It is not yet the time to stop screening diabetic patients for silent myocardial ischaemia

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Abstract

Despite the intensified control of risk factors, silent myocardial ischaemia (SMI) is still a frequent complication of diabetes that is also associated with a higher risk of cardiac events. The objectives of this review are to summarize the importance of screening for SMI in a subset of asymptomatic diabetic patients. There is evidence that screening markedly improves the evaluation of cardiovascular risk compared with the usual risk scores. New markers, validated by large-scale studies, are needed to help in identifying the patients with silent coronary stenoses, thereby lowering the number of screened patients. Some indications of benefit with revascularization in patients with silent coronary stenoses are also available. Although it is not yet time to stop screening diabetic patients for SMI, such screening should focus on patients who are at high or intermediate cardiovascular risk. Guidelines need to be updated to increase the value of screening.

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Keywords: Diabetes; Coronary artery disease; Silent myocardial ischaemia; Cardiovascular risk; Revascularization

Résumé

Le temps n’est pas encore venu d’arrêter le dépistage de l’ischémie myocardique silencieuse du diabétique.
Malgré le contrôle intensif des facteurs de risque, l’ischémie myocardique silencieuse (IMS) demeure une complication fréquente du diabète et est associée à un risque accru d’événements cardiaques. Les objectifs de cette revue sont de résumer l’intérêt du dépistage de l’IMS dans une sous-population de diabétiques asymptomatiques. Au minimum existe la preuve que le dépistage améliore nettement l’évaluation du risque cardiovasculaire comparativement aux scores de risque usuels. De nouveaux marqueurs, validés dans de grandes études, sont nécessaires pour aider à identifier les patients avec sténoses coronaires silencieuses et réduire le nombre de patients chez qui l’IMS doit être dépistée. Quelques données suggèrent le bénéfice de la revascularisation chez les patients avec sténoses coronaires silencieuses. Le temps n’est pas encore venu d’arrêter le dépistage de l’IMS mais le dépistage doit être mieux ciblé, chez des patients à risque élevé ou intermédiaire. Les recommandations doivent être actualisées pour augmenter le rendement du dépistage.

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Mots clés : Diabète ; Maladie coronaire ; Ischémie myocardique silencieuse ; Risque cardiovasculaire ; Revascularisation

1. Introduction

Coronary artery disease (CAD) is known to be more frequent and more severe in diabetic patients. Myocardial infarction is often silent, probably as often as it is symptomatic. Many diabetic patients live with coronary stenoses with no signs or symptoms of coronary disease [1]. Therefore, detecting CAD appears logical for preventing cardiac events. Several studies have shown that silent myocardial ischaemia (SMI), detected by non-invasive tests such as the electrocardiography (ECG) stress test, myocardial scintiscan and stress echocardiography, affects 20–35% of diabetic patients who have additional risk factors and that 35–70% of patients with SMI have significant coronary stenoses on angiography [2]. In addition, the predictive value of SMI for cardiac events is well demonstrated, with the poorest
prognosis found in patients who have both SMI and coronary stenoses [3,4].

While some institutions encourage screening for SMI in diabetic patients at high cardiovascular risk [5,6], a controversy based on several arguments has recently emerged over the usefulness of such screening [7–9]. The first argument deals with feasibility: given the huge number of diabetic patients with other risk factors, it is not possible to screen all of these patients. Another argument is related to the marked improvement in cardiovascular prognosis with intensification of preventative medical treatments. In addition, the question of the cost-effectiveness ratio has been raised: coronary revascularization has been performed in a few patients screened for SMI, yet the benefits of revascularization have not been clearly established.

The randomized detection of ischemia in asymptomatic diabetics (DIAD) study tested whether or not, among type 2 diabetic patients with no cardiac symptoms, routine screening for CAD, using adenosine-stress radionuclide myocardial perfusion imaging, can identify those at high risk and also affect cardiac outcomes. The recently published results of the DIAD study suggest that routine screening does not appear to affect overall outcomes [10]. Furthermore, the benefit provided by coronary revascularization in patients with stable CAD has recently been questioned [11,12].

Our objective in the present review is to summarize the importance of screening for SMI in a subset of diabetic patients who are at high or intermediate cardiovascular risk. Also, there is evidence that screening can improve the evaluation of cardiovascular risk compared with the usual risk scores, as well as some indications of benefit with revascularization in patients with silent coronary stenoses.

2. Predictive value of silent myocardial ischaemia

The rate of coronary events has markedly decreased since the 1990s, as suggested by a recent epidemiological study [13] and the observation of placebo-treated patients in major randomized studies that included diabetic patients [14–16]. However, this rate, nevertheless, remains high. A multifactorial approach that targets several risk factors reduces the rate of cardiovascular and microangiopathic complications by around 50% [17]. The current guidelines stand in favour of intensification of preventative treatments targeting blood glucose, blood pressure and blood lipid levels. However, even under perfect conditions, this leaves a 50% residual risk [17]. In addition, changes in clinical practice take place slowly in real life [18] and patient compliance with multiple treatments is difficult to achieve. Treatment intensification may also be dangerous due to the risk of severe hypoglycaemic events in elderly patients and in those whose diabetes is of long duration [19,20]. Treatment intensification has to be started earlier to prevent diabetic complications more effectively.

2.1. Scores to evaluate cardiovascular risk

The UK Prospective Diabetes Study (UKPDS) risk score can identify the type 2 diabetic patients at higher cardiovascular risk [21]. Recently, the validity of this score was confirmed in a French diabetic population wherein the rate of events was similar as that predicted by the score [22]. In addition, the predictive value of microalbuminuria or proteinuria and of peripheral artery disease have also been demonstrated [23]. However, these criteria are not included in the UKPDS risk score. The current French guidelines for the detection of myocardial ischaemia in diabetic patients offer criteria by which to identify high-risk diabetic patients [6] and, recently, these criteria were validated by showing that the annual rate of major cardiac events was 3% in patients who fulfilled the criteria [22].

2.2. Silent myocardial ischaemia evaluates cardiovascular risk above and beyond scores

Despite the better control of risk factors, SMI is still associated with a high incidence of cardiac events. Indeed, data from a series of 781 diabetic patients, screened for SMI since 1992 using stress myocardial scintigraphy, were recently reported [24] and showed that the patients screened since 2000 had higher-risk profiles (more had hypertension and/or microalbuminuria). In the patients included after 2000, no cardiovascular event was reported after a mean 3-year follow-up period in the patients free of SMI whereas, in those with SMI, the prognosis was as severe as in the group included before 2000. This suggests that SMI needs to be managed specifically, using other treatments that go beyond just the control of risk factors and/or revascularization. Moreover, SMI is predictive of major cardiac events whether or not patients fulfill the French criteria for high cardiovascular risk (>3% per year). At the very least, these data show that screening for SMI provides a better estimate of cardiovascular risk and is additional to score evaluation. SMI screening may even be proposed for patients with high or intermediate risk greater than 0.6% per year, as estimated by the UKPDS risk score and the French guidelines. As SMI per se is associated with a higher rate of cardiac events even in the subset of patients not fulfilling the French guidelines criteria, other surrogate markers for SMI or CAD – such as ankle–brachial index, coronary artery calcification score or certain biological markers – would be helpful.

2.3. Prognostic value of parameters recorded during non-invasive screening

It is also worth noting that, when screening for SMI with an ECG stress test, other predictive factors can be obtained. In particular, alterations in functional capacity have been shown to be better predictors than the usual scores [25,26], with altered heart-rate recovery after a stress event and ectopic ventricular beats during and after stress, being predictive of a higher risk of death [27,28]. This supports the role of stress-testing to evaluate the prognosis of asymptomatic patients [29].
3. Are there any specific treatments and is revascularization useful?

3.1. Anti-ischemic treatment and further cardiovascular risk factor control in patients with silent myocardial ischemia

Due to their high risk, patients with SMI should be treated more intensively to achieve lower risk-factor targeted levels [30] – in particular, to lower low-density lipoprotein (LDL) cholesterol to levels less than 100 mg/dL or 70 mg/dL, as in secondary prevention [31]. These patients should also be prescribed antiaggregant and anti-ischaemic treatments based on beta-blockers. The benefit of beta-blockers has been demonstrated in patients with asymptomatic CAD in one study [32], although this was more moderate in another [33].

3.2. Some studies support revascularization for silent coronary artery disease, while the Detection of Ischemia in Asymptomatic Diabetics study did not address the issue

The French guidelines encourage coronary angiography in patients with SMI [6]. Indeed, the usefulness of screening asymptomatic diabetic patients for SMI relies considerably on the opportunity to perform coronary angiography and to revascularize those with significant stenoses. This point has been specifically tested in only a few studies. One pilot randomized study included 141 patients, half of whom were screened for SMI; those with SMI underwent coronary angiography, with revascularization in nine patients who had coronary stenoses. A significant 80% reduction in cardiac event rate was seen in the screened group [34]. A retrospective and convincing study wherein 54 of 261 asymptomatic diabetics with high-risk scans were revascularized showed a survival advantage in the revascularized patients [35]. However, the DIAD study attempted to address the usefulness of screening for SMI but failed to throw any further light on revascularization. The DIAD study included 1123 patients who were well controlled for the usual risk factors [10]. An adenosine-induced stress scintiscan was performed in 522 of these patients and revealed moderate or large defects, or other, non-perfusion abnormalities, in 63 cases. The annual cardiac event rate (cardiac death or non-fatal myocardial infarction) for all 1123 patients averaged 0.6% but was 2.4% in those with moderate or large defects and met the first objective of the study: screening can identify type 2 diabetic patients who are at unacceptable risk despite intensified control of risk factors. However, only 25 of the 63 patients with SMI underwent coronary angiography within 3 months of screening and eight of the nine patients with stenoses were revascularized. Yet, the cardiac event rate was not reduced in the screened compared with unscreened patients. Moreover, around 10% of each group in the DIAD study eventually underwent coronary angiography (more than 3 months after screening), paradoxically leading to revascularization in fewer screened than unscreened participants (22/522 vs. 42/562 patients; \( P < 0.05 \)). These angiographies were performed not only for cardiac events (similar rate in screened and unscreened patients: 36 and 31, respectively) but were also probably often requested following stress tests (also paradoxically more numerous in unscreened patients; \( P < 0.001 \)) and other investigations as well. Secondary revascularizations may be considered an endpoint and this endpoint was reached in the DIAD study. However, the number of stress tests and angiographies performed in the unscreened patients most certainly eroded the power of the study.

In our series, 65 patients with significant coronary stenoses on angiography were followed-up, with 26 of them vascularized upon the decision of the investigator based mostly on the possibility to vascularize and the expected benefit. In fact, there was a trend towards a lower rate of major cardiac events in those who were vascularized. In particular, of the 14 patients with stenosis in one major coronary artery treated with percutaneous coronary intervention (PCI) and of the five patients with multivessel stenoses treated by coronary artery bypass grafting (CABG), there was one and no cardiac event, respectively.

This suggests that a large-scale randomized study to compare cardiac outcomes specifically in asymptomatic diabetic patients with SMI after revascularization and during medical treatment is urgently needed.

3.3. Coronary artery bypass grafting when indicated; with a drug-eluting stent, if percutaneous coronary intervention

Several years ago, the Bypass Angioplasty Revascularization Investigation (BARI) and the Coronary Artery Surgery Study (CASS) showed that surgical revascularization improves the prognosis of patients with stenoses in the left main coronary artery or with multivessel CAD [36,37]. Recently, the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial failed to show any improvement in cardiac prognosis after PCI was added to the optimal medical treatment in patients with stable CAD [12]. However, PCI reduced the number of secondary revascularizations and ischaemic burden and improved the quality of life [38,39]. In addition, in a subset of patients drawn from the COURAGE study, serial myocardial scintigraphy was performed in 314 patients. The data showed that adding PCI to the optimal medical therapy resulted in a greater reduction of major cardiovascular events with a larger decrease in ischaemia, particularly if baseline ischaemia was moderate to severe (>10% of myocardium affected) [38]. However, it must be emphasized that only 3% of the COURAGE patients were revascularized using drug-eluting stents which, compared with bare-metal stents, were associated with reduced mortality, myocardial infarction and revascularization rates in the long-term follow-up of patients in a large Massachusetts registry [40]. A decrease in revascularization rates when using drug-eluting stents has also been reported in a recent meta-analysis but with no difference in overall mortality [41]. The BARI-2D used an excellent study design specifically to compare cardiac outcomes in diabetic patients with CAD (18% asymptomatic, 21% with angina equivalents, 51% with stable angina and 11% with unstable angina) who were either revascularized or treated medically [11]. This study included 2368 patients who were considered by the investigators to be potentially eligible for either PCI (\( n = 1605 \)) or CABG (\( n = 763 \)).
the PCI arm, the cardiac event rate was the same whether the patients were revascularized or treated medically. In contrast, in the CABG arm, where the patients had more severe CAD than in the PCI arm, those who were revascularized enjoyed a better prognosis than those treated medically. These data suggest that CABG should be performed when appropriate whereas PCI is not useful. However, it must be borne in mind that only 30% of the PCs were performed with drug-eluted stents. In addition, 42% of the patients who had initially entered the medical treatment group went on to undergo the revascularization procedure during follow-up, suggesting that medical treatment alone is, in fact, often inadequate. The Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM) Trial, an international study designed to define the optimal revascularization strategy for diabetic patients with multivessel CAD, is expected to provide additional information [42]. At present, it is possible to consider that CABG is able to improve the prognosis of diabetic patients with silent coronary stenoses. The main issue in the SMI screening strategy is, therefore, to identify patients who have coronary stenoses and, in particular, those with the most severe CAD, who are most likely to benefit from CABG, as shown in the BARI-2D trial.

4. How to identify which diabetic patients to screen for silent coronary artery disease

4.1. Age, retinopathy and male gender should be taken into account

Several studies have clearly shown that SMI is not inevitably associated with coronary stenoses but may be the result of endothelial dysfunction and reduced coronary reserve [43–47]. In our series, significant coronary stenoses were found on angiography in only 40% of patients with SMI and in only 10% of our total patient population, of which only 30% were revascularized. However, the value of SMI screening might be increased by including patients with higher a priori cardiovascular risk, as suggested by the Bayes theorem. Along this line, it should be mentioned that the predictive value of SMI for coronary stenoses is higher in patients aged more than 60 years, a criterion included in the French guidelines [6]. Our data showed that these guidelines could identify a subset of diabetic patients at higher risk of silent CAD. However, retinopathy and male gender are other significant predictors [22] and these criteria need to be also included in the guidelines.

4.2. Structural, biochemical and endothelial markers may be helpful

Other markers of coronary stenoses may be helpful – in particular, left ventricular hypokinesia or hypertrophy [48], a high coronary artery calcification score [49] and, possibly, carotid intima–media thickness [50]. Biochemical markers, such as serum osteoprotegerin levels [51], low levels of serum L-selectin [52] and slightly increased plasma pro-brain natriuretic peptide (BNP) levels in patients without heart failure, may also prove to be helpful [53]. Furthermore, coronary angiography should be performed in patients who have strongly positive ECG stress tests or extensive defects (>10%) on scintiscan, as they are more likely to have significant coronary stenoses. Peripheral endothelial dysfunction may also indicate the presence of coronary stenoses [54]. The role of angiography scans, which expose patients to high levels of X-ray radiation and iodine load on SMI screening, also needs to be defined.

5. Conclusion

In conclusion, despite the intensified control of risk factors, SMI remains associated with a higher risk of cardiac events. Screening asymptomatic diabetic patients for SMI markedly improves estimates of cardiovascular risk. However, new markers validated in large-scale studies are needed to help to identify patients with silent coronary stenoses and, thus, lower the number of screened patients. Patients with SMI need to have their risk factors treated more aggressively by antiaggregant and anti-ischaemic drugs. Those with coronary stenoses are more likely to benefit from revascularization by CABG whereas those eligible for PCI, if treated with this procedure, should probably use drug-eluted stents. Although further studies are needed to determine the optimal means of detecting SMI and to demonstrate the benefit of early detection of SMI in diabetic patients, it is not yet the time to stop screening diabetic patients for SMI. Indeed, SMI screening should focus on patients who are at high or intermediate cardiovascular risk, while guidelines should be updated to increase the value of screening.

Conflict of interest

The authors declare no conflicts of interest.

References


