## 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.