Post-challenge hyperglycaemia is strongly associated with future macrovascular events and total mortality in angiographed coronary patients

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Aims
The prevalence of post-challenge hyperglycaemia in coronary patients is high. Until now, it is unclear whether post-challenge hyperglycaemia is associated with an increased risk for future macrovascular events in this clinically important patient population.

Methods and results
We enrolled 1040 patients undergoing coronary angiography for the evaluation of suspected or established coronary artery disease. In patients without previously established diabetes mellitus, an oral glucose tolerance test (oGTT) was performed. Prospectively, mortality and macrovascular events were recorded over a mean follow-up period of 3.8 years. From our patients, 394 had normal glucose tolerance (NGT), 280 post-challenge hyperglycaemia (this subgroup includes both impaired glucose tolerance and post-challenge diabetes) and 366 had conventional diabetes. The incidence of macrovascular events was significantly higher in patients with post-challenge hyperglycaemia as well as in patients with conventional diabetes than in subjects with NGT (23.6 and 29.5% vs. 18.5%; P = 0.013 and P < 0.001, respectively). Adjusted hazard ratios were 1.46 (95% CI 1.03–2.07, P = 0.033) for patients with post-challenge hyperglycaemia and 1.73 (1.25–2.37, P = 0.001) for patients with conventional diabetes.

Conclusion
Post-challenge hyperglycaemia is associated with future macrovascular events in patients undergoing coronary angiography for the evaluation of stable coronary artery disease (CAD). Oral glucose tolerance tests in this high-risk population thus identify patients with a particularly unfavourable prognosis.

Keywords
Impaired glucose tolerance † Post-challenge hyperglycaemia † Macrovascular risk † Coronary artery disease

Introduction
Type 2 diabetes is associated with a two- to four-fold increased risk of cardiovascular events.1 Typically, overt diabetes is preceded by impaired glucose tolerance (IGT), which is characterized by hyperglycaemia after a glucose challenge. Previously published data suggest that already this pre-diabetic state is associated with an adverse macrovascular outcome.2,3 However, unequivocal data on the prognostic value of post-challenge hyperglycaemia in high-risk patients are not available yet. The GAMI trial (Glucose tolerance in patients with Acute Myocardial Infarction) suggested that post-challenge hyperglycaemia is a major risk factor for future cardiovascular events in patients with acute myocardial infarction.4 The Euro Heart Survey on Diabetes and the Heart, which included both patients with acute coronary syndrome and patients with stable angina...
Coronary angiography in current clinical practice is the gold standard method to diagnose CAD in high-risk patients. The study of risk factors in angiographed patients therefore is of major clinical interest. The prevalence of post-challenge hyperglycaemia in angiographed coronary patients exceeds 60%. Further, as we have recently shown, post-challenge hyperglycaemia is associated with the angiographically determined extent of CAD. However, the impact of post-challenge hyperglycaemia on prognosis in patients undergoing coronary angiography for the evaluation of stable CAD remains unclear. We therefore aimed at investigating the impact of post-challenge hyperglycaemia on the incidence of macrovascular events in this clinically important patient population.

Methods

We enrolled 1046 consecutive Caucasian patients who underwent coronary angiography for the routine evaluation of suspected or established stable CAD at the Medical University of Graz or at the Academic Teaching Hospital of Feldkirch between October 1999 and March 2005. The patients were referred for angiography solely on the basis of the clinical indication made by the referring physicians according to current guidelines. Patients who had suffered myocardial infarctions or acute coronary syndromes within 3 months prior to the angiography were not enrolled. Six patients with type 1 diabetes (C-peptide negative) were excluded from the analyses.

Venous blood samples were collected after an overnight fast of at least 12 h before angiography was performed and laboratory analyses were performed as described previously.

According to American Diabetes Association criteria, patients with a fasting plasma glucose (FPG) <126 mg/dL (<7.0 mmol/L) and a post-challenge glucose (i.e., plasma glucose 2 h after the 75 g glucose load) <140 mg/dL (<7.8 mmol/L) were classified as having a normal glucose tolerance (NGT). Impaired glucose tolerance was diagnosed in patients with FPG <126 (<7.0 mmol/L) mg/dL and post-challenge glucose between 140 and 200 mg/dL (≥7.8 and <11.1 mmol/L) isolated post-challenge diabetes was diagnosed in patients with a FPG <126 mg/dL (7.0 mmol/L) and post-challenge glucose ≥200 mg/dL (≥11.1 mmol/L); and conventional diabetes was diagnosed in patients with FPG ≥126 mg/dL or previously established diabetes.

Among patients with established diabetes, 26% were not receiving any glucose lowering medication, and 37, 35, and 32% were receiving—alone or in combination—sulfonlureas, biguanides, and insulin, respectively, at baseline. Overall, 71% of our patients were on aspirin, 44% on statins, 3% on fibrates, 12% on calcium antagonists, 55% on beta adrenoreceptor blocking agents, 44% on angiotensin-converting enzyme-inhibitors, and 3% on angiotensin II receptor blocking agents at baseline.

Follow-up data were collected by follow-up visits at our institutions, by telephone contacts with patients and family physicians, and through a national registry of death. Both mortality and the incidence of macrovascular events were recorded. The primary study endpoint was a composite of vascular deaths, non-fatal myocardial infarctions, non-fatal strokes, percutaneous coronary interventions, bypass graftings, and revascularizations of non-coronary arteries, whichever occurred first. Secondary endpoints were (i) overall mortality and (ii) the following three secondary composite endpoints: secondary composite endpoint A, encompassing any death, non-fatal myocardial infarction, non-fatal stroke, percutaneous coronary intervention, bypass grafting, and revascularization of non-coronary arteries; secondary composite endpoint B, encompassing vascular death, non-fatal myocardial infarction, non-fatal stroke, percutaneous coronary intervention, and bypass grafting; and secondary composite endpoint C, encompassing any death, non-fatal myocardial infarction, non-fatal stroke, percutaneous coronary intervention, and bypass grafting.

Contact by telephone led to follow-up and verification of vital status in 97.5%. After review of autopsy, death certificate (ICD-9 codes 434.0–434.9, 410.0–414.9, and 429.2), or hospital charts, an overall number of 52 deaths (57%) were classified vascular and 49 of the vascular deaths (54% of the overall number of deaths) occurred as first vascular events and thus were included in the primary composite study endpoint of first vascular events. Deaths from all other causes were classified as non-vascular.

The Ethics Committee of the University of Innsbruck approved the present study, and informed consent was obtained from all participants.

Statistical analysis

Differences in study variables were tested for statistical significance with the \( \chi^2 \) test for categorical variables, with the unpaired \( t \)-test and analysis of variance for normally distributed continuous variables, and with the Mann–Whitney U test and Kruskal–Wallis test for non-normally distributed continuous variables. Testing for normal distribution was performed with the Kolmogorov–Smirnov test. The Wilcoxon–Gehan statistic was used to compare differences in the cumulative incidence rates of vascular events. Adjusted hazard ratios (HRs) for the incidence of first vascular events were derived from Cox proportional hazard models; for these calculations, continuous variables were transformed. Thus, standardized adjusted HRs were calculated for continuous variables, giving the increase in relative risk with a one standard deviation increase of the continuous variable. Besides the glucometabolic status, the non-metabolic syndrome risk factors age, gender, smoking, LDL cholesterol, as well as the presence of significant stenoses at baseline were forced into the models. Hazard ratios for the glucometabolic variables therefore are adjusted for age, gender, smoking, LDL cholesterol, and the presence of significant coronary stenoses at baseline. Results are given as mean (standard deviation) if not denoted otherwise. A two-sided \( P < 0.05 \) was regarded as statistically significant. All statistical analyses were performed with the software package SPSS 11.0 for Windows.

Results

Baseline characteristics of the study population

The baseline characteristics of our study population were typical for a cohort undergoing coronary angiography for the evaluation of CAD, with a mean age of 64 ± 10 years, a preponderance of male gender (64%), a high prevalence of hypertension (78%), and a 63.3% prevalence rate of significant coronary stenoses.

Three hundred and ninety-four (37.8%) of our patients had an NGT, 280 (26.9%) post-challenge hyperglycaemia, which subsumes IGT (\( n = 190 \)) together with type 2 diabetes mellitus (T2DM) newly diagnosed solely on the basis of elevated post-challenge glucose in the oGTT (isolated post-challenge diabetes, \( n = 90 \)).
and 366 (35.2%) of our patients had conventional diabetes, i.e. T2DM previously established (n = 244) or newly diagnosed on the basis of fasting glucose values (n = 122). Thus, 62.2% had some abnormality of glycaemia.

Demographic and biochemical characteristics of our patients with respect to the glycaemic state are summarized in Table 1. Both among patients with post-challenge hyperglycaemia and among patients with conventional diabetes, average age, BMI, and waist circumference were higher, and LDL cholesterol as well as HDL cholesterol were lower when compared with NGT subjects. Further, in patients with post-challenge hyperglycaemia, the prevalence of smoking was lower and patients with conventional diabetes exhibited higher triglycerides than NGT subjects.

The prevalence of angiographically determined CAD and the prevalence of significant coronary stenoses were significantly higher both in patients with post-challenge diabetes and in patients with conventional diabetes when compared with NGT subjects.

**Incidence of death and of macrovascular events**

Over a mean follow-up period of 3.8 ± 1.3 years, we recorded 247 first macrovascular events; thus, 23.8% of our patients suffered the primary endpoint, corresponding to an annual event rate of 6.3%. First events encompassed 49 vascular deaths, 29 non-fatal myocardial infarctions, 24 non-fatal strokes, 95 percutaneous coronary interventions, 22 bypass graftings, and 28 revascularizations of non-coronary arteries. Total mortality was 8.7% (n = 90). The 90 deaths encompassed 46 cardiac deaths, 6 fatal strokes, and 38 non-vascular deaths. The total number of vascular deaths thus was 52; of these, three occurred after another composite of the primary study endpoint and therefore did not count as first vascular events.

**Post-challenge hyperglycaemia, conventional diabetes, and macrovascular events**

Figure 1A shows event-free survival with respect to the glycaemic state. The incidence of macrovascular events in NGT subjects was 18.5%; it was significantly higher in patients with both post-challenge hyperglycaemia (23.6%; P = 0.013) and conventional diabetes (29.5%; P < 0.001). Considering the subgroup of IGT subjects separately, the macrovascular event rate in the 190 IGT patients compared with that in NGT subjects was significantly increased (22.6%; P = 0.035) and was not significantly different from that in the 90 patients with isolated post-challenge diabetes (25.6%; P = 0.817).

The results from univariate analyses were confirmed in Cox regression analyses after adjustment for age, gender, presence of significant coronary stenoses at the baseline angiography, as well as for the non-metabolic syndrome risk factors LDL cholesterol and smoking, with adjusted HRs of 1.46 (95% CI 1.03–2.07, P = 0.033) for patients with post-challenge hyperglycaemia and 1.73 (1.25–2.37, P = 0.001) for those with conventional diabetes.

**Impaired glucose tolerance, newly diagnosed diabetes, and macrovascular events**

From our study population, 212 patients had newly diagnosed diabetes; this category includes patients with newly diagnosed diabetes irrespective of whether the diagnosis of diabetes was made on the basis of fasting glucose values or on the basis of post-challenge glucose values.

**Figure 1B** shows the results of a secondary analysis addressing event-free survival in the categories of NGT, IGT, newly diagnosed...

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**Table 1** Baseline characteristics with respect to glycaemic state

<table>
<thead>
<tr>
<th></th>
<th>Normal glucose tolerance (n = 394)</th>
<th>Post-challenge hyperglycaemia (n = 280)</th>
<th>Conventional diabetes (n = 366)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>61 ± 10</td>
<td>66 ± 10*</td>
<td>65 ± 10*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male gender (%)</td>
<td>70.1</td>
<td>56.9*</td>
<td>60.9*</td>
<td>0.007</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.6 ± 3.7</td>
<td>27.6 ± 4.8*</td>
<td>28.8 ± 4.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Waist (cm)</td>
<td>93 ± 11</td>
<td>98 ± 10*</td>
<td>103 ± 12</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>64.5</td>
<td>85.0*</td>
<td>89.9*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>16.0</td>
<td>8.2*</td>
<td>15.8</td>
<td>0.006</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>217 ± 40</td>
<td>205 ± 44*</td>
<td>201 ± 49*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dL)</td>
<td>133 ± 33</td>
<td>122 ± 37*</td>
<td>116 ± 39*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dL)</td>
<td>51 ± 15</td>
<td>53 ± 14*</td>
<td>48 ± 15*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>144 ± 78</td>
<td>145 ± 82</td>
<td>182 ± 130*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fasting glucose (mg/dL)</td>
<td>98 ± 12</td>
<td>110 ± 11*</td>
<td>161 ± 52*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Post-challenge glucose (mg/dL)</td>
<td>105 ± 22</td>
<td>192 ± 46*</td>
<td>n.a</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>5.7 ± 0.4</td>
<td>5.7 ± 0.5</td>
<td>7.1 ± 1.4*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CAD</td>
<td>80.7</td>
<td>90.4*</td>
<td>89.1*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Significant coronary stenoses</td>
<td>57.4</td>
<td>65.3*</td>
<td>68.0*</td>
<td>0.007</td>
</tr>
</tbody>
</table>

*P-values are given for the overall comparison between groups. To convert values for fasting plasma glucose to mmol/L multiply by 0.0555, to convert values for triglycerides to mmol/L multiply by 0.0113, and to convert values for total cholesterol, LDL cholesterol, or HDL cholesterol to mmol/L multiply by 0.0259.

*Statistical significance for the comparison vs. normal glucose tolerance.
diabetes, and established diabetes. When compared with NGT subjects, the macrovascular event rate as described above was significantly increased in IGT patients. It was also higher in patients with newly diagnosed diabetes (22.6%; $P = 0.038$) and in patients with established diabetes (34.0%; $P < 0.001$) than in NGT subjects. Importantly, in our cohort of coronary patients, vascular risk was practically identical in patients with IGT and those with newly diagnosed diabetes ($P = 0.648$). However, IGT patients were at a lower risk than those with established diabetes ($P = 0.047$).

After adjustment for age, gender, presence of significant coronary stenoses at baseline, as well as for smoking and LDL cholesterol in Cox regression analyses adjusted HRs were 1.51 (1.02–2.22, $P = 0.039$), 1.39 (0.94–2.05, $P = 0.099$), and 1.97 (1.39–2.80, $P = 0.0010$ for patients with IGT, newly diagnosed diabetes, and established diabetes, respectively, when compared with NGT subjects.

Post-challenge glucose as a continuous variable

Similar results as for the category of hyperglycaemic patients were obtained when post-challenge glucose was treated as a continuous variable: Post-challenge glucose proved significantly associated with macrovascular events among patients without conventional diabetes both univariately [standardized adjusted HR = 1.32 (1.10–1.60); $P = 0.004$] and after adjustment for age, gender, presence of significant coronary stenoses at baseline, as well as for smoking and LDL cholesterol [standardized adjusted HR = 1.21 (1.04–1.41), $P = 0.016$].

Patients with significant coronary stenoses at angiography

The results were consistent in the subgroup of patients with significant coronary stenoses at angiography: The respective adjusted HRs for post-challenge hyperglycaemia in the total study population and in patients with significant CAD were 1.46 (95% CI 1.03–2.07, $P = 0.033$) and 1.42 (0.96–2.11, $P = 0.083$); the adjusted HRs for conventional diabetes were 1.73 (1.25–2.37, $P = 0.001$) in the total study population and 1.85 (1.30–2.64, $P = 0.001$) in patients with significant CAD at angiography, respectively. Interaction terms hyperglycaemia by significant baseline CAD were not significant ($P = 0.743$ for post-challenge hyperglycaemia and $P = 0.568$ for conventional diabetes), indicating that the baseline CAD state did not significantly affect the association between hyperglycaemia and future vascular events.

Secondary study endpoints

As secondary study endpoints, we investigated total mortality and the respective composites of (i) any death, non-fatal myocardial infarction, non-fatal stroke, percutaneous coronary intervention, bypass grafting, and revascularization of non-coronary arteries, (ii) vascular death, non-fatal myocardial infarction, non-fatal stroke, percutaneous coronary intervention, and bypass grafting, and (iii) any death, non-fatal myocardial infarction, non-fatal stroke, percutaneous coronary intervention, and bypass grafting.

As is summarized in Tables 2 and 3, the results were very similar for these secondary study endpoints as for the primary study endpoint. Irrespective of the endpoint definition, post-challenge hyperglycaemia, and in particular IGT, were associated with a significantly worse outcome than NGT. Most importantly, post-challenge hyperglycaemia indicated an increased overall mortality risk.

Discussion

From our data, we conclude that post-challenge hyperglycaemia confers a strongly increased risk of future macrovascular events in patients undergoing coronary angiography for the evaluation
of stable CAD. In particular, vascular risk is already significantly increased in patients with post-challenge hyperglycaemia in the IGT range. Quantitatively, post-challenge hyperglycaemia confers about half the risk increase of established T2DM.

Because of the very high prevalence of post-challenge hyperglycaemia in coronary patients, this finding is of major clinical importance. In our study cohort, post-challenge hyperglycaemia was diagnosed in almost one out of four patients. Concordant with this result, high prevalence rates of post-challenge hyperglycaemia of up to 40% had been described in previous studies addressing glucometabolic disorders in CAD patients.7,8,10,11

Importantly, about every second subject from the patients with newly diagnosed diabetes and two out of five subjects from the total subgroup of patients with diabetes in our investigation were diagnosed as having diabetes solely on the basis of post-challenge glucose. These data are well in line with the previously reported curves started to disperse after 1 year, the time point when the follow-up in the Euro Heart Survey ended. From our data, thus, the follow-up duration of 1 year in the Euro Heart Survey was very short. Of note, in our study, survival curves started to disperse after 1 year, the time point when the follow-up in the Euro Heart Survey ended. From our data, thus, we conclude that, as in acute coronary syndromes, also in stable CAD post-challenge hyperglycaemia is a marker of increased vascular risk. Post-challenge hyperglycaemia even indicated an increased overall mortality risk.

### Post-challenge hyperglycaemia and macrovascular risk: potential mechanisms

Recent trials (ACCORD, ADVANCE)15,16 failed to show a reduction in macrovascular events with intensive blood glucose lowering and
thus have put the role of plasma glucose as an independent macrovascular risk factor at debate. Importantly, the targets for glucose lowering therapy were based on HbA1c in these studies, which reflect the mean blood glucose. However, important aspects of glucose metabolism are lost when solely mean blood glucose is taken into consideration. High amplitudes of glucose oscillation have been shown to activate the protein kinase C pathway, and to induce inflammatory markers, much more than elevated but stable glucose levels. Concordantly, recently published data demonstrated that oscillating glucose levels have a significantly more deteriorating effect on endothelial function than elevated, but stable glucose levels. Endothelial dysfunction in turn is a key player in the development of diabetes complications and strongly associated with future cardiovascular events. Also, platelets were shown to be activated not only in diabetes but already in the IGT state. Our observation that post-challenge hyperglycaemia strongly correlates with macrovascular risk in angiographied coronary patients therefore fits well in the existing frame of pathophysiological knowledge.

**Strengths and limitations**

Important strengths of our investigation are the large sample size, the very high follow-up rate of 97.5%, which is exceptional for an observational study, and the meticulous characterization of study subjects. By design, our study focuses on a selected group of patients; our results from angiographied coronary patients therefore are not necessarily applicable to the general population. In line with recent large intervention trials, we had chosen a combined study endpoint of major vascular events which also included revascularization procedures. The necessity to ascertain sufficient statistical power of course was an important reason behind the selection of this relatively broad combined endpoint. Whatsoever, the constituents of our study endpoint are of unquestionable clinical relevance as indicators of the progression of atherosclerotic disease. The population we chose to investigate is at a high risk for macrovascular events and therefore deserves particular clinical attention and fills the gap between acute coronary syndrome and non-coronary patient cohorts previously described.

**Clinical consequences**

Several clinical consequences of the present investigation appear important. First, post-challenge hyperglycaemia in the high-risk population of angiographied coronary patients identifies subjects at a particularly high vascular risk. Intensified treatment to decrease macrovascular risk in the identified patients therefore is mandatory. Indeed, the STOP-NIDDM trial showed that lowering post-prandial glucose excursions with acarbose in patients with IGT may improve the cardiovascular outcome. In addition, data from the Euro Heart Survey suggest that glucose-lowering

<table>
<thead>
<tr>
<th>Table 3 Secondary study endpoints</th>
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<tr>
<td><strong>Normal glucose tolerance (n = 394)</strong></td>
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<tr>
<td>Overall mortality (%)</td>
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<tr>
<td>Event rate</td>
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<tr>
<td>Unadjusted HR</td>
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<td>Adjusted HR</td>
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<tr>
<td>Secondary composite endpoint A</td>
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<tr>
<td>Event rate</td>
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<tr>
<td>Unadjusted HR</td>
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<tr>
<td>Adjusted HR</td>
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<tr>
<td>Secondary composite endpoint B</td>
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<tr>
<td>Event rate</td>
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<tr>
<td>Unadjusted HR</td>
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<tr>
<td>Adjusted HR</td>
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<td>Secondary composite endpoint C</td>
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<tr>
<td>Event rate</td>
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Secondary study endpoints are total mortality, and the following three secondary composite endpoints: secondary composite endpoint A, encompassing any death, non-fatal myocardial infarction, non-fatal stroke, percutaneous coronary intervention, bypass grafting, and revascularization of non-coronary arteries; secondary composite endpoint B, encompassing vascular death, non-fatal myocardial infarction, non-fatal stroke, percutaneous coronary intervention, and bypass grafting; and secondary composite endpoint C, encompassing any death, non-fatal myocardial infarction, non-fatal stroke, percutaneous coronary intervention, and bypass grafting. P-values and hazard ratios are given for the comparisons with normal glucose tolerance. Adjusted hazard ratios are adjusted for age, gender, presence of significant coronary stenoses at baseline, smoking, and LDL cholesterol. The Wilcoxon–Gehan statistic was used to compare differences in event rates. Unadjusted and adjusted hazard ratios were derived from Cox proportional hazard models.
therapy in newly detected diabetes improves prognosis. Overall, however, the available data are insufficient to support the lowering of post-prandial glucose as the main intervention to reduce the risk of macrovascular disease. From the background of currently available evidence, it therefore appears most prudent to strictly enforce treatment goals for other cardiovascular risk factors in the high-risk coronary patients with post-challenge hyperglycaemia, e.g. for LDL cholesterol. Second, because subjects with post-challenge hyperglycaemia in the IGT range are at a high risk of diabetes, diabetes prevention should be a major aim in these patients. Third, two out of five angiographed coronary patients with diabetes are solely diagnosed as having diabetes on the basis of post-challenge hyperglycaemia. Because the diagnosis of diabetes according to current guidelines has a significant impact on the management of CAD patients, this fact alone makes it mandatory to perform oGGTs in angiographed coronary patients.

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Conflict of interest: none declared.

References


Atrial tachycardia in congenital left atrial appendage aneurysm: three-dimensional computed tomography imaging with electro-anatomical mapping

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A 29-year-old woman was admitted for the evaluation of atrial tachycardia (AT) associated with palpitation during exercise. She had been diagnosed with a left atrial appendage (LAA) aneurysm at the age of 19 years. She was followed by echocardiography annually because she was asymptomatic, and evidence of thrombus formation and/or atrial tachyarrhythmia was not found. She developed AT 2 months before admission. The 12-lead electrocardiogram (ECG) revealed AT with a 2:1 ventricular response (Panel A). The P-wave morphology indicated the origin of AT as the superior portion of the left atrium. The chest X-ray showed an abnormal upper left heart border. The transthoracic echocardiogram demonstrated a very large LAA aneurysm. Her left ventricular function and cardiac valves were normal. Both transeosophageal echocardiography and cardiac 64-slice multi-detector computed tomography (CT) showed no evidence of thrombus formation in the aneurysm. The derived LAA volume was 74 mL by CT and 75 mL by three-dimensional transesophageal echocardiography. In the electrophysiological study, the activation sequence indicated an AT cycle length of 282 ms, which originated from the left atrium. Three-dimensional electro-anatomical mapping fusion with CT imaging of the left atrium (CARTO Merge, Biosense Webster, Inc.) was performed. The earliest activation site during AT was mapped at the anterior site at the roof of the LAA aneurysm, 66 mm from the neck (Panel B, Supplementary material online, Movie). An LAA aneurysmectomy was performed via left thoracotomy (Panel C). There was no thrombus formation within the aneurysm. Histological findings demonstrated marked thinning of the LAA wall with increased fibrous tissue consistent with an aneurysm (Panel D). The patient has remained asymptomatic and in sinus rhythm without medication for 8 months postoperatively.

Panel A. A 12-lead ECG showing atrial tachycardia with a 2:1 ventricular response. Note the negative P-waves in lead aVL and the positive P-waves in the V1 and inferior leads, suggesting that the origin of the tachycardia was in the superior portion of the left atrium. The chest X-ray showed an abnormal upper left heart border. The transthoracic echocardiogram demonstrated a very large LAA aneurysm. Her left ventricular function and cardiac valves were normal. Both transesophageal echocardiography and cardiac 64-slice multi-detector computed tomography (CT) showed no evidence of thrombus formation in the aneurysm. The derived LAA volume was 74 mL by CT and 75 mL by three-dimensional transesophageal echocardiography. In the electrophysiological study, the activation sequence indicated an AT cycle length of 282 ms, which originated from the left atrium. Three-dimensional electro-anatomical mapping fusion with CT imaging of the left atrium (CARTO Merge, Biosense Webster, Inc.) was performed. The earliest activation site during AT was mapped at the anterior site at the roof of the LAA aneurysm, 66 mm from the neck (Panel B, Supplementary material online, Movie). An LAA aneurysmectomy was performed via left thoracotomy (Panel C). There was no thrombus formation within the aneurysm. Histological findings demonstrated marked thinning of the LAA wall with increased fibrous tissue consistent with an aneurysm (Panel D). The patient has remained asymptomatic and in sinus rhythm without medication for 8 months postoperatively.

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Panel B. CARTO map of the LAA aneurysm displaying activation time during atrial tachycardia. The focal site of an early activation pattern is observed in the anterolateral site of the roof of the LAA, 66 mm from the neck. LAA, left atrial appendage.

Panel C. Intra-operative findings after pericardiectomy.

Panel D. Histological findings of the LAA aneurysm (the roof of the LAA). The aneurysmal wall was thinned diffusely to <1 mm. Although the trabeculated endocardial structure of the LAA is obscure, the left atrial myocardial bundles remain in the aneurysmal wall. END, endocardium, EPI, epicardium. Masson’s trichrome stain. Bar = 1 mm.

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