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RESEARCH LETTER

A 3-year follow-up of the Silent Diabetes Study

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Abbreviations

CAD	Coronary artery disease
FPG	Fasting plasma glucose
hs-CRP	High-sensitivity C-reactive protein
NT-proBNP	N-terminal pro-brain natriuretic peptide

To the Editor: The Silent Diabetes Study compared the results of HbA_{1c} measurement with those of an OGTT in 1,015 patients without pre-diagnosed diabetes undergoing coronary angiography [1]. All patients provided written informed consent and the study was performed in accordance with the Declaration of Helsinki. Ethics approval was obtained from the local ethics committee (Saechsische Landesaerztekammer, Registration Number EK-BR-36/06-1). According to OGTT measurements, 14% were diagnosed with diabetes; but on the basis of HbA_{1c} measurements, only 4% were diagnosed with diabetes. In the entire group, the prevalence of newly detected impaired glucose regulation was 49%. The proportion of patients with impaired glucose tolerance and diabetes increased with the extent of coronary artery disease (CAD) [1]. Post hoc pairwise comparisons showed differences in mean 2 h post-load plasma glucose between the patients without CAD and the groups with single-, double- and triple-vessel disease (all $p<0.0001$). Differences were also seen between the minor CAD group and the groups with single-, double- and triple-vessel disease (all $p<0.0001$). HbA_{1c} levels, however, showed no differences among the groups with different extents of CAD [1].

The aim of the 3-year follow-up of the Silent Diabetes Study was to analyse the mortality and to retrospectively identify baseline risk factors for mortality. The follow-up analysis was performed in 886 (87.3%) of the 1,015 patients. No information was obtained from 129 patients (12.7%). At follow-up, 825 (93.1%) patients had survived and 61 patients (6.9%) had died. Table 1 compares baseline variables in survivors and non-survivors at the 3-year follow-up.

At follow-up, 25 (5.5%) of 426 patients, who had been defined as normoglycaemic by OGTT at baseline, had died. Among 434 patients with impaired glycaemic control (impaired fasting glucose, impaired glucose tolerance, diabetes) at baseline, 36 (8.3%) had died.

Baseline HbA_{1c}, fasting plasma glucose levels (FPG) and 2 h post-load plasma glucose levels (2 h OGTT) were not significantly different between survivors and non-survivors: (HbA_{1c}: 5.6% vs 5.7% [37.7 vs 38.8 mmol/mol], $p=0.853$; FPG: 4.4 vs 4.3 mmol/l, $p=0.639$; 2 h OGTT: 8.0 vs 8.6 mmol/l, $p=0.068$). Baseline differences between survivors and non-survivors, however, were seen between the 2 h OGTT and FPG levels (Δ 2 h OGTT–FPG).

Those who died presented with a higher baseline mean Δ 2 h OGTT–FPG compared with that of the survivors (4.26 vs 3.54 mmol/l, $p=0.034$). A relationship between the extent of CAD and the mean Δ 2 h OGTT–FPG was also present at baseline: no CAD (2.30 mmol/l, 2.28 SD, 2.00 median); beginning CAD (2.71 mmol/l, 2.49 SD, 2.00 median); single-vessel disease (3.68 mmol/l, 2.67 SD, 3.00

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Table 1 Comparison of data in survivors and deceased patients

Variable	Survivors, n=825	Non-survivors, n=61	p value
Age (years)	72.7±8.63 (73.7)	77.7±9.14 (78.8)	<0.0001
Male	563 (68.2%)	44 (72.1%)	0.571
Female	262 (31.8%)	17 (27.9%)	
BMI (kg/m^2)	27.5±3.72 (27.0)	27.3±4.7 (26.8)	0.41
Systolic BP (mmHg)	141±17.5 (140)	139±18.9 (140)	0.472
Diastolic BP (mmHg)	78±9.1 (80)	78±8.6 (80)	0.716
BG, fasting (mmol/l)	4.4±0.8 (4.0)	4.3±0.7 (4.0)	0.639
BG, 2 h OGTT (mmol/l)	8.0±2.9 (8.0)	8.6±2.9 (8.0)	0.068
Δ 2 h OGTT–FPG (mmol/l)	3.54±2.63 (3.00)	4.26±2.65 (4.00)	0.034
HbA_{1c} (%)	5.6±0.6 (6.0)	5.7±0.5 (6.0)	0.853
HbA_{1c} (mmol/mol)[a]	37.7 (42.1)	38.8 (42.1)	
Haemoglobin (mmol/l)	8.9±0.8 (8.9)	8.6±1.1 (8.7)	0.062
Leucocytes (×10^9/l)	6.9±1.76 (7.0)	7.4±2.3 (7.0)	0.044
Thrombocytes (×10^9/l)	229±63 (226)	227±76.6 (217)	0.635
Creatinine (μmol/l)	89.9±36.0 (87.0)	105.5±68.8 (93.0)	0.078
Estimated GFR (ml/min)	76.0±18.3 (75.0)	72.0±25.9 (71.0)	0.168
hs-CRP (nmol/l)	47.60±80.0 (21.0)	116.2±270.54 (36.2)	0.006
NT-proBNP (pg/ml)	447±618 (211)	1214±1060 (874)	<0.0001
CAD			
No CAD	53 (6.4%)	0 (0%)	0.45
Minor CAD	145 (17.6%)	7 (11.5%)	
Single-vessel disease	184 (22.3%)	11 (18.0%)	
Double-vessel disease	183 (22.2%)	20 (32.8%)	
Triple-vessel disease	259 (31.4%)	23 (32.7%)	
Glycaemic status			
Normoglycaemia	426 (51.7%)	25 (41.0%)	0.113
Impaired fasting glucose	8 (1.0%)	1 (1.6%)	0.476
Impaired glucose tolerance	274 (33.3%)	23 (37.7%)	0.485
Diabetes	116 (14.1%)	12 (19.7%)	0.256

Data are presented as mean ± SD (median) or n (%) unless otherwise indicated

[a] Data are presented as mean (median)

BG, blood glucose

median); double-vessel disease (3.86 mmol/l, 2.62 SD, 4.00 median) and triple-vessel disease (4.17 mmol/l, 2.53 SD, 4.00 median). Post hoc pairwise comparisons of baseline Δ 2 h OGTT–FPG showed significant differences between the no CAD group and the groups with single-, double- and triple-vessel disease (all p<0.0001). Significant differences were also seen between the minor CAD group and the groups with single-, double- and triple-vessel disease (all p<0.0001), and between single- and triple-vessel disease groups (p=0.025). No significant differences were observed between the no CAD and minor CAD groups (p=0.286), between the single- and double-disease groups (p=0.497) and between the double- and triple-disease groups (p=0.142).

Differences in mortality were seen between the patients without CAD and those in the groups with different extents of CAD at baseline (p=0.045). Among the deceased patients, 11.5% had been diagnosed with minor CAD at baseline, 18.0% with single-vessel, 32.8% with double-vessel and 32.7% with triple-vessel disease. Among the survivors, the percentages were: 6.4% (no CAD), 17.6% (minor CAD), 22.3% (single-vessel disease), 22.2% (double-vessel disease) and 31.4% (triple-vessel disease).

A significant relationship with mortality risk was also found for N-terminal pro-brain natriuretic peptide (NT-proBNP) and high-sensitivity C-reactive protein (hs-CRP). At baseline, mean NT-proBNP was 1,214 pg/ml among the 61 deceased patients vs 447 pg/ml among the 825 survivors (p<0.0001). For hs-CRP, the levels were 116.2 among deceased patients vs 47.6 nmol/l for the survivors (p=0.006). Age, but not sex, was found to be related to mortality.

The 3-year follow-up of the Silent Diabetes Study extends the knowledge on risk factors for mortality in patients without

pre-diagnosed diabetes undergoing coronary angiography. HbA_{1c} at baseline was not related to the 3-year outcome. In addition, baseline FPG and 2 h post-load plasma glucose of the OGTT was not different between survivors and non-survivors. It is of interest that the difference between the 2 h OGTT and FPG of the OGTT at baseline was different in survivors and non-survivors. This could indicate that glycaemic variability plays a prognostic role. In line with this, an impact of glucose variability on cardiovascular outcome has been reported [2, 3]. The non-significant difference in 2 h post-load plasma glucose (8.6 vs 8.0 mmol/l; $p=0.068$) may also support the view.

C-reactive protein on admission has previously been found to be a strong predictor for hospital mortality in both diabetic and non-diabetic patients with an acute myocardial infarction [4]. The predictive value of NT-pro BNP for mortality is also confirmed by a recently published study in patients who underwent elective or acute coronary angiography [5].

The 3-year follow-up of the Silent Diabetes Study emphasises the impact of glucose variability as well as inflammatory and structural cardiac processes for a potential adverse outcome in patients undergoing coronary angiography.

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