function. This association was not dependent on T2DM status. Only in T2DM patients were higher BNP levels associated with increase in LV mass. Thus, the presence or absence of T2DM should be taken into account if BNP levels are used to assess CVD risk.

Table 1. LV Function.

LV Systolic Function Regression coefficients, β (95% CI) per 10-pmol/L increase of baseline BNP for EF			
EF (%)	Non-T2DM n=143	T2DM n=62	Total population n=205
Age & gender	-2.5 (-5.4, 0.6)	-3.4 (-8.2, 1.4)	-2.5 (-4.9, -0.01)*
+ baseline EF	-2.6 (-5.6, 0.4)	-3.0 (-7.5, 1.4)	-2.7 (-5.2, -0.3)*
+ use of antihypertensives, BMI, & HR	-2.6 (-5.8, 0.6)	-4.0 (-8.3, 0.2)	-3.2 (-5.8, -0.7)*
LV Diastolic Function Regression coefficients, β (95% CI) per 10-pmol/L increase of baseline BNP for LAVI			
LAVI (mL/m²)	Non-T2DM n=165	T2DM n=71	Total population n=236
Age & gender	5.3 (2.8, 7.7)*	6.8 (2.5, 11.2)*	5.3 (3.2, 7.4)*
+ baseline EF	4.3 (1.7, 6.9)*	5.6 (1.2,10.1)*	4.2 (2.0, 6.4)*
+ use of antihypertensives, BMI, & HR	4.5 (1.8, 7.1)*	6.1 (1.7, 10.5)*	4.5 (2.4, 6.7)*
LV Mass Regression coefficients, β (95% CI) per 10-pmol/L increase of baseline BNP for LVMI			
LVMI (g/m²)	Non-T2DM n=151	T2DM n=73	
Age & gender	4.6 (-1.5, 10.0)	31.0 (14.7, 47.3)*	
+ baseline EF	1.0 (-4.9, 6.9)	26.4 (10.3, 42.5)*	
+ use of antihypertensives, BMI, & HR	0.1 (-5.9, 6.2)	30.6 (14.3, 46.8)*	

LV=left ventricular; CI=confidence interval; BNP= B-type natriuretic peptide; EF=ejection fraction; LAVI=left atrial volume index; LVMI-left ventricular mass index; *p <0.05

An Update on the DIGAMI Studies

Acute myocardial infarction (AMI) in patients with diabetes increases the risk of poor outcome. In the Diabetes Mellitus-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study, insulin-glucose infusion, followed by multidose insulin treatment, improved long-term prognosis in diabetic patients with AMI at 1 year [Malmberg K et al. *J Am Coll Cardiol* 1995].

In DIGAMI 2, patients with type 2 diabetes or blood glucose >11 mmol/L and suspected myocardial infarction (MI) were randomized to one of three treatment strategies: Group 1–acute insulin-glucose infusion followed by insulin-based long-term glucose control (n=474); Group 2–insulin-glucose infusion followed by standard glucose control (n=473); or Group 3–routine metabolic management according to local practice (n=306) [Malmberg K et al. *Eur Heart J* 2005]. Subjects were treated for a mean of 2.1 years and, in an extended part of the trial, followed up for a maximum of 8.3 years (median 4.1). At the end of the study, there were no significant differences in morbidity, expressed as nonfatal reinfarctions and strokes, among the three groups. The data did suggest that glucose level is a strong, independent predictor of long-term mortality in this patient category, indicating that glucose control seems to be an important part of their management.

Results of a later post hoc analysis from DIGAMI 2, assessing the impact of glucose-lowering treatment with insulin, sulfonylureas, or metformin on long-term mortality and morbidity prognosis, showed no significant difference in mortality between the three treatments. The risk of nonfatal MI and stroke increased significantly with insulin, while metformin was protective [Mellbin LG et al. *Eur Heart J* 2008].

Linda Mellbin, MD, Department of Cardiology, Karolinska Institutet, Stockholm, Sweden, discussed recent data from the extended follow-up (maximum 8.3 years; median 4.1 years) for 1145 subjects in the DIGAMI 2 study. Total mortality was 34% (24% cardiovascular [CV]; 9.5% malignancies). Cox regression analysis did not show any difference in total or CV mortality among the treatment groups. The total number of fatal malignancies was 37, with the highest risk in Group 1 (HR vs Group 2, 1.83; 95% CI, 0.90 to 3.71; p=0.10 and Group 3, 3.57; 95% CI, 1.22 to 10.39; p=0.02). Treatment with insulin was associated with a significant increase in the risk of nonfatal MI and stroke (OR, 1.90; 95% CI, 1.38 to 2.60; p<0.0001) but not mortality (OR, 1.30; 95% CI, 0.94 to 1.80; p=0.11), while metformin was associated with a lower mortality (HR, 0.65; 95% CI, 0.47 to 0.90) and a lower risk of death due to malignancies (HR, 0.25; 95% CI, 0.08 to 0.83).

Long-term mortality is high after MI in patients with type 2 diabetes. The drug that is used for glucose control appears to have a prognostic impact. Prof. Mellbin suggested that the beneficial effects of metformin may be due to 5' AMP-activated protein kinase-induced improved endothelial

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%