comparisons of aspirin alone versus oral factor Xa blockers alone, or comparisons of aspirin alone versus aspirin plus oral factor Xa blockers.”

### Direct Renin Inhibitors

The first agents in the new class of antihypertensive agents, direct renin inhibitors, failed to make it to market because of their lack of oral availability, low efficacy, short-half-life, or costly synthesis. Aliskiren (Rasilez, Novartis), an oral agent from this class, appeared to overcome those shortcomings in clinical trials, according to experts at the meeting. Its 40-hour half-life allows once-daily dosing (with the maximum concentration occurring about one to three hours after the dose), and the evidence shows that its pharmacokinetics remained unaltered in elderly patients, diabetic patients, and patients with renal or hepatic impairment.

A meta-analysis that pooled data from multicenter, randomized, double-blind trials showed that aliskiren offered long-lasting, dose-dependent reductions in BP and plasma renin activity. The trials included more than 7,000 patients with hypertension who were receiving aliskiren.

According to professor Matthew Weir, MD, of the University of Maryland School of Medicine in Baltimore, MD, the trials shared similar protocol features; they all included six to eight weeks of active treatment following the washout and placebo run-in periods. In addition, each trial had the same primary endpoint: a change in mean sitting diastolic BP (msDBP).

The trials assessed aliskiren in doses from 75 to 600 mg as monotherapy or in combination with other antihypertensive agents: the ARB valsartan, the diuretic hydrochlorothiazide (HCTZ), the ACE-inhibitor ramipril (Altace, King), or the calcium-channel blocker amiodipine (Norvasc, Pfizer).

In the overall patient population, baseline msDBP was 99.3 mm Hg, and mean sitting systolic BP (msSBP) was 153.6 mm Hg. Although BP reductions proved to be dose-dependent, the highest dose, 600 mg, did not provide substantially greater antihypertensive effects than 300 mg.

Among five placebo-controlled trials (two involving monotherapy, three involving combination therapy), msDBP was reduced by 3.3 to 8.6 mm Hg in the placebo groups and by 10.3 to 12.3 mm Hg in the aliskiren 300-mg groups ($P < .05$).

Systolic BP reductions were similarly significant: by 2.9 to 10 mm Hg with placebo and by 14.1 to 15.8 mm Hg with aliskiren 300 mg. Responder rates were higher with all aliskiren doses than with placebo (27.8% to 48.3%). With aliskiren 300 mg, responder rates ranged from 63.7% to 69.3%.

No adverse drug effects were significantly higher for aliskiren 300 mg than for placebo. Furthermore, discontinuation rates were higher with placebo (3.5%) than with aliskiren 300 mg (2.6%).

Dr. Weir noted also that aliskiren effects were independent of age or sex and that when aliskiren 150–300 mg was added to other antihypertensive agents, it safely provided further BP reductions. He concluded:

“Aliskiren, as add-on therapy to ramipril, hydrochlorothiazide, or amiodipine, provides significant additional blood pressure–lowering effects without compromising tolerability.”