to 7.66%), duration of diabetes (6.1 to 6.2 years), estimated glomerular filtration rate (85 mL/min/1.73 $m^2$), serum creatinine (77 mmol/L), and systolic (136 to 137 mm Hg) and diastolic (80 to 81 mm Hg) blood pressure (SBP and DBP, respectively).

The median albumin-to-creatinine ratio was higher (4.00 mg/g; 95% CI, 1.0 to 46.8) for the olmesartan group versus the placebo group (3.00 mg/g; 95% CI, 1.0 to 35.0), and the olmesartan group had higher serum triglyceride levels at baseline (2.13 ± 1.70 mmol/L) than the placebo group (2.03 ± 1.28 mmol/L).

Hermann Haller, MD, University of Hannover Medical School, Hannover, Germany, presented data from ROADMAP. Over the 48 months of the study, the olmesartan group achieved a reduction of sitting SBP/DBP of 3.0/1.9 mm Hg compared with the control group. Similarly, more patients in the olmesartan arm reached the blood pressure goal of <130/80 mm Hg than in the placebo arm (78.2% vs 71.3% of patients, respectively). Interestingly, fewer olmesartan patients were at goal at baseline (28%) compared with the placebo group (30%).

At 48 months, more patients in the placebo group had reached the primary endpoint of time to first occurrence of microalbuminuria compared with those who received olmesartan. Olmesartan use was associated with a 23% reduction in risk of reaching this endpoint (HR, 0.770; 95% CI, 0.630 to 0.941; p=0.0104).

Olmesartan was associated with a 19% risk reduction, even after the time to first occurrence of microalbuminuria was corrected for the last mean blood pressure differences (SBP-corrected HR, 0.814; p=0.0451; DBP-corrected HR, 0.810; p=0.0398). However, when the values were corrected for the areas under the blood pressure curves from baseline to last assessment, there was no significant difference between the groups (SBP-corrected HR, 0.834; p=0.0789; DBP-corrected HR, 0.823; p=0.0596).

Olmesartan did not prove to be different from placebo in terms of preventing CV morbidity and mortality, all CV morbidity, or transient ischemic attack and atrial fibrillation. In a *post hoc* analysis, olmesartan was shown to reduce the risk of cardiac morbidity by 36% (HR,0.64; p=0.03).

Prof. Haller reported that there were 15 deaths in the olmesartan arm compared with 3 in the placebo arm. However, the increased mortality was seen only among patients who had preexisting CV disease (n=1104; p=0.02 between olmesartan and placebo). Furthermore, among such patients, the quartiles with the lowest SBP before the event or the greatest reduction in SBP had the highest CV mortality (eg, in the quartile with SBP <122.3 mm Hg, there was about a 2.5-fold increased incidence of events vs the next highest quartile; SBP 122.3 mm Hg to <126.4 mm Hg).

In summary, olmesartan was associated with a 23% risk reduction and delayed the occurrence of microalbuminuria, with the majority of the effect being independent of blood pressure. Olmesartan was highly efficacious in controlling blood pressure, with nearly 80% of patients reaching goal at 48 months. Prof Haller cautioned that blood pressure reduction below 120/70 mm Hg is not recommended for patients with T2DM and known coronary heart disease.

## Candesartan Fails to Prevent Microalbuminuria in Hypertensive Diabetics When Stringent Criteria Are Used

Four years of candesartan, an angiotensin receptor blocker, reduced incident microalbuminuria in hypertensive patients with type 2 diabetes mellitus (T2DM) when albumin excretion was defined by a single positive urine sample but not with multiple collections. No effect was evident in normotensive T2DM subjects using either definition. Given the difference in results when multiple or single urine samples were included, the method of detection needs to be considered when evaluating studies of primary prevention of microalbuminuria in patients with T2DM.

Previously, renin-angiotensin system (RAS) blockade was shown to prevent microalbuminuria in people with T2DM who were at high cardiovascular risk. Most of these findings were based on single determinations of the albumin-to-creatinine ratio. In contrast, the pooled results of three Diabetic Retinopathy Candesartan Trials (DIRECT; NCT00252694, NCT00252720, NCT00252733), using multiple, timed overnight urine collections, failed to show a benefit of RAS blockade on the development of persistent microalbuminuria (defined as 3 of 4 consecutive samples with albumin >20 µg/min).

Rudolf Bilous, MD, James Cook University Hospital, Middlesbrough, United Kingdom, presented a reanalysis of those data with the aim of investigating whether candesartan reduced incident microalbuminuria in normotensive (blood pressure [BP] <130/85 mm Hg) and well-controlled hypertensive T2DM patients, using the

less stringent definition of microalbuminuria of a single value >20 µg/min.

The three DIRECT studies involved subjects with mild to moderate retinopathy, and these pooled results are based on those populations. Overall, 1905 people with T2DM were randomized to receive either candesartan (titrated to 32 mg daily) or placebo. At study entry, all subjects had normal albumin excretion (median albuminuria 5.5 µg/min), 62% were hypertensive (mean BP 139/69 mm Hg), and 38% were normotensive (BP <130/85 mm Hg, mean 123/75 mm Hg). Each subject collected 2 timed, overnight urine specimens annually for at least 4 years. BP was measured semiannually. The two arms of the trial were well matched for gender (49% to 51% male), age (mean age 57 years), diabetes duration (mean duration 9 years), and HbA1C (mean 8.2% ± 1.6).

Candesartan lowered systolic blood pressure (SBP) as early as 6 months in both cohorts, and at 4 years of follow-up (using the last value carried forward), SBP decreased by 4.3 mm Hg in the normotensive group and by 2.9 mm Hg in the hypertensive subjects.

At 5 years of follow-up, based on a single positive sample, candesartan significantly lowered the risk of microalbuminuria by 20% when all patients were considered together (HR, 0.80; 95% CI, 0.67 to 0.96; p=0.016). The result was similar for the groups of patients who were hypertensive or normotensive at baseline but was not statistically significant for the normotensive group. However, when using the more stringent criterion of 3 of 4 positive samples, candesartan had no effect on the development of microalbuminuria.

**Table 1. Efficacy of Candesartan in Preventing Microalbuminuria [HR (95% CI)].**

| | Single sample positive | p value | 3 of 4 samples positive | p value |
|---|---|---|---|---|
| All patients (n=1905) | 0.80 (0.67 to 0.96) | 0.016 | 0.80 (0.58 to 1.11) | 0.187 |
| Normotensive at baseline (n=725) | 0.81 (0.61 to 1.09) | 0.166 | 0.66 (0.40 to 1.09) | 0.105 |
| Hypertensive at baseline (n=1180) | 0.79 (0.63 to 0.99) | 0.037 | 0.91 (0.60 to 1.40) | 0.685 |

Prof. Bilous summarized the findings by saying that candesartan 32 mg daily for 4 years was effective in reducing incident microalbuminuria in patients with T2DM who were normotensive at baseline when defined by a single positive urine sample but not by the more stringent criterion of multiple positives. He added that the drug's apparently greater efficacy in patients who were hypertensive at baseline may have been the result of the larger sample size and number of events. Overall, these results suggest that the method of detection strongly influences the results of studies that investigate the primary prevention of microalbuminuria. Furthermore, the possibility of patient benefit needs to take into account baseline vascular risk and the definition of the endpoint.

Prof. Bilous concluded that the DIRECT results do not support universal RAS blockade for T2DM patients who are at low vascular risk, and he advised developing standardized definitions of early nephropathy for intervention trials.