Markers for silent myocardial ischemia in diabetes. Are they helpful?

E Cosson, JR Attali, P Valensi

SUMMARY
Silent myocardial ischemia (SMI) and silent coronary stenoses (CS) are two to seven times more frequent in diabetic patients than in non-diabetic patients. In addition to this, they have a higher predictive value for cardiovascular events than the classical cardiovascular risk factors, either taken alone or combined. Coronary arterial disease is the leading cause of mortality and morbidity in the diabetic population. Altogether, these data suggest that screening for SMI and silent CS is an important issue. We assume that detecting SMI and silent CS improves patient management, and leads to optimised follow-up, action taken on nutrition, exercise and lifestyle, management of the cardiovascular risk factors, and revascularisation procedures whenever possible. However, screening for SMI and silent CS is expensive and may induce morbidity. Selecting the patients with a high a priori risk of SMI and silent CS is therefore of major concern. Carotid or lower limb peripheral arterial disease, proteinuria, male gender, an age greater than 60 years, and two or more cardiovascular risk factors among smoking, microalbuminuria, dyslipidemia, hypertension, a family history of premature cardiac disease, and cardiac autonomic neuropathy have been demonstrated to be the best current predictors of SMI and silent CS. New markers, such as adhesion molecules, Lp(a), inflammation parameters or homocysteine, and endothelium function assessment might be of further help in the future.

Key-words: Silent myocardial ischemia · Silent coronary stenosis · Diabetes mellitus · Review · Markers.

RÉSUMÉ
Les marqueurs de l’ischémie myocardique silencieuse sont-ils utiles chez le diabétique ?
L’ischémie myocardique silencieuse (IMS) et les sténoses coronariennes silencieuses (SC) sont deux à sept fois plus fréquentes chez les diabétiques que chez les non-diabétiques. En outre, elles ont une plus forte valeur prédictive d’événements cardiovasculaires que les facteurs de risque cardiovasculaire classiques, soit pris isolément soit de façon combinée. La coronaropathie est la cause dominante de mortalité et de morbidité dans la population diabétique. Au total, ces données suggèrent que le dépistage de l’IMS et des SC silencieuses est un problème important. Nous estimons que le dépistage de l’IMS et des SC silencieuses améliore la prise en charge des patients, et conduit à une optimisation du suivi, des mesures concernant la diététique, l’activité physique et le mode de vie, la gestion des facteurs de risque cardiovasculaire, et à des procédures de revascularisation quand elles sont possibles. Cependant, le dépistage de l’IMS et des SC silencieuses est coûteux et peut induire des complications. La sélection des patients avec un haut risque d’IMS et de SC silencieuses a priori est donc un enjeu majeur. Il est établi que l’artériopathie des carotides ou des membres inférieurs, la protéinurie, le sexe masculin, un âge supérieur à 60 ans, et au moins deux facteurs de risque cardiovasculaire tels que le tabagisme, la microalbuminurie, la dyslipidémie, l’hypertension artérielle, l’hérédité de coronaropathie précoce, et la neuropathie autonome cardiaque sont les meilleurs prédicteurs d’IMS et de SC silencieuses. Des nouveaux marqueurs, tels que les molécules d’adhésion, la Lp(a), les paramètres de l’inflammation ou l’homocystéine, et l’évaluation de la fonction endothéliale, pourraient se révéler utiles dans l’avenir.

Mots-clés : Ischémie myocardique silencieuse · Sténose coronarienne silencieuse · Diabète sucré · Revue · Marqueurs.
When compared with the non-diabetic population, the relative risk for coronary artery disease shows a two- to four-fold increase in diabetic men, and even more in diabetic women. Coronary artery disease is the major cause of mortality in patients with diabetes. The coronary lesions are more extensive than in non-diabetic patients, and the prognosis following coronary events is also worse for diabetic patients [1]. Silent myocardial ischemia (SMI) is defined as objective documentation of myocardial ischemia in the absence of angina or angina equivalents [2]. SMI detection therefore implies functional testing. The SMI definition ranges from transient asymptomatic ST-depression detected during continuous ambulatory electrocardiographic monitoring to stress-induced electrocardiographic changes during an exercise tolerance test, and inducible myocardial perfusion defects or reversible regional wall-motion abnormalities during stress imaging techniques [2]. In the 1980s Cohn et al. proposed considering three separate populations of patients with SMI: first, totally asymptomatic individuals; second, asymptomatic patients who have had myocardial infarction; and third, those with both symptomatic and asymptomatic ischemic episodes [3]. The present review will focus on the asymptomatic primary prevention population, i.e. type 1 SMI, highlighting the importance of screening for SMI, and the value of certain markers for SMI.

Detecting SMI is clinically meaningful

SMI in diabetes: a high prevalence

It is thought that symptomatic coronary arterial disease may reflect the tip of the iceberg representing the overall burden of coronary arterial disease in the diabetic population [4, 5]. SMI and silent coronary stenoses (CS) are two to seven times more frequent in diabetic patients than in non-diabetic patients [6-9]. The prevalence of SMI is also higher in patients with end-stage renal disease [10] and hypertension [11], and increases with age [12]. The lowest rates of SMI — 5% to 10% — in the diabetic population were reported in several series of patients without complications, who exhibited no or few cardiovascular risk factors [13, 14]. Moreover, SMI was defined in these reports as abnormalities in both the exercise stress test and myocardial scintigraphy [13, 14]. Selecting diabetic patients with additional cardiovascular risk factors leads to a higher prevalence — 30% to 55% [15-19].

What is the prognosis for SMI and silent CS in diabetes?

Very recent data have demonstrated that SMI, either detected by the exercise stress test [20, 21] or by myocardial scintigraphy [17, 20, 22], was associated with both major and minor cardiovascular outcomes [17]. Furthermore, testing may provide further qualitative prognostic data. Vanzetto et al. showed that large perfusion defects on scintigraphy were associated with a 22.3% annual mortality rate [22]. We and other authors have reported a particularly poor prognosis for the patients who had abnormal results on both the exercise stress test and the myocardial scintigraphy [23, 24]. It is therefore important to compare the coronary risk profile and SMI as predictors of cardiac events. In a preliminary series, Torremocha et al. reported that the Framingham score had a better predictive value for cardiac events than the presence of SMI [25]. Since that time, two studies have shown that SMI, defined as an abnormal ECG stress test, was the unique significant predictor of major cardiac events after multivariate analysis [21, 23]. The authors suggested that SMI was a stronger predictor for adverse cardiac outcomes in the asymptomatic patients with diabetes than the traditional cardiovascular risk factors.

SMI has been associated with significant CS in 40 [8, 18, 26, 27] to 90% [9, 13, 25] of the cases. Recent data from our group have demonstrated that the presence of silent CS associated with SMI was the main predictive factor for subsequent major cardiac events in diabetic patients [17, 20]. Furthermore, SMI was of poor prognostic value only when associated with silent CS [20]. We therefore recommended that patients with SMI undergo a coronary angiography, not only to determine the degree of severity, but also the suitability of the vessels for coronary revascularisation procedures, in agreement with ALFEDIAM [28] and the American Diabetes Association [29] guidelines.

Would identifying SMI change the clinical management of the patients?

Once silent CS or SMI or both are detected, the decision on how to manage the patients becomes crucial. No control trial has at the present time shown that angiography or revascularisation has an advantage over a conservative approach to patients with SMI. The results of the ACIP trial revealed a better outcome after 2 years in revascularised patients compared to the medical treatment for SMI [30]. However the study did not address the diabetic population, and included patients with known coronary arterial disease. In addition, the study was designed before publication of the results of the major secondary prevention trials with statin therapy. New perspectives are now available for the improvement of reperfusion results achieved by angioplasty, including in particular active stenting, and platelet anti-Gb IIb/IIIa inhibitor, and optimistic results may nowadays be hoped for [31, 32]. Medical treatment for SMI, such

Abbreviations

CS: coronary stenoses
SMI: silent myocardial ischemia
as betablockers, calcium channel blocking agents or both, have been shown to be effective in the general population [33]. Finally, statins [34], inhibitors of the angiotensin-converting enzyme [35], and obtaining good glycemic control are effective in improving coronary vascular dysfunction. Another strategy is to consider treating the asymptomatic patients with SMI or silent CS like those with known coronary arterial disease. But the current recommendations still consider diabetic patients, especially those exhibiting additional cardiovascular risk factors, to be high-risk patients. Thus optimal management is recommended in any case, including the attainment of specific lipid goals and the use of aspirin. Optimised action taken to improve glycemic control, lifestyle, hypertension, and to stop smoking is also routinely recommended and effective [36].

Thus far, screening for SMI and silent CS has proved to be more predictive for subsequent cardiac and cardiovascular events than the traditional cardiovascular risk factors. Whether diabetic patients benefit from screening is still unknown. The Detection of Ischemia in Asymptomatic Diabetics (DIAD) study is a randomised study dealing with this issue. However, only a few patients with diagnosed SMI have been recommend for coronary angiography in this study [37]. Therefore the role of the revascularisation procedure will not be properly evaluated. Until the results are obtained, screening for SMI and silent CS should still be recommended in the diabetic population. These procedures are expensive and may induce some morbidity. Thus selecting the patients with a high a priori probability of SMI or silent CS is a major concern.

**A need to identify the markers for SMI and silent CS?**

Three approaches have been described when identifying predictive factors. If it is decided that SMI is the diabetic complication to screen, the predictive factors of abnormal functional non-invasive cardiac tests are important (Tab I), whereas if it is decided that silent CS are the lesions to detect the predictors of silent CS are important (Tab II). The third approach is to go through angiography, not in all diabetic patients with SMI but only those who exhibit predictive factors for silent CS (Tab III).

**Traditional cardiovascular and diabetes-specific risk factors**

Regarding the traditional cardiovascular risk factors, the main predictors for SMI in the diabetic population are male gender, ageing, hypertension, dyslipidemia, and smoking (Tab I). Diabetes-specific predictors have been studied, such as diabetes duration, glycemic control, and the presence of microangiopathic complications. Diabetes duration and glycemic control presumably correlate with SMI, because the diabetic population has been shown to have a higher risk of SMI. Moreover, a longer duration of diabetes is a strong predictor of fatal coronary heart disease among diabetic women [38] and men [39]. However, no study has shown any correlation between diabetes duration and SMI. Most studies often include patients who have had diabetes for at least five years. Regarding glycemic control, recent data in asymptomatic patients with type 1 diabetes have shown that the increase in coronary artery area stenosis, assessed by intravascular ultrasound examination during coronary angiography, correlated with the mean HbA1c level over 18 years [40].

Among microangiopathic complications, diabetic nephropathy is the main predictor for SMI. In a case-control study, Rutter et al. have shown that the patients with microalbuminurie had a significantly higher prevalence of SMI than the patients without it (65% vs 44% respectively). Furthermore, the urinary albumin excretion rate was demonstrated to be the strongest independent predictor for SMI [15]. Other papers have found concordant data on the predictive value of albuminuria for SMI [14, 41, 42] and silent CS [13], but others have not [17, 43, 44].

Another possible marker among the diabetic complications is cardiac autonomic neuropathy. The cardiac sympathetic afferent fibres represent the main pathway for the transmission of cardiac pain [45]. At least five studies have shown that SMI was more prevalent in patients with autonomic neuropathy than in those with normal autonomic function [45, 46]. A meta-analysis showed a 2-fold increase in the risk of SMI when cardiac autonomic neuropathy was present [46]. Although there is no convincing evidence that autonomic neuropathy is the major factor responsible for the lack of ischemic pain in diabetic patients, or is a sensitive or specific marker for SMI, cardiac autonomic neuropathy should nevertheless be considered. Indeed cardiac autonomic neuropathy is associated with a poor cardiovascular prognosis. In addition, in asymptomatic diabetic patients, the risk linked to cardiac autonomic neuropathy has been shown to be independent of SMI, and the highest when cardiac autonomic neuropathy was associated with SMI [27].

Selecting the patients with SMI who should undergo a coronary angiography because of a high probability of significant CS remains difficult (Tab III). The same diabetes-specific factors and cardiovascular risk factors may be useful, but multivariate analyses fail to disclose any predominant predictor. Another way to approach the problem is to identify directly the patients with both SMI and silent CS (Tab II). Gender and age have commonly been cited as predictors. Special attention should be given to the male subjects, who exhibit a three- to six-fold increased risk compared with the female subjects [17, 43], and to those who are > 60 years old [17, 20]. No cardiovascular risk factor alone has been demonstrated to have sufficient specificity and specificity to predict SMI and silent CS. Therefore, in addition to age and gender, the number of additional

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cardiovascular risk factors might be a good tool for selecting the patients [17, 43].

**Arterial disease markers**

Because no cardiovascular risk factor alone is able to identify patients with silent CS, measurements of vascular disease markers may be an alternative. Cohn et al. have proposed recently that focusing on the vasculature should improve the specificity and sensitivity needed to detect the asymptomatic individuals in need of therapy in order to prevent the vascular disease for progressing [47]. Patients with peripheral arteriopathy, defined as stenosis greater than 50% detected by arterial ultrasound examination, have shown a three-fold increased risk of silent CS, compared to patients who had no history of peripheral arteriopathy [17, 43]. Boucher et al. have suggested in a preliminary report on 52 patients that intima-media thickness of the common carotid artery was the main predictor of SMI [48].

Electron beam computed tomography has been proposed to assess atherosclerosis in asymptomatic patients. When compared with non-diabetic patients, those with diabetes have higher median calcium artery coronary score [49]. Furthermore, the coronary calcium score provides information for predicting death in asymptomatic patients in addition to the traditional cardiovascular risk factors [50]. This point has yet to be confirmed specifically in the diabetic population. If detecting a high calcium coronary artery score is assessed, a functional method for detecting SMI should be undertaken, as there is nowadays no available data on the association of coronary calcifications with SMI.

### Table I

Predictive factors for silent myocardial ischemia in the diabetic population.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Number of patients</th>
<th>Selection criteria</th>
<th>Cardiac testing for SMI</th>
<th>Predictors of silent myocardial ischemia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Univariate analysis</td>
</tr>
<tr>
<td>Misad 1997 [14]</td>
<td>866</td>
<td>No CV risk factor specified, no insulin</td>
<td>ECG stress test and myocardial scintigraphy</td>
<td>gender, age, systolic blood pressure, total chol, triglycerides, proteinuria abnormal ECG at rest</td>
</tr>
<tr>
<td>Valensi 1997 [18]</td>
<td>92</td>
<td>≥ 2 CV risk factors</td>
<td>ECG stress test or myocardial scintigraphy or continuous ECG monitoring</td>
<td>none</td>
</tr>
<tr>
<td>Janand-Delenne 1999 [43]</td>
<td>92</td>
<td>≥ 2 CV risk factors</td>
<td>ECG stress test or myocardial scintigraphy or continuous ECG monitoring</td>
<td>gender</td>
</tr>
<tr>
<td>Rutter 1999 [15]</td>
<td>86</td>
<td>microalbuminuria (case-control)</td>
<td>ECG stress test</td>
<td>age, albuminuria, diastolic blood pressure age, proteinuria</td>
</tr>
<tr>
<td>Inoguchi 2000 [42]</td>
<td>140</td>
<td>&gt; 60 years</td>
<td>ECG stress test and myocardial scintigraphy</td>
<td>age &gt; 60 years</td>
</tr>
<tr>
<td>Valensi 2000 [44]</td>
<td>404</td>
<td>≥ 2 CV risk factors</td>
<td>ECG stress test or myocardial scintigraphy or continuous ECG monitoring</td>
<td>age &gt; 60 years</td>
</tr>
<tr>
<td>Cosson 2001 [68]</td>
<td>400</td>
<td>≥ 1 CV risk factor</td>
<td>ECG stress test or myocardial scintigraphy</td>
<td>Gender, HbA1c</td>
</tr>
<tr>
<td>Bacci 2002 [51]</td>
<td>206</td>
<td>≥ 2 CV risk factors</td>
<td>ECG stress test</td>
<td>gender, leg and carotid arteriopathy</td>
</tr>
</tbody>
</table>
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The lessons learned from the patients with SMI but no CS

The prognosis for patients with a normal myocardial scintigraphy, and those with an abnormal scintigraphy but without CS, was found to be similar on a mean 3-yr follow-up [20]. However, a limitation of this study is related to the numerous false negative non-invasive tests for SMI when considering the presence of silent CS in type 1 [40] and type 2 [51] diabetic patients. For example, Bacci et al. reported that 18% of the diabetic patients without SMI according to the ECG stress test had in fact significant CS on angiography [51]. Furthermore, performing different tests on the same person has shown discordant results, and many false negative results have been confirmed for continuous ambulatory ECG monitoring [7, 18, 26, 52], the exercise ECG stress test [7, 18, 19, 23, 26, 52], myocardial scintigraphy [7, 18, 19, 23, 26, 52], and stress echocardiography [19]. Thus, because only patients with positive stress tests generally undergo angiographic examinations, the prognostic impact of silent CS in the patients with normal non-invasive testing may be underestimated. Indeed, the prognosis is described as “good” in the patients without SMI as in the patients with SMI but no CS, whereas it may be as “poor” due to CS in around 20% of the patients with a normal test.

Artefacts due to obesity, or breast attenuation, may explain some false positive tests for SMI, defined as abnormal myocardial scintigraphy in patients with angiographically normal coronary arteries [53]. Such artefacts are well known by specialists of nuclear medicine and were excluded in all our studies. In fact various functional changes in coronary blood flow may account for the discrepancy between an abnormal functional test and a normal coronary angiography. Indeed, it has been shown that endothelium-dependent epicardial coronary artery vasodilation in response to acetylcholine [54] and physiological stimuli [55] was impaired in such patients. Coronary microcirculation dysfunction may also account for myocardial perfusion defects on scintigraphy, and may contribute to myocardial ischemia when myocardial oxygen demand is increased, even in the absence of coronary artery stenosis [56].

Nitenberg et al. have recently reported the impact of epicardial coronary dysfunction, assessed by coronary artery response to the cold pressure test, in diabetic patients with SMI but no CS [57]. As previously shown in the general population [58, 59], the patients with endothelial dys-

Table II
Predictive factors for coronary stenoses in the diabetic population.

In these studies, a coronary angiography is performed only in patients with abnormal non-invasive tests. Thus, the patients with false negative functional tests are considered not to have coronary stenoses. The patients with both silent myocardial ischemia and silent coronary stenoses are compared to those with silent myocardial ischemia but normal coronary angiography and those without silent myocardial ischemia.


<table>
<thead>
<tr>
<th>Reference</th>
<th>Number of patients</th>
<th>Selection criteria</th>
<th>Cardiac testing for silent myocardial ischemia</th>
<th>Predictors of silent coronary stenoses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Koistinen 1990 [7]</td>
<td>136</td>
<td>No complication</td>
<td>ECG stress test or myocardial scintigraphy or continuous ECG monitoring</td>
<td>none</td>
</tr>
<tr>
<td>Janand Delenne 1999 [43]</td>
<td>92</td>
<td>≥ 2 CV risk factors</td>
<td>ECG stress test or myocardial scintigraphy or continuous ECG monitoring</td>
<td>gender, retinopathy, arteriopathy, ≥ 2 CV risk factors, familial history of CAD</td>
</tr>
<tr>
<td>Gazzaruso 2002 [13]</td>
<td>1323</td>
<td>No complication</td>
<td>ECG stress test or myocardial scintigraphy or both</td>
<td>albuminuria, hdI chol, apo(a) polymorphism, Lp(a)</td>
</tr>
<tr>
<td>Gazzaruso 2002 [67]</td>
<td>1971</td>
<td>No complication</td>
<td>ECG stress test or myocardial scintigraphy or both</td>
<td>albuminuria, hdI chol, apo(a) polymorphism, homocysteine, smoking</td>
</tr>
<tr>
<td>Cosson 2003 [17]</td>
<td>362</td>
<td>≥1 CV risk factor</td>
<td>ECG stress test or myocardial scintigraphy</td>
<td>gender, age &gt; 60 years, arteriopathy, ≥ 2 CV risk factors</td>
</tr>
</tbody>
</table>

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function had a poor prognosis [57]. The first cardiac event occurred 27 months after inclusion for the diabetic patients with endothelial dysfunction, vs 57 months after inclusion for the patients without endothelial dysfunction [57]. We assume that the delay for cardiac events in patients with coronary artery dysfunction instead of CS results from the time needed for the development of atherothrombogenic processes. Thus identifying a peripheral marker for endothelial dysfunction could be a useful tool for selecting the patients to screen for SMI. We previously reported that investigating together lower limb and myocardial perfusion by single-photon emission tomography did not have additional diagnostic value, although lower limb perfusion abnormalities could reflect microcirculation disorders [60]. In vivo exploration of the endothelium function in the forearm has yet to be tested as a marker for coronary endothelial dysfunction, SMI or CS.

New biological markers

Emerging new markers could improve the global risk assessment currently in use. Both the role of the endothelium as a primary target organ for atherosclerosis and the involvement of adhesion molecules in the genesis of macroangiopathic complications have been suggested [61]. Albertini et al. have shown that the level of soluble L-selectin was low in the diabetic patients with symptomatic or silent CS, and lower than in the patients free of SMI, whereas other adhesion molecules, such as the soluble forms of intercellular adhesion molecule-1, vascular cell adhesion molecule-1, E-selectin, and P-selectin, did not differ [62]. The data on L-selectin were confirmed by a new series of patients [63]. Three chemokines, also known to be involved in atherogenesis, i.e. the chemokine regulated upon activation, normal T cell expressed and secreted (RANTES), the stromal cell-derived factor 1 (SDF-1α), and the monocyte chemotactic protein-1 (MCP-1), were tested, with negative results [63]. In addition, inflammation markers were measured. The levels of high-sensitivity C-reactive protein, orosomucoid, and haptoglobin were similar in the patients without SMI, with SMI but no CS on angiography, and with both SMI and silent CS [63]. These data were at variance with a recent paper, which showed that high-sensitivity C-reactive protein and fibrinogen levels, and the leukocyte count were higher in the patients with SMI and silent CS than in those with SMI but no CS [64].

Apoptosis plays an important role in atherogenesis. The Fas/Fas ligand system is a key regulating system responsible for the activation of apoptosis in various cell types, including cellular constituents of the vessel wall [65]. The soluble forms of Fas and Fas Ligand have been reported to correlate with peripheral arterial disease and coronary arterial disease in patients with end-stage renal disease, and with the intima-media thickness of the carotid artery in patients with hypertension. However, we failed to show any correlation between the soluble forms of Fas and Fas Ligand and SMI or silent CS [66].

Gazzaruso et al. obtained more encouraging results when assessing the role of the lipoprotein(a) level, apolipo-
protein(a) polymorphism, and the homocysteine level [13, 67]. These three parameters were independently predictive for silent angiographically documented CS in patients with type 2 diabetes [13, 67]. However, the sensitivity and specificity of these new markers were not sufficient to allow their use alone. They might therefore be considered in addition to the classical cardiovascular risk factors.

In conclusion, screening for SMI and consequently for silent CS in the diabetic population improves the global risk assessment currently in use. The crucial question facing us is the management of these patients. On one hand, no randomised study addressing the question of revascularisation procedures for silent CS has yet been performed. On the other hand, whether a specific medical treatment for the patients with SMI and silent CS is useful remains unknown. However, although screening remains a major concern, as SMI and silent CS are very common in the diabetic population (20% to 60% of the patients), selecting the patients to be screened is important for economic reasons. Cost-effectiveness will be improved if a good a priori evaluation of CS risk is available. The duration of diabetes, gender and an age greater than 60 years are important. The patients with signs of peripheral arterial disease, or proteinuria, or with at least two additional cardiovascular risk factors among microalbuminuria, smoking, hypertension, dyslipidemia, a family history of coronary arterial disease, and cardiac autonomic neuropathy should be considered. These criteria should be tested in a new series. Moreover, the assessment of new markers, such as adhesion molecules, inflammation parameters, Lp(a), or homocysteine, and the endothelium function might be of further help in screening in the future.

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