function, tumor suppression, and increased insulin sensitivity. The negative effects of insulin were attributed to it being proatherogenic, its effect on the insulin-like growth factor-1 axis, survival and proliferation of malignant cells, and hypoglycemia.

ADDITION Shows No Increased Benefit Of Early Multifactorial Intensive Therapy

The issue of intensive diabetes therapy became a bit more perplexing after the latest results of the ADDITION (Anglo-Danish-Dutch Study of Intensive Treatment. In People with Screen Detected Diabetes in Primary Care; NCT00237549) trial found no significant differences in overall cardiovascular (CV) events between such care and the routine management of patients with screen-detected diabetes.

Simon J. Griffin, DM, Medical Research Council Epidemiology Unit, Cambridge, UK, presented the latest findings of the 3000-patient multifactorial trial. The trial was designed to evaluate various stepped screening programs to identify diabetes in at-risk individuals; determine whether primary care practices could provide intensive therapy; and assess the differences between intensive and routine management of diabetes over 5 years, based on continually updated clinical guidelines.

The trial was conducted in three countries: The Netherlands, the UK, and Denmark. Most participants were obese and had high blood pressure (>120/80 mm Hg) and a median HbA1C of 6.6% upon entry. The primary endpoint was a composite of the first CV event, including CV mortality and morbidity (nonfatal myocardial infarction or nonfatal stroke), revascularization, and nontraumatic amputation.

General practitioners in the intensive intervention arm were encouraged to provide education on lifestyle changes that were designed to reduce their patients' CV risk and improve glycemic levels, and treatment started once HbA1C levels reached ≥6.5%, blood pressure was >120/80 mm Hg, and/or total cholesterol was >3.5 mmol/L. Physicians in this arm also received practice-based education.

Routine care was based on national guidelines. Over time, it is important to note that the national guidelines changed and became more similar to the intensive treatment guidelines, with more intensive goals for blood pressure, cholesterol, and HbA1C levels. In fact, Prof. Griffin noted that this congruence of treatment goals was a possible reason for the lack of significant effects that were associated with intensive treatment.

Both groups demonstrated improvements in CV risk factors during the study, with the intensive treatment arm demonstrating significant, albeit modest, greater improvements in risk factors and achievement of treatment targets. Rates of CV events in both groups over 5 years were lower than expected (7.2% [intensive] vs 8.5% [control]; HR, 0.83; 95% CI, 0.65 to 1.05; p=0.12). An analysis from William Herman, MD, University of Michigan, Ann Arbor, Michigan, USA, postulated that had the patients in the trial not been screened, diagnosed with diabetes, and treated, the composite endpoint would have doubled, regardless of the type of care that was provided.

There was no increased mortality in the intensive treatment arm, though such increases were seen in other large diabetes trials that assessed the role of intensive treatment in CV risk.

Early Treatment With Olmesartan Delays Progression of Nephropathy in Patients With Type 2 Diabetes

Preventing the progression of normal albumin excretion to microalbuminuria should be a goal in the management of patients with type 2 diabetes mellitus (T2DM), since microalbuminuria is an early sign of diabetic nephropathy and elevated cardiovascular (CV) risk. The Randomized Olmesartan And Diabetes MicroAlbuminuria Prevention (ROADMAP; NCT00185159) study investigated whether early administration of an angiotensin receptor blocker (ARB) to diabetic patients with normal albumin excretion could delay or prevent the first occurrence of microalbuminuria and whether it could affect the incidence of CV and renal events.

This multinational European trial randomly assigned 4447 patients (aged 18 to 75 years) with T2DM and at least one additional CV risk factor and normoalbuminuria to olmesartan 40 mg (n=2232) or placebo (n=2215). Patients could also receive other antihypertensive medication that did not act on the renin-angiotensin system but could not have been treated with an angiotensin-converting enzyme inhibitor or ARB in the previous 6 months. The groups were well matched at baseline for gender, age (58 years), body mass index (31 kg/m^2), glycated hemoglobin (7.65%

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