Results from the ALTITUDE Trial

Written by Lori Alexander

The addition of aliskiren, a novel direct renin inhibitor that lowers plasma renin activity, to standard therapy (an angiotensin-converting enzyme [ACE] inhibitor or an angiotensin receptor blocker [ARB]) did not improve outcomes for people with type 2 diabetes and renal impairment who are at high risk for cardiovascular (CV) and renal events. This finding is among the preliminary results of Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints [ALTITUDE; NCT00549757], which was stopped early in December 2011 because of futility and a high rate of adverse events in the aliskiren group. Using aliskiren with an ACE inhibitor or ARB in this population is not recommended and may even be harmful, said Hans-Henrik Parving, MD, DMSc, University of Copenhagen, Copenhagen, and Aarhus University, Aarhus, Denmark, who presented the findings.

ALTITUDE included 8561 patients who were randomly assigned to treatment with standard therapy (an ACE inhibitor or ARB) plus aliskiren, 150 mg QD for 1 month, followed by 300 mg QD (4272 patients) or placebo (4285 patients). All patients had type 2 diabetes, renal dysfunction, and were at high risk for CV disease. The trial was designed to determine if the addition of aliskiren would provide better cardiorenal protection than monotherapy.

The primary endpoint was a composite of CV and renal outcomes, including CV death, resuscitated sudden death, non-fatal myocardial infarction, non-fatal stroke, unplanned hospitalization for heart failure, onset of end-stage renal disease or renal death, or doubling of the baseline serum creatinine level (sustained for at least 1 month).

At a median follow-up of 32 months, the rate of the composite endpoint was 17.9% in the aliskiren group and 16.8% in the placebo group (HR, 1.08; 95% CI, 0.98 to 1.20; p=0.14). Prof. Parving noted that when the individual components of the endpoint were analyzed separately, some occurred more frequently in the aliskiren group, but the differences were not significant (Table 1).

Hyperkalemia was the most common adverse event in the aliskiren group (38.7% vs 28.6%). Among the patients in that group, 8.8% had a serum potassium level ≥6 mmol/L, compared with 5.6% in the placebo group. The serum potassium level was ≥5.5 to 6.0 mmol/L in 21.0% of the aliskiren group and 16.0% of the placebo group. One death was associated with hyperkalemia. Other frequent adverse events in the aliskiren group included hypotension (12.1% vs 8.0%), diarrhea (9.6% vs 7.2%), and falls (2.8% vs 2.6%).

Table 1. ALTITUDE HRs for Individual Components of the Primary Endpoint.

	Patients with Event (%)			
	Aliskiren	Placebo	Hazard Ratio (95% CI)	p value
Stroke	3.4	2.8	1.25 (0.98-1.60)	0.07
CV death	5.6	5.0	1.13 (0.94-1.36)	0.18
Death	8.8	8.3	1.07 (0.92-1.23)	0.39
Resuscitated sudden death	0.4	0.2	2.28 (0.99-5.23)	0.053
MI	3.3	3.3	1.02 (0.81-1.29)	0.86
Unplanned hospitalization for heart failure	4.7	5.1	0.93 (0.77-1.13)	0.46
Doubling of baseline serum creatinine level	4.8	5.0	0.96 (0.79-1.16)	0.65
Onset of end-stage RD or renal death	2.8	2.5	1.10 (0.85-1.43)	0.47

CV=cardiovascular; MI=myocardial infarction; RD=renal disease.

In discussing the study, Johannes Mann, MD, Friedrich Alexander University, Erlangen, Germany, and McMaster University, Hamilton, Ontario, Canada, noted that the reason for a possible increased risk of stroke was unclear. Dual inhibition of the renin system was not associated with such an increased risk in the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial [ONTARGET], in which the combination of ramipril (an ACE inhibitor) and telmisartan (an ARB) was compared with each drug used as monotherapy [Tobe SW et al. *Circulation* 2011]. Both Prof. Mann and Prof. Parving said that the observed risk could be a direct effect of aliskiren or could be a chance finding.

Results of the WOEST Trial

Written by Maria Vinall

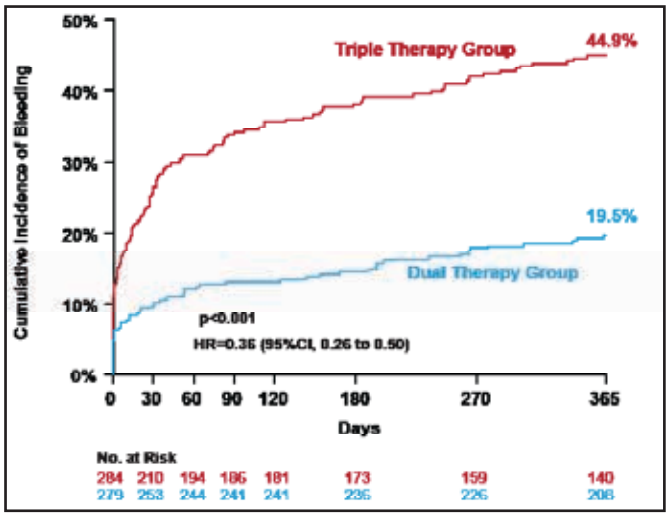
Results of the first randomized trial to address optimal antiplatelet therapy in patients on oral anticoagulants (OACs) undergoing coronary stenting showed that treatment with dual antithrombotic therapy (OAC plus clopidogrel alone) caused less bleeding than triple antithrombotic therapy (OAC plus aspirin plus clopidogrel), with no excess of thrombotic/thromboembolic events and less all-cause mortality.

Long-term OAC therapy is necessary in most patients with atrial fibrillation (AF) or a mechanical heart valve. The addition of aspirin and clopidogrel are indicated when these patients undergo percutaneous coronary intervention (PCI), but when all 3 drugs are coadministered, the risk of major bleeding is substantially increased [Sorensen et al. *Lancet* 2009]. In this context, the What Is the Optimal Antiplatelet and Anticoagulant Therapy in Patients with Oral Anticoagulation and Coronary Stenting [WOEST; NCT00769938] trial was designed to test the hypothesis that in patients on OAC therapy undergoing PCI, the addition of clopidogrel alone is superior to the combination of aspirin and clopidogrel with respect to bleeding. The results of the trial were presented by Willem Dewilde, MD, Twee Steden Hospital, Tilburg, the Netherlands.

WOEST was an investigator-initiated, prospective, randomized study conducted in 15 Danish and Belgium hospitals between November 2008 and November 2011. Patients with a prior history of AF (69%), a mechanical heart valve (10%), or other indication for OAC (eg, thromboembolic disease or severe systolic heart failure) were openly randomized to either dual (warfarin+clopidogrel 75 mg QD; n=279) or triple (warfarin+clopidogrel 75 mg QD+aspirin 80 mg QD; n=284) therapy. Patients were treated with clopidogrel for a minimum of 1 month after placement of a bare-metal stent (~30% of patients) and 1 year after placement of a drug-eluting stent (~65%). All patients were followed for 1 year. The primary outcome was the occurrence of any bleeding event (Thrombolysis in Myocardial Infarction [TIMI] major or minor criteria), and the study was statistically powered to detect a 60% reduction in bleeding based on prior cohort data (annual expected bleeding rate on triple therapy was projected to be 12%). Secondary exploratory endpoints included ischemic events, a combination of stroke, death, myocardial infarction (MI); stent thrombosis (ST) and target vessel revascularization (TVR); and individual components of these endpoints [Dewilde W and Berg JT. *Am Heart J* 2009].

Baseline characteristics in the WOEST study revealed the mean age of patients was ~70 years, ~80% were men, ~70% had a history of hypertension, 70% had hypercholesterolemia, and 25% to 30% had a prior history of either diabetes, MI, or heart failure. Concurrent use of proton pump inhibitors was ~35%. Despite the exclusion of patients with a recent history of major bleeding, peptic ulcer disease, or other major risk factors, bleeding in this study was higher than expected (~45% of patients assigned to triple therapy experienced a bleeding endpoint within 1 year). However, patients treated with dual therapy experienced significantly less bleeding compared with triple therapy (19.5% vs 44.9%; HR, 0.36; 95% CI, 0.26 to 0.50; p<0.001; Figure 1).

Figure 1. Primary Endpoint: Total Number of Bleeding Events (TIMI Criteria).



TIMI=thrombolysis in myocardial infarction.
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Results were consistent among major subgroups, including when analyzed by a threshold age of 75 years, gender, presentation with acute coronary syndrome, indication for OAC, and stent received. The difference in bleeding between the 2 treatment groups was driven predominantly by TIMI minimal and minor bleeding from the access site, gastrointestinal, and superficial locations. There was no difference between the 2 groups in TIMI major bleeding (3.3% vs 5.8%; p=0.159) or intracranial bleeds (3 in each group).

Patients receiving dual therapy experienced significantly fewer composite ischemic events compared with those receiving triple therapy (11.3% vs 17.7%; HR, 0.60; 95% CI, 0.38 to 0.94; p=0.025). Each component of the composite ischemic endpoint was consistently less frequent among patients assigned dual therapy except for TVR.

The investigators concluded that a strategy of omitting aspirin is an option in high-risk patients on chronic anticoagulation undergoing PCI. Although it was an open-label study, this provocative trial will hopefully open the door for further investigations of the optimal long-term treatment strategy to balance ischemic and bleeding outcomes in high-risk patients.

Results from the Aldo-DHF Trial

Written by Maria Vinall

Results from the Aldosterone Receptor Blockade in Diastolic Heart Failure [Aldo-DHF; ISCRTN94726526] trial, presented by Burkert Mathias Pieske, MD,