Original Article

Prognostic significance of asymptomatic coronary artery disease in patients with diabetes and need for early revascularization therapy


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Abstract

Aims Information on the clinical outcome of patients with diabetes with silent myocardial ischaemia is limited. We compared the clinical and angiographic characteristics, and the clinical outcomes of diabetic patients with asymptomatic or symptomatic coronary artery disease (CAD).

Methods Three hundred and ten consecutive diabetic patients with CAD were divided into two groups according to the presence of angina and followed for a mean of 5 years. Fifty-six asymptomatic patients with a positive stress test and CAD on coronary angiography were compared with 254 symptomatic patients, 167 with unstable angina and 87 with chronic stable angina.

Results Although the severity of coronary atherosclerosis was similar in asymptomatic and symptomatic patients, revascularization therapy was performed less frequently in the asymptomatic than the symptomatic patients (26.8 vs. 62.0%; \( P < 0.001 \)). Asymptomatic patients experienced a similar number of major adverse cardiac events (MACEs; death, non-fatal myocardial infarction, and revascularization; 32 vs. 28%; \( P = 0.57 \)), but had higher cardiac mortality than symptomatic patients (26 vs. 9%; \( P < 0.001 \)). However, patients who underwent revascularization therapy at the time of CAD diagnosis in these two groups showed similar MACE and cardiac mortality (20.0 vs. 22.3%, 6.7 vs. 5.3%, respectively; all \( P > 0.05 \)).

Conclusions This study suggests that diabetic patients with asymptomatic CAD have a higher cardiac mortality risk than those with symptomatic CAD, and that lack of revascularization therapy may be responsible for the poorer survival.


Keywords coronary artery disease, diabetes mellitus, prognosis, revascularization, silent ischaemia

Abbreviations ASx-CAD, asymptomatic coronary artery disease; CAD, coronary artery disease; CAG, coronary angiography; DES, drug-eluting stent; ETT, exercise treadmill test; HR, hazard ratio; LV, left ventricular; MACE, major adverse cardiac event; SPECT, single-photon emission computed tomography; Sx-CAD, symptomatic coronary artery disease

Introduction

It is recommended that asymptomatic patients with coronary artery disease (CAD), including patients with diabetes, should receive medical treatment or revascularization therapy based on angiographic findings and the results of non-invasive tests [1,2]. However, it is unknown whether invasive revascularization therapy in these patients is likely to have the same beneficial effect as it has in symptomatic CAD patients. Moreover, asymptomatic patients may be treated less aggressively because of the absence of ischaemic symptoms.

Patients with diabetes are known to have a poorer prognosis after revascularization therapy than non-diabetic patients [3–7]. Moreover, patients with diabetes have a high prevalence...
Definitions

Diabetes was defined as a fasting plasma glucose level ≥ 7.0 mmol/l or current diabetes treatment by dietary modification, oral glucose-lowering agents, or insulin. Hypertension was defined as a fasting serum total cholesterol ≥ 6.2 mmol/l or current treatment with lipid-lowering agents or by dietary modification. Significant left ventricular (LV) dysfunction was defined as a resting LV ejection fraction < 40% by echocardiography, and renal insufficiency was defined as a serum creatinine level ≥ 180 µmol/l [18]. The following clinical events were considered to be major adverse cardiac events (MACEs): cardiac death, non-fatal MI, and revascularization therapy. Cardiac death was defined as death as a result of acute LV failure, fatal MI death during or immediately after revascularization therapy or sudden death. Early and late revascularization therapies were defined as revascularizations performed at the time of CAD diagnosis and during follow-up, respectively. Re-hospitalization for congestive heart failure was defined by occurrence of acute pulmonary oedema requiring hospital re-admission and with supportive documentation such as chest radiograph.

Non-invasive stress tests

A symptom-limited Bruce protocol exercise treadmill test (ETT) was performed. Patients were instructed to discontinue β-blockers, calcium channel blockers, and nitrates before ETT. The ETT was considered positive when ≥ 1 mm ST-segment depression occurred at 80 ms after J point. Technetium-99 m sestamibi single-photon emission computed tomography (SPECT) in 41 patients, the exercise treadmill test (ETT) in eight, and both tests in seven. Non-invasive stress tests were performed as follows: 23 for preoperative cardiac risk assessment; 28 for candidates for a screening cardiac stress test (four for history of peripheral or carotid occlusive disease; four for abnormal resting electrocardiogram; 12 for multiple risk factors as recommend in the American Diabetes Association consensus statement; eight for renal transplantation evaluation) and five for other reasons (four for incidentally detected resting abnormality on echocardiography and one for unknown reason) [17]. The symptomatic CAD (Ax-CAD) group consisted of 56 patients with positive non-invasive stress test results. The non-invasive stress tests conducted in these patients were: stress technecium-99 m sestamibi single-photon emission computed tomodigraphy (SPECT) in 41 patients, the exercise treadmill test (ETT) in eight, and both tests in seven. Non-invasive stress tests were performed as follows: 23 for preoperative cardiac risk assessment; 28 for candidates for a screening cardiac stress test (four for history of peripheral or carotid occlusive disease; four for abnormal resting electrocardiogram; 12 for multiple risk factors as recommend in the American Diabetes Association consensus statement; eight for renal transplantation evaluation) and five for other reasons (four for incidentally detected resting abnormality on echocardiography and one for unknown reason) [17].

Coronary angiographic analysis

CAG was performed using a standard technique via the femoral artery. Two independent experienced observers interpreted and graded the coronary angiograms obtained. CAD was defined as > 50% reduction in the diameter of a major coronary artery or a first branch artery. Per cent stenosis was measured in the view demonstrating maximal coronary artery narrowing. A diffuse lesion was defined as a long lesion involving more than two consecutive coronary segments. In a given patient, the number of main vessels showing significant stenosis was summed. This sum is referred to as ‘vessel score’, and these scores ranged from 0 to 5. Left main artery stenosis was scored as two-vessel disease. The extent of coronary atherosclerosis was analysed using ‘extent score’ [19,20]. First-order segments were scored as 1 if there was any evidence of atherosclerosis; second-order segments were scored as 0.5. Extent score was thus defined as the sum of individual segment scores. Coronary atherosclerosis severity was assessed using the Gensini score, which grades the narrowing of coronary artery lumens as: 1 for 1–25% narrowing, 2 for 26–50%, 4 for 51–75%, 8 for 76–90%, 16 for 91–99%, and 32 for total occlusion [21]. This score was then multiplied by a factor that reflects the importance of the lesion in the coronary arterial tree. The Gensini score was thus defined as the sum of coronary artery lumen narrowing scores times the appropriate weighting factors for all coronary arteries.

Initial and follow-up data collection

Baseline demographic, clinical, angiographic, and procedural data, including information on complications were acquired

Of silent myocardial ischaemia, and may initially present with a major cardiac event without previous warning [8–16]. Thus, it is difficult to detect progression of CAD during follow-up in such patients because of the absence of ischaemic symptoms. Finally, the degree of revascularization and the long-term prognosis of diabetic CAD patients with silent myocardial ischaemia are not well known.

In the present study, we compared the clinical and angiographic characteristics and the treatment strategies adopted in symptomatic and asymptomatic CAD patients with diabetes. In addition, we determined long-term clinical outcomes to assess the impact of different treatment strategies on prognosis.

Patients and methods

Patient population

Between March 1997 and April 2001, 492 patients with diabetes had undergone coronary angiography (CAG) at our institution. Patients with normal or insignificant luminal narrowing on CAG, acute myocardial infarction (MI), a previous history of MI, coronary artery bypass graft surgery or previous percutaneous coronary intervention, and those with a limited expected survival because of the presence of co-morbid conditions (inoperable malignancy) were excluded. Finally, 310 patients with diabetes with significant luminal narrowing on CAG were enrolled. The study was approved by our institutional review board and all patients gave written, informed consent. [Statement added after online publication: 18 May 2007].

At the time of coronary angiography, patients were divided into two groups according to the presence of angina or angina-like chest pain. The asymptomatic CAD (ASx-CAD) group consisted of 56 patients with positive non-invasive stress test results. The non-invasive stress tests conducted in these patients were: stress technecium-99 m sestamibi single-photon emission computed tomodigraphy (SPECT) in 41 patients, the exercise treadmill test (ETT) in eight, and both tests in seven. Non-invasive stress tests were performed as follows: 23 for preoperative cardiac risk assessment; 28 for candidates for a screening cardiac stress test (four for history of peripheral or carotid occlusive disease; four for abnormal resting electrocardiogram; 12 for multiple risk factors as recommend in the American Diabetes Association consensus statement; eight for renal transplantation evaluation) and five for other reasons (four for incidentally detected resting abnormality on echocardiography and one for unknown reason) [17]. The symptomatic CAD (Ax-CAD) group consisted of 167 patients with unstable angina and 87 with chronic stable angina. Nineteen patients (three in the Ax-CAD group and 16 in the Ax-CAD group) were lost to follow-up (a successful follow-up rate of 94%), leaving 291 patients available for analysis.
from our institution’s computerized database. Long-term follow-up data were obtained from medical records and over the telephone by trained personnel. Patients were asked to provide details about: symptoms, the reasons for all hospital admissions, the occurrence of myocardial infarction, and on the occurrence of additional angioplasty or coronary surgery. If a patient had experienced more than one event during follow-up, only the first event was considered in the analysis. Mean follow-up duration was 60 ± 24 months and median duration was 65 months.

Statistical analysis
Continuous variables are expressed as means ± SD, whereas categorical variables are presented as absolute values and percentages. Differences between continuous variables in the two groups were analysed by the unpaired Student t-test, and categorical variable differences were analysed using the χ²-test or Fisher’s exact test. Cox proportional hazard regression (HR) analysis was used to identify predictors of cardiac death (enter method). Survival curves were generated using the Kaplan–Meier method, and survival curve comparisons were performed using the log-rank test. P-values of < 0.05 were considered statistically significant and SPSS version 12.0 (SPSS Inc., Chicago, IL, USA) was used for all calculations.

Results
Baseline characteristics
The clinical characteristics of the 310 study subjects are listed in Table 1. Mean age was 63 years (range: 38–81 years), and 58.7% were male. Of these, 13.5% were treated by diet control alone, 28.7% with insulin, and 57.7% with oral glucose-lowering agents. Mean duration of diabetes and mean glycated haemoglobin level were 11.8 ± 8.3 and 8.2 ± 1.7% years, respectively. The incidence of current smokers, hypercholesterolaemia, significant LV dysfunction, and renal insufficiency was higher, duration of diabetes was longer, and obesity less common in the 56 patients in the ASx-CAD group than those in the Sx-CAD group. At discharge, patients in the ASx-CAD group were prescribed angiotensin-converting enzyme inhibitor/angiotensin receptor blocker more frequently, and anti-platelet agents and beta-blockers less frequently than patients in the Sx-CAD group. However, the use of lipid-lowering agents and the mean number of drugs being administered at discharge were similar in the two groups. Comparing baseline characteristics according to revascularization therapy, the 174 patients in the revascularization therapy group were less likely to have asymptomatic CAD, to smoke currently and to have renal insufficiency than those with the medical therapy group.

Angiographic findings and early revascularization therapy
Coronary angiographic characteristics are shown in Table 2. No significant differences were found between the two groups in terms of Gensini, vessel, or extent score, except for the mean numbers of diffuse lesions. Patients in the ASx-CAD group received less early revascularization therapy than those in the Sx-CAD group [26.8 vs. 62.6%, OR 0.22 (95% CI: 0.12–0.42); P < 0.001]. After adjusting for angiographic variables, age,
significant LV dysfunction, and renal insufficiency, use of early revascularization therapy remained lower in the ASx-CAD group \( [OR 0.25 (95\% CI: 0.12–0.52); P < 0.001] \).

### Clinical outcomes—type of cardiac events

The frequencies of adverse cardiac events are summarized in Table 3. During the 5-year follow-up period, 84 MACEs occurred in the 291 study subjects \( [\text{annual patient event rates} = \frac{84}{291 \times 5}, = 5.8\%] \). Total MACE and non-fatal infarction were not different between the two groups \( [P = 0.455 \text{ and } P = 0.569, \text{ respectively}] \). However, cardiac death was more common in asymptomatic patients \( [26.4 \text{ vs. } 8.8\%; P < 0.001] \), whereas revascularization was more frequent in symptomatic patients \( [5.7 \text{ vs. } 18.1\%; P = 0.015] \). Median duration from CAG to cardiac death was not different between the two groups \( [\text{ASx-CAD: } 21 (1–64), \text{ months, Sx-CAD: } 15 (1–83) \text{ months, respectively}; P = 0.609] \). Event-free survival curves are shown in Fig. 1. Cox proportional hazards regression analysis, adjusting for other variables, demonstrated that asymptomatic CAD was not a significant predictor of cardiac death \( [P = 0.611] \). However, the absence of early revascularization therapy \( [HR 4.53 (95\% CI: 1.94–10.6); P < 0.001] \), significant LV dysfunction \( [HR 10.6 (95\% CI: 4.21–26.6); P < 0.001] \), and age \( [\text{per year, HR 1.07 (95\% CI: 1.02–1.13); P = 0.006}] \) were significant independent predictors of cardiac mortality (Table 4).

### Impact of early revascularization therapy

Subgroup analysis was performed to determine whether early revascularization therapy had similar impacts on the clinical outcomes of patients in the two groups. Asymptomatic and symptomatic patients who received early revascularization therapy \( [n = 166] \), had similar MACE, cardiac death and late

### Table 2: Coronary angiographic characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ASx-CAD (n = 56) N (%)</th>
<th>Sx-CAD (n = 254) N (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gensini score</td>
<td>57.0 ± 28.9</td>
<td>60.1 ± 33.8</td>
<td>0.514</td>
</tr>
<tr>
<td>Vessel score</td>
<td>2.2 ± 0.9</td>
<td>2.2 ± 1.0</td>
<td>0.833</td>
</tr>
<tr>
<td>Extent score</td>
<td>3.7 ± 1.6</td>
<td>3.6 ± 1.8</td>
<td>0.894</td>
</tr>
<tr>
<td>Mean number of significant lesions</td>
<td>3.4 ± 1.9</td>
<td>3.5 ± 2.0</td>
<td>0.849</td>
</tr>
<tr>
<td>Mean number of diffuse lesion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>with significant luminal stenosis</td>
<td>0.7 ± 0.8</td>
<td>0.4 ± 0.7</td>
<td>0.005</td>
</tr>
<tr>
<td>with insignificant luminal stenosis</td>
<td>1.0 ± 1.0</td>
<td>0.6 ± 0.8</td>
<td>0.004</td>
</tr>
<tr>
<td>No. of diseased vessels</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-vessel disease</td>
<td>10 (18)</td>
<td>71 (28)</td>
<td>0.120</td>
</tr>
<tr>
<td>2-vessel disease</td>
<td>23 (41)</td>
<td>79 (31)</td>
<td>0.151</td>
</tr>
<tr>
<td>3-vessel disease</td>
<td>23 (41)</td>
<td>104 (41)</td>
<td>0.986</td>
</tr>
<tr>
<td>Revascularization therapy</td>
<td>15 (27)</td>
<td>159 (63)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PCI</td>
<td>5 (9)</td>
<td>79 (31)</td>
<td>0.001</td>
</tr>
<tr>
<td>CABG</td>
<td>10 (18)</td>
<td>80 (32)</td>
<td>0.042</td>
</tr>
</tbody>
</table>

Data are mean ± SD or \( N (\%) \).

CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention.

### Table 3: Events during 5-year follow-up

<table>
<thead>
<tr>
<th></th>
<th>ASx-CAD (n = 53) N (%)</th>
<th>Sx-CAD (n = 238) N (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major adverse cardiac events</td>
<td>17 (32)</td>
<td>67 (28)</td>
<td>0.569</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>14 (26)</td>
<td>21 (9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Non-fatal myocardial infarction</td>
<td>0 (0)</td>
<td>4 (2)</td>
<td>0.445</td>
</tr>
<tr>
<td>Late revascularization therapy</td>
<td>3 (6)</td>
<td>43 (18)</td>
<td>0.015</td>
</tr>
<tr>
<td>PCI</td>
<td>2 (4)</td>
<td>36 (15)</td>
<td>0.016</td>
</tr>
<tr>
<td>CABG</td>
<td>1 (2)</td>
<td>7 (3)</td>
<td>0.355</td>
</tr>
<tr>
<td>Rehospitalization for congestive heart failure</td>
<td>3 (6)</td>
<td>7 (3)</td>
<td>0.267</td>
</tr>
<tr>
<td>Others*</td>
<td>3 (6)</td>
<td>12 (5)</td>
<td>0.336</td>
</tr>
</tbody>
</table>

Data are mean ± N (%).

CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention.

*Non-cardiac death, re-hospitalization for unstable angina without revascularization therapy, or cerebrovascular events.
revascularization rates during the 5-year follow-up (20.0 vs. 22.5%, 6.7 vs. 5.3%, 13.3 vs. 16.6%, respectively, Fig. 2). Early revascularization therapy in the asymptomatic patients was associated with a lower rate of cardiac death than those treated medically (6.7 vs. 34.2%; \( P = 0.038 \)). Thus, early revascularization therapy was identified as an independent predictor of survival after adjusting for other covariates in the ASx-CAD group [HR 0.07 (95% CI 0.07–0.77)].

We analysed the beneficial effects of early revascularization therapy according to LV function and severity of coronary atherosclerosis. The beneficial effect of revascularization therapy on cardiac survival was found only in the multivessel disease group (revascularization therapy group vs. medial therapy group = 93.0 vs. 69.7%; \( P < 0.001 \)). In the subgroup with normal LV function (\( n = 283 \)), patients receiving revascularization therapy had better cardiac survival (96.1 vs. 83.6%; \( P < 0.001 \)). In the LV dysfunction subgroup (\( n = 27 \)), patients undergoing revascularization therapy had slightly better cardiac survival than those with medical therapy (66.7 vs. 33.3%; \( P = 0.086 \); Fig. 3).

Table 4  Predictors of cardiac mortality

<table>
<thead>
<tr>
<th>Variables</th>
<th>Univariate ( \chi^2 ) (95% CI)</th>
<th>( P )-value</th>
<th>Multivariate¶ ( \chi^2 ) (95% CI)</th>
<th>( P )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.04 (1.00–1.09)</td>
<td>0.086</td>
<td>1.07 (1.02–1.12)</td>
<td>0.006</td>
</tr>
<tr>
<td>Sex</td>
<td>1.62 (0.80–3.32)</td>
<td>0.183</td>
<td>1.87 (0.68–5.12)</td>
<td>0.223</td>
</tr>
<tr>
<td>Obesity*</td>
<td>0.77 (0.40–1.49)</td>
<td>0.436</td>
<td>1.54 (0.68–3.47)</td>
<td>0.299</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.75 (0.37–1.50)</td>
<td>0.408</td>
<td>1.08 (0.46–2.53)</td>
<td>0.860</td>
</tr>
<tr>
<td>Hypercholesterolaemia†</td>
<td>1.41 (0.64–3.11)</td>
<td>0.391</td>
<td>1.84 (0.67–5.09)</td>
<td>0.239</td>
</tr>
<tr>
<td>Smoking</td>
<td>1.74 (0.90–3.37)</td>
<td>0.103</td>
<td>1.09 (0.44–2.71)</td>
<td>0.855</td>
</tr>
<tr>
<td>Duration of diabetes</td>
<td>1.03 (0.99–1.07)</td>
<td>0.202</td>
<td>1.00 (0.96–1.06)</td>
<td>0.874</td>
</tr>
<tr>
<td>Renal insufficiency‡</td>
<td>1.52 (0.59–3.91)</td>
<td>0.390</td>
<td>1.45 (0.46–4.57)</td>
<td>0.527</td>
</tr>
<tr>
<td>Gensini score</td>
<td>1.01 (1.00–1.02)</td>
<td>0.021</td>
<td>1.00 (0.99–1.02)</td>
<td>0.710</td>
</tr>
<tr>
<td>Extent score</td>
<td>1.33 (1.10–1.60)</td>
<td>0.003</td>
<td>1.14 (0.83–1.36)</td>
<td>0.412</td>
</tr>
<tr>
<td>Vessel score</td>
<td>1.67 (1.23–2.30)</td>
<td>0.002</td>
<td>1.72 (0.96–3.07)</td>
<td>0.067</td>
</tr>
<tr>
<td>ASx-CAD</td>
<td>3.38 (1.72–6.64)</td>
<td>&lt;0.001</td>
<td>1.25 (0.53–2.95)</td>
<td>0.611</td>
</tr>
<tr>
<td>Significant LV dysfunction§</td>
<td>8.99 (4.51–17.9)</td>
<td>&lt;0.001</td>
<td>10.6 (4.21–26.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No early revascularization therapy</td>
<td>4.34 (2.03–9.27)</td>
<td>&lt;0.001</td>
<td>4.53 (1.94–10.6)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*BMI \( \geq 25 \) kg/m².
†Fasting serum total cholesterol \( \geq 6.2 \) mmol/l or current treatment with lipid-lowering agents.
‡Serum creatinine \( \geq 180 \) µmol/l.
§Resting LV ejection fraction \( < 40\% \) by echocardiography.
¶Cox proportional hazard regression analysis adjusting with age, sex, obesity, hypertension, hypercholesterolaemia, ASx-CAD, significant LV dysfunction, early revascularization therapy, duration of diabetes, renal insufficiency, vessel score, extent score, and Gensini score.

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**FIGURE 1** Event-free survival curve in symptomatic and asymptomatic diabetic patients with coronary artery disease; (a) major adverse cardiac events and (b) cardiac death.
Discussion

To the best of our knowledge, this is the first study to have compared diabetic patients with asymptomatic and symptomatic CAD with respect to angiographic characteristics, treatment modalities and clinical outcomes. The main finding of the present study is that asymptomatic diabetic CAD patients had more significant LV dysfunction and renal insufficiency with longer duration of diabetes, and received less early revascularization therapy, than symptomatic diabetic CAD patients, even although coronary atherosclerosis severities in the two study groups were similar. These differences in revascularization and LV function are associated with poor survival in asymptomatic diabetic CAD patients.

Coronary atherosclerosis in patients with diabetes and asymptomatic CAD

The Asymptomatic Cardiac Ischaemic Pilot study reported that asymptomatic patients with ambulatory electrocardiographic ischaemia frequently have multivessel disease, severe proximal stenosis and features of complex plaque [22]. Moreover, several studies on patients with diabetes with asymptomatic CAD have reported that 61–65% of those with high-risk SPECT
findings have angiographic high-risk CAD [23,24]. However, little comparative data are available on the characteristics of coronary atherosclerosis in asymptomatic and symptomatic CAD in patients with diabetes.

In our study, the severity of CAD in the ASx-CAD group was similar to that in the Sx-CAD group. However, asymptomatic patients had a longer duration of diabetes and a higher prevalence of significant LV dysfunction and renal insufficiency. This finding suggests the possibility of a relatively late diagnosis of CAD in the asymptomatic group, and stresses the need for regular non-invasive tests for CAD in asymptomatic patients with diabetes. This result was in accord with a previous report that preclinical diagnosis of CAD in patients with diabetes is effective in reducing the risk of cardiac events [25]. Even although our study showed the problems of later diagnosis of CAD in asymptomatic patients with diabetes, the benefit of screening by stress testing in these population is yet to be verified.

Screening for CAD in asymptomatic subjects with diabetes is currently not recommended by the American Heart Association or by the US Preventive Services Task Force [26,27]. However, the ongoing DIAD trial will show the role of non-invasive screening in asymptomatic patients with diabetes [28].

Impact of early revascularization on the clinical outcomes of patients with diabetes and asymptomatic CAD

Recent studies have shown that patients with diabetes with asymptomatic CAD gain more survival benefit from early revascularization therapy than medical therapy [23,31,35,36]. However, information on whether early revascularization therapy in patients with diabetes with asymptomatic CAD has the same long-term beneficial effect as it has in symptomatic patients is lacking. In our study, early revascularization therapy was offered. If CAD was diagnosed earlier than significant LV dysfunction or cardiac death as a first cardiac event [30]. In the present study, multivariate analysis identified the absence of significant LV dysfunction and age as independent predictors of cardiac mortality. Several studies have reported that the presence of myocardial ischaemia by non-invasive stress testing is of prognostic importance in patients with CAD regardless of the presence of angina [31–34]. Therefore, we speculate that the cardiac survival of patients with diabetes with asymptomatic CAD might be improved if CAD was diagnosed earlier than significant LV dysfunction and if more aggressive early revascularization therapy was offered.

Early revascularization therapy in patients with diabetes and asymptomatic CAD

In our study, 73% of asymptomatic patients with diabetes had not received early revascularization therapy despite angiographically significant coronary atherosclerosis. Even after adjusting for other covariates, asymptomatic patients were less likely to receive revascularization therapy than symptomatic patients.

Several retrospective studies have reported that only 5.6–21% of patients with diabetes with asymptomatic CAD received early revascularization therapy, even although half of these patients had CAD involving the left main, proximal left anterior descending artery, or three-vessel disease [23,29]. Moreover, as has been found by previous studies, it is difficult to determine why asymptomatic patients with diabetes are less likely to receive early revascularization. Two possible explanations may be proposed. First, coronary lesions in the ASx-CAD group might have been considered unsuitable for early revascularization therapy because of the high-risk characteristics of the lesions or patients. Second, these patients were treated medically because of the absence of angina. In the present study, despite no difference between the angiographic characteristics of the two groups (other than the number of diffuse lesions), the use of early revascularization remained lower in the ASx-CAD group even after adjusting for other angiographic and clinical parameters. These findings indicate that the absence of subjective symptoms appears to be the main cause of decisions not to adopt early revascularization therapy.

Poor cardiac survival in patients with diabetes and asymptomatic CAD

No difference was observed between the two groups in terms of total MACE rates. Zellweger et al. [14] reported that patients with diabetes with silent myocardial ischaemia experience the same number of critical events annually as those with angina. However, in the present study, patients with asymptomatic CAD died of a cardiac cause more frequently than those with symptomatic CAD, which concurs with the findings of a previous study, which found that many patients with diabetes with asymptomatic CAD experience incidents of silent myocardial infarction or cardiac death as a first cardiac event [30]. In the present study, multivariate analysis identified the absence of significant LV dysfunction and age as independent predictors of cardiac mortality. Several studies have reported that the presence of myocardial ischaemia by non-invasive stress testing is of prognostic importance in patients with CAD regardless of the presence of angina [31–34]. Therefore, we speculate that the cardiac survival of patients with diabetes with asymptomatic CAD might be improved if CAD was diagnosed earlier than significant LV dysfunction and if more aggressive early revascularization therapy was offered.
with diabetes [38, 39]. Therefore, it may be that patients with diabetes with asymptomatic CAD may benefit from DES-based early revascularization therapy.

**Study limitations**

The main limitations of the present study are its retrospective nature and the relatively small number of patients enrolled. In particular, the former limitation prevents our determining why asymptomatic patients treated medically had not received early revascularization. Furthermore, asymptomatic patients were selected from those referred for stress testing based on clinical circumstances and we included only those who had angiographically documented CAD. Therefore, we could not extrapolate the results of this study to general asymptomatic patients with diabetes because of possible selection bias. Second, the method used to assess coronary atherosclerosis could have underestimated the atherosclerosis burden, and intravascular ultrasound studies could have provided more accurate information. Third, patient clinical outcome in the AxS-CAD group would have been improved had more aggressive contemporary medical treatment been administered.

In conclusion, despite a similar severity of coronary atherosclerosis, patients with diabetes with asymptomatic CAD received early revascularization therapy less frequently and had poorer long-term survival than those with symptomatic CAD. In the present study, early revascularization therapy was identified as an independent predictor of cardiac survival, and asymptomatic and symptomatic patients who underwent early revascularization therapy had similar cardiac outcomes. Therefore, our data suggest that asymptomatic patients with diabetes and CAD may benefit from early revascularization. However, carefully conducted clinical trials are required to assess the clinical benefit of CAD screening and revascularization in asymptomatic patients with diabetes.

**Competing interests**

None to declare.

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