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Identification of myocardial ischemia in the diabetic patient Joint ALFEDIAM and SFC recommendations

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Epidemiological perspectives, showing a clear trend towards a considerable increase in the number of people with diabetes mellitus, and recent advances in the exploration and treatment of coronary artery disease incited the French-speaking Association for the Study of Diabetes and Metabolic Diseases, ALFEDIAM (Association de Langue Française pour l'Etude du Diabète et des Maladies Métaboliques), and the French Society of Cardiology, SFC (Société Française de Cardiologie) to hold their first joint conference devoted to updating recommendations for the identification of myocardial ischemia in diabetics.

It has long been recognized that diabetes, a major cardiovascular risk factor, can be considered as an authentic vascular disease due to the frequency and the clinical severity of arterial, cardiac, cerebral or peripheral complications, which still too often lead to late diagnosis of impaired glucose control. In France, the increasing number of diabetic people whose life expectancy is determined by coronary complications makes diabetes mellitus an important public health priority. Due to the specific features of diabetic coronary artery disease, dominated by insidious onset and course, diagnosis of silent myocardial ischemia (SMI) and potential atheromatous lesions of the epicardial coronary vessels is crucial for appropriate therapeutic management of these patients.

Progress in drug and instrumental treatment modalities for coronary insufficiency naturally lead to a reconsideration of the most appropriate therapeutic approach, and by consequence of early screening for SMI, to reduce cardiac morbidity and mortality in diabetic patients. Interest in the prognostic and therapeutic potential of early identification of myocardial ischemia in the symptom-free diabetic has nevertheless been insufficient to incite large-scale multicentric prospective studies searching for clear management guidelines recognized by diabetes specialists, cardiologists, and general practitioners [1-5]. It was thus in a context of ongoing debate concerning the appropriate diagnostic and therapeutic approach that the working group, fully aware of the lack of powerful evidence, attempted to provide consensual responses to four questions raised by the problem of searching for possible myocardial ischemia in the asymptomatic diabetic.

–What is the potentially beneficial therapeutic effect of early diagnosis of SMI?

– Which symptom-free diabetics should be screened for SMI?

– What are the most appropriate screening tests?

– What should be done after screening for SMI?

Starting with studies specifically reporting cohorts of diabetic patients, generally with type 2 diabetes, or with large-scale studies devoted to coronary artery disease where diabetics are an occasional subgroup, the working group attempted to draw up the following recommendations. These recommendations cannot be formal guideline statements for good clinical practice and will have to be re-evaluated prospectively by the two specialties. They basically concern type 2 diabetes mellitus. Type 1 disease is integrated into the general screening strategies.

Context

Diabetes mellitus

Diabetes mellitus is an entity defined by its biological phenotype marked by blood sugar above or equal to 1.26 g/l (7 mmol/l) recorded at two separate tests performed in an apparently healthy subject who has fasted for at least eight hours. The current etiopathogenic classification distinguishes [6]:

– Type 1 diabetes which generally results from autoimmune destruction of the pancreatic beta cells, leading to an absolute insulin deficiency. Type 1 is more commonly observed in subjects aged less than 40 years and requires early initiation of insulin therapy.

– Type 2 diabetes, which is more frequent and generally observed in older subjects. Type 2 is characterized by a variable combination of insulin resistance and deficient insulin secretion.

– Other exceptional causes of diabetes: genetic disorders leading to defective beta cell function or defective insulin action, pancreatic or endocrine diseases, toxic or infectious causes.

– Moderate hyperglycemia, close to glucose intolerance, defined by fasting glucose in the 1.10-1.26 g/l range, which also increases the vascular risk and can progress to diabetes in approximately 50% of the subjects [7].

– The metabolic syndrome which generally accompanies type 2 diabetes and which, according to the National Cholesterol Education Program [8], European Group for the Study of Insulin Resistance [9], is defined by the association of at least three of the following criteria: abdominal obesity (waist circumference > 102 cm for men and 88 cm for women), triglycerides ≥ 1.5 g/l, HDL-cholesterol < 0.4 g/l for men and 0.5 g/l for women, and blood pressure ≥ 135 mmHg (systolic) or ≥ 85 mmHg (diastolic).

The incidence of diabetes is rising constantly. According to the WHO projections, the population of diabetics will double by 2025, especially because of the progression of diabetes in developing countries [10]. In France, the current population of diabetics is estimated at 2.5 million persons, predominantly (90%) subjects with type 2 diabetes. An estimated 300,000-500,000 persons, i.e. 10-15% of the diabetic population, are unaware of their diabetes. Moreover, excessive abdominal adipose tissue, a condition favoring the development of type 2 diabetes, occurs in an estimated 10 million persons.

Cardiovascular complications, which are 2- to 3-fold more frequent than in non-diabetic subjects [11], determine the prognosis of diabetes and contribute to the shorter life expectancy of diabetic subjects, 8 years less for subjects aged 55-64 years and 4 years less for older subjects [12]. The cause of death in diabetics involves a cardiovascular condition in approximately 65-80% of the cases. Cardiac events, the lead-

ing event being myocardial infarction, are more frequent and more severe in diabetic than non-diabetic subjects [15, 16]. After a myocardial revascularization procedure, cardiac events are more frequent in diabetics. In the NHLBI registry, the chance of survival 9 years after coronary angioplasty is 68% for diabetics and 83.5% for non-diabetics; diabetics have a higher rate of myocardial infarction and new revascularization procedures required because of secondary stenosis or progression of the atheromatous process [17]. The proportion of diabetic patients in cardiology units is rising constantly, with up to 33% of all patients hospitalized for myocardial infarction presenting diabetes [18]. The proportion of coronary patients undergoing coronary angiography who have diabetes reaches 20-30% [19]. Diabetes is thus recognized as an important independent risk factor for cardiovascular disease [20, 21]. Traditionally, coronary mortality in a non-coronary diabetic patient is identical to that of a non-diabetic coronary patient [22]. Recent observations, although disputing this statement with a less pessimistic view, clearly confirm that the cardiovascular risk (CVR) in a diabetic patient is greater than that of a non-diabetic person [23, 24].

The gravity of coronary artery disease in diabetics is due to specific anatomic, functional, and biological features of the disease. Although the lesions present a similar morphology, parietal infiltration is more diffuse, more distal, and more calcified in the diabetic subject as demonstrated by coronary angiographic findings [25], and as confirmed by necropsy studies [26]. Endothelial dysfunction, which participates in all the phases of atherosclerosis, is aggravated in the diabetic due to the hyperglycemia and insulin resistance [27]. Together with coagulation disorders related to increased platelet adhesion and aggregation [28] and an imbalance between fibrin formation and lysis [29] which are characteristic features of diabetes, endothelial dysfunction accounts for the accelerated progression of atheromatous lesions in the diabetic. Coagulation disorders and endothelial dysfunction also contribute to microcirculation anomalies, which can lead to SMI even if the epicardial vessels are not involved [30]. Cardiac autonomic neuropathy is frequent in diabetics and largely explains the often silent nature of myocardial ischemia [31].

Silent myocardial ischemia

Transient changes in myocardial perfusion, together with temporary alterations of cardiac muscle action and function, which occur without chest pain or angina-equivalent manifestations, is a theoretical pathophysiological definition of SMI. Clinical confirmation is naturally less formal. Depending on the clinical circumstances, three types of SMI are generally distinguished: type 1 in symptom-free patients with no clinical history of coronary artery disease, type 2 in symptom-free patients with a history of myocardial infarction, and type 3 in patients with angina related to coronary artery disease who also experience episodes of SMI [32]. Clinically, type 1 SMI is defined as an electrocardiographic (and/or scintigraphic and/or echocardiographic) anomaly which is silent and transient, and observed during a period of stress in subjects whose electrocardiogram is strictly normal at rest.

Type 1 SMI is two to six times more common in the diabetic subject than in the non-diabetic subject, depending on the series [33]. In the diabetic, the prevalence of SMI varies widely from 10 to 30%, depending on patient selection and the acuity of the screening tests [34, 35]. It is more frequent in diabetics with two other cardiovascular risk factors and can be observed in one-third of the patients [36, 37]. This wide variability is one of the reasons underlying the weak yield of systematic screenings for SMI in known diabetics and highlights the need for rigorous patient selection based on an evaluation of global cardiovascular risk in each diabetic.

SMI, which is premonitory for secondary cardiovascular events, is a factor of poor prognosis [38]. Studies monitoring diabetics demonstrate that SMI is regularly associated with the risk of a major coronary event [39-42]. Several studies have shown that after the age of 60 years the relative risk of a secondary major cardiovascular event is 3.2-fold higher in diabetics with than without SMI [40-42].

The correspondence between SMI and angiographically significant narrowing of the coronary arteries is neither certain nor constant. In the small series reported to date, coronary angiography in patients with SMI demonstrates the presence of one or more zone of ≥ 70% angiographic stenosis in 30-60% of the cases [36, 42]. Alteration of coronary reserve secondary to intramyocardial microangiopathy, vasomotor disorders due to endothelial dysfunction, and coagulation disorders can be associated and account for the discordance between cardiac function and angiographic findings in the diabetic. Nevertheless, it

Table I

1. The severity of the cardiovascular prognosis in diabetes calls for secondary prevention in patients with asymptomatic disease.
2. Silent myocardial ischemia, which occurs more frequently in diabetics than non-diabetics, is a poor prognosis factor, premonitory for major cardiac events.
3. The prevalence of silent myocardial ischemia is high when other vascular risk factors are associated with diabetes.
4. Silent myocardial ischemia can develop without involvement of the large epicardial coronary vessels.
5. Nevertheless, the prognosis of silent myocardial ischemia depends on the presence of angiographically significant coronary narrowing.
6. Search for silent myocardial ischemia in diabetics should not be systematic but rather based on an evaluation of the overall cardiovascular risk of each individual diabetic patient.
7. Coronary angiography, employing all the safety measures required for this type of exploration in diabetics, is warranted to search for coronary narrowing in diabetic patients presenting silent myocardial ischemia.

appears that the prognosis of SMI is closely dependent on the presence or not of angiographically significant coronary stenosis. Two French studies have recently demonstrated that the presence of significant stenosis is a strong predictive factor for major cardiac events at 2 and 3.5 years in patients with SMI, while in patients with an abnormal scintigraphy but no coronary narrowing, the prognosis is similar to that observed in patients without SMI [16, 42]. Today, coronary angiography, employing all the safety measures required for this type of exploration in diabetics, is warranted to search for coronary narrowing in patients with SMI.

Due to its high prevalence and the potentially serious prognosis, the diagnostic and therapeutic approach to the asymptomatic diabetic patient should focus on SMI. A natural junction between diabetology and cardiology, SMI leads to a discussion concerning the potential therapeutic benefit which could be expected from early screening, and then on adequate selection of diabetic patients with high cardiovascular risk who could benefit from screening tests, as well as on the choice of the best tests, and finally on diagnostic and follow-up strategies based on the screening test results.

Stenosis and atheromatous lesions. Current data

The relationship between angiographically significant coronary artery stenosis of ≥ 70% and myocardial ischemia together with long-term prognosis is well established. Prognostic scores, defined from data collected in large cohorts of coronary patients with stable or asymptomatic disease, distinguish between patients with low and high myocardial risk depending on the severity of the coronary lesions. The risk of coronary mortality at five years is an estimated 7.5% in patients with single-vessel disease not involving the anterior interventricular, and rises to 40% for those with triple-vessel disease (of course with involvement of the anterior interventricular) [43, 44]. These angiographic and prognostic data have been used to develop surgical and interventional revascularization treatments [43, 45].

In vivo, progress in morphological, functional, and biological explorations of atheromatosis has led to a better understanding of the atherosclerotic process which occurs as a discontinuous phenomenon where alternating phases of stability and instability modify the vulnerability of the atheromatous lesions. The atheromatous plaque exhibits constant histological and biochemical activity which either favors its stability or its instability. The plaque is rich in lipidocellular material maintained loosely in a thin fibrous sheath. Vulnerable unstable lesions may fissure or erode leading to the formation of a more or less obstructive endoluminal thrombus [46, 47]. Instability of the atheromatous plaque is a multifactorial phenomenon controlled by numerous independent mechanisms involving mechanical events (loading of the lipidocellular heart), biochemical activity (metalloproteases), vasomotricity (endothelial dysfunction), and hemodynamic (shear forces) and inflammatory events [48, 49]. All these factors of plaque instability are exacerbated by diabetes. There is no correlation between the qualitative vulnerability of the plaque and the quantitative angiographic assessment of arterial stenosis. Certain angiographic findings suggest that the unstable plaque, the causal agent of acute coronary events, does not produce significant stenosis. Angiograms occasionally performed just before a myocardial infarction show that the coronary artery implicated in the eminent necrosis exhibits less than 50% angiographic stenosis in more than 60% of the patients [50, 51]. The small volume of the unstable lesion and the remodeling of the arterial wall would explain, in this situation, the minimal narrowing demonstrated at angiography [52]. Moreover, endocoronary ultrasound explorations performed at the moment of acute coronary events reveal multiple unstable plaques in 75% of the cases [53]. It thus appears that lesion instability is a multifactorial diffuse phenomenon; while a single plaque can lead to an acute coronary event, numerous lesions can also remain asymptomatic yet expose the patient to the risk of acute or subacute obstruction leading to a paroxysmal episode or remain insidious with the development of scar formation and angiographically significant stenosis.

The complexity of the atheromatous process is reflected in the difficulty encountered in clinical evaluation of coronary atherosclerosis and explains the limitations of functional and morphological explorations. In the asymptomatic diabetic subject, minimally significant atherosclerotic lesions of the arterial wall may go unrecognized at angiography and fail to disclose SMI during exercise, yet can be potentially vulnerable due to the endothelial dysfunction and coagulation disorders characteristic of diabetes. Thus the diagnostic value of functional and morphological explorations, which demonstrate more readily fixed tight coronary stenosis, is not unconditional. Screening for non-stenosing lesions with a high risk of instability using magnetic resonance imaging, endocoronary ultrasound, thermography, palpography and optical coherence tomography (OCT) remains within the realm of clinical research. In everyday practice, the goal focuses less on identifying atheromatous lesions with a risk of instability than on identifying subjects with a high cardiovascular risk. Furthermore, cardiological evaluation only explores a given instant within the course of an unpredictable disease which may progress to a paroxysmal event or remain quiescent or insidiously stenosing. The predictive value of negative exploration results is thus not formal so repeated cardiological evaluations must be peformed during the surveillance of the diabetic subject at risk in order to search for progression of silent stenosis.

From a therapeutic point of view, advancing knowledge of the mechanisms leading to the onset and development of atherosclerosis emphasizes the importance of pharmacological and dietetic preventive measures which, *via* numerous pathways, contribute to preventive and curative stabilization of the vulnerable plaque.

Table II

8. The diffusion and site of angiographic coronary stenoses define high and low myocardial risk.
9. Nevertheless, the severity of the atherosclerotic progression depends as much on lesion instability as on the severity of the stenosis.
10. Functional and morphological explorations can fail to reveal potentially unstable non-stenosing coronary lesions.
11. The diagnostic and predictive value of exercise tests and coronary angiography is not unconditional.
12. Nevertheless, since stenosis may arise insidiously, complementary cardiological evaluations should be repeated during the follow-up of diabetic patients at risk.
13. Identifying patients at risk is of greater importance and usefulness than identifying potentially unstable non-stenosing atheromatous lesions.

Potential therapeutic benefit

The therapeutic advantage of early systematic screening for SMI has not been formally demonstrated in the diabetic population. Results of therapeutic interventions performed in diabetic patients with clinically overt coronary artery disease or in asymptomatic subjects with a diabetic or non-diabetic atheromatous risk do suggest however certain advantages. A potential beneficial effect can be expected from three possible therapeutic measures: initiation of an anti-ischemia treatment, reinforcement of cardiovascular preventive measures, and, if needed, revascularization intervention.

Anti-ischemia treatment

Discovery of SMI can, and should, lead to early prescription of anti-ischemia drugs. The ACIP study of asymptomatic coronary patients who developed SMI has demonstrated the efficacy of anti-ischemia treatment which reduces the severity and the number of episodes of silent ischemia. This study also confirmed the superiority of betablockers over calcium channel inhibitors [54]. The efficacy of betablockers is also demonstrated in the diabetic coronary patient. In the BIP study, the risk of cardiac death in diabetics was 44% lower in the group of patients receiving betablockers [55]. This positive effect is more pronounced after myocardial infarction and in the presence of moderately altered left ventricle function [56].

Reinforcement of preventive measures

Discovery of SMI places the diabetic patient in a context of secondary prevention. Early diagnosis can lead to anticipated initiation and reinforcement of dietetic and lifestyle therapeutic measures with more rigorous control of associated risk factors by the prescription of drugs with a proven preventive effect.

A large body of evidence has been accumulated favoring the efficacy of statins in the diabetic subject. Large-scale studies devoted to secondary prevention have proven the efficacy of therapeutic lowering serum cholesterol, with a 55% reduction of the relative risk of major coronary events at five years in the hypercholesterolemic diabetic treated with simvastatin in the 4S study [57] and a 25% reduction in the normocholesterolemic diabetic given pravastin [CARE study, 58]. In a population of 5,963 diabetics, the Heart Prevention Study (HPS) has confirmed these results showing a significant 22% reduction of the relative risk, a reduction equivalent to that observed in a cohort of non-diabetic subjects [59]. With a 33% reduction of the relative risk, this beneficial effect was also observed in the group of 2,912 asymptomatic diabetics. This gain in prognosis is recorded irrespective of the type of diabetes, its duration, or the quality of glucose control, irrespective of the patient's age or gender, and finally irrespective of the initial blood pressure, total cholesterol or LDL-cholesterol (LDL-C) levels. Although fewer trials have been conducted with fibrates, these agents have also proven their efficacy for secondary prevention in the diabetic subject [60]. Clinical and biological results reported in these trials have led to the elaboration of guidelines defining therapeutic intervention thresholds depending on the vascular risk and the LDL-C level. For the diabetic patient with two other risk factors, as in the coronary patient, the AFFSAPS (the french drug agency) set the intervention threshold at 1.3 g/l LDL-C, with a target value of 1 g/l in the most recent European guidelines [61].

Strict control of blood pressure is also important in improving vascular prognosis in diabetics. In the UKPDS trial, lowering systolic and diastolic pressures 10 and 5 mmHg respectively led to a 5% reduction in the absolute risk of stroke or vascular death at 5 years [62]. Other studies devoted to prognosis and treatment of hypertensive patients have reported similar results in the subgroup of diabetics [63]. In the latest recommendations the objective is to achieve blood pressure below 130/80 mmHg in the hypertensive diabetic subject [61, 64]. In line with the ADA guidelines, converting enzyme inhibitors should be favored in diabetics with proteinuria or altered left ventricle function [65]. This drug class has proven efficacy in diabetics. In the early phase after myocardial infarction, the 6-week mortality was significantly lower in diabetics treated with lisinopril (8.7% *versus* 12.4% in the placebo group) in the GISSI3 trial [66]. In diabetics presenting a cardiovascular event or having another cardiovascular risk factor, ramipril produced a significant 25% reduction of relative risk of a cardiovascular event at 4 years in the diabetic subgroup of the HOPE study [67]. The EUROPA trial also recently demonstrated the efficacy of perindopril in combination with a betablocker in reducing the vascular risk in the stable coronary patient with, in the diabetic population, a favorable trend which did not reach the level of significance [68].

A meta-analysis of numerous comparative trials shows that aspirin also has proven efficacy for reducing vascular risk both in the diabetic and non-diabetic subject [69]. In diabetics with retinopathy and no sign of coronary artery disease, prescription of aspirin is associated with a 15% reduction of the relative risk of myocardial infarction at 7 years [70]. Thienopyridins have not been evaluated for primary prevention in the diabetic subject. In patients with clinical expression of peripheral, coronary or cerebral artery disease, clopidogrel was found more effective than aspirin in the subgroup of diabetic patients in the CAPRIE study with a 2.1% reduction in the absolute annual risk of a major arterial event [71].

Careful strict control of blood glucose also contributes to improved vascular prognosis in the diabetic. The DIGAMI study demonstrated that the use of insulin following myocardial infarction, from the hospital phase through the third month at least, yielded a 29% reduction in mortality at one year [72]. Finally, in the UKPDS study which recruited asymptomatic patients with type 2 diabetes, a 1% rise in glycated hemoglobin (HbA_{1c}) above the 6.2% threshold is associated with a 11% increase in coronary risk at 10 years [73].

Affirmation of SMI can thus lead to more rigorous and sustained management of the overall cardiovascular risk via more individually adapted drug prescription. In men with a high vascular risk whose SMI has been identified with a positive exercise test, attentive preventive measures contribute to significant reduction of cardiovascular mortality which reaches 61% at 7 years [74]. In subjects with type 2 diabetes presenting microalbuminuria, aggressive therapeutic management (strict blood glucose control, blood pressure controlled at 135/80 mmHg, and prescription of statin and aspirin) decreases the vascular risk by 50% at 7 years in comparison with conventional and occasional treatment of associated risk factors [75].

Myocardial revascularization

A revascularization intervention can be envisaged after discovery of SMI and angiographic demonstration of tight stenosis in arteries supplying a large myocardial territory. Due to the lack of studies specifically devoted to revascularization in the diabetic, and particularly in the asymptomatic diabetic, and in light of continuing progress in surgical and interventional methods, the principle of revascularization and its modalities remains a controversial topic. Large trials have nevertheless pointed out a certain number of notions particularly important for therapeutic decision-making in diabetics with myocardial ischemia.

In patients with stable coronary disease, the efficacy of surgical revascularization has been proven in a group of patients with high myocardial risk presenting stenosis of the left common coronary, a multiple-vessel lesion involving the anterior interventricular and an alteration of left ventricle function [76]. In patients with single-vessel disease and a low cardiovascular risk, revascularization by angioplasty does not have a notable effect on the risk of a major cardiac event but significantly improves functional outcome in patients with a proximal lesion of the anterior interventricular [77]. In coronary patients with SMI, published trials tend to demonstrate the superiority of myocardial revascularization in comparison with anti-ischemic medication alone. Although it lacked power, the ACIP study [78] demonstrated that bypass patients exhibit fewer infraclinical ischemic events and have a significantly lower mortality at one year (0% *versus* 1.6% in the group given anti-ischemic medications).

In diabetic candidates for revascularization of their multivessel disease, results of large comparative trials favor the surgical option [79]. At 7 years, the BARI trial [80] showed lower mortality in the surgery group (24.5% *versus* 44% in the balloon angioplasty group) with a clearer benefit for revascularization with using internal mammary. Stent insertion was unable to breach the difference between angioplasty and surgery. In the ARTS trial devoted to diabetics with multivessel disease, one-year mortality was 6.3% in the stent group *versus* 3.1% in the surgery group in [81]. Conversely, data from registries which recruit a less selected population of diabetics do not show any significant difference in the long-term outcome after angioplasty or surgery [82]. Thus no one option predominates for the diabetic with multivessel disease and decisions must be made on an individual basis taking into consideration the etiological context, including age and associated disease, and the analysis of the coronarogram.

When the indication for angioplasty is retained and when the angiographic conditions are favorable, stent insertion should be preferred. The risk of restenosis, which is particularly high in the diabetic [83], is significantly reduced by stent insertion [84] and reaches, in the best situations, a level equivalent to that observed in non-diabetics [85]. Administration of antiGPIIb-IIIa, and more specifically Abciximab, when inserting a stent contributes to the significant reduction of the restenosis rate [86] and mortality risk at one year [87]. Finally, the results obtained with active stents appear promising and if confirmed should lead to wider indications for angioplasty in the diabetic subject and possibly to more indications for revascularization in these patients [88]. In the population of 379 diabetics included in the SIRIUS trial (26% of the study population), the rate of new revascularization of the stented coronary was 22.3% in the group with an inactive stent and 6.6% in the group with a sirolimus-eluting stent [89].

Coronary risk stratification and patient selection (Table III)

The diabetic population is exposed to a higher cardiovascular risk, but all asymptomatic diabetic subjects do not have SMI or even less so high-risk coronary artery disease which could be improved with revascularization. Large-scale systematic screening for SMI in the asymptomatic diabetic population would have a very low yield and would be almost impossible to implement as well as very costly. Screening must be limited to subjects with a high cardiovascular risk

whose likelihood of having SMI is high. Ideally, the selection process should allow identifying subjects whose cardiovascular risk could be improved by therapeutic intervention with a result at least equivalent to that obtained by implementation of appropriate curative and preventive measures. This risk/benefit ratio remains to be established. Selection is thus an empirical process searching to identify subjects whose potential risk is high and whose likelihood of having stenosing coronary disease is theoretically high. An evaluation of prior recommendations can be helpful in selecting at-risk subjects. In 1995, the ALFEDIAM recommended screening for SMI in asymptomatic diabetics presenting one of the following features: an associated vascular co-factor, age over 60 years, nephropathy, arteriopathy of the lower limbs [1]. Later application of these recommendations in several French studies enabled discovery of SMI in only 18 to 30% of the screened populations and discovery of coronary artery disease in only 10% [39, 42]. The insufficient selectivity of these earlier recommendations thus led the expert group to add further selection criteria for asymptomatic diabetics who should be included in screening programs. The goal is to retain diabetics with a strong probability of having SMI, basing selection first on age and duration of diabetes, and then on other risk factors, and finally on the presence of peripheral vascular disease or nephropathy.

Table III

High-risk asymptomatic diabetics selected for SMI screening

- Patients with type 2 diabetes aged over 60 years with recognized diabetes for more than 10 years who present at least two of the following classical cardiovascular risk factors:
- Dyslipidemia with total cholesterol > 2.5 g/l and/or LDL-cholesterol > 1.6 g/l, HDL-cholesterol < 0.35 g/l, triglycerides > 2 g/l and/or lipid lowering medication*.
- Blood pressure > 140/90 mmHg or anti-hypertensive treatment.
- Active smoking or cessation for less than three years.
- Major cardiovascular event before the age of 60 years in a first-degree relative.
- Patients with type 1 diabetes aged over 45 years and treated for at least 15 years and presenting at least two other classical risk factors.
- Patients with type 1 or type 2 diabetes, irrespective of age or level of classical risk factors:
- Either lower limb arteriopathy and/or carotid atheroma.
- Or proteinuria.
- Patients with type 1 or type 2 diabetes, irrespective of age, with microalbuminuria and at least two other classical risk factors.
- Patients over 45 years of age resuming sports activities after sedentary lifestyle.

* prescribed for dyslipidemia and not for primary prevention alone.

Overall cardiovascular risk

The two major factors determining cardiovascular risk are age and duration of diabetes. The expert group set the threshold at ≥ 60 years. This corresponds to the mean age of patients included in the most recent primary or primo-secondary prevention trials of subjects with high cardiovascular risk [59, 90]. Beyond 60 years, the prevalence of SMI is high and can be found in 25% of the subjects [91]. Moreover, the predictive value of SMI for major cardiac events is much higher above the age of 60 years (33.3% *versus* 13.2% before 60 years) [40]. Gender is not a selection criterion because diabetes exposes women to the same cardiovascular risk as observed in men [92, 93]. Duration of diabetes, a factor which is obviously underestimated because diagnosis and therapeutic management of type 2 diabetes occur late after onset of the glycemic disorder, is also an important prognostic determinant. In both men and women whose diabetes has been known for more than 10 years, the relative risk of death from a coronary event is at least three times greater than in non-diabetic subjects of comparable age [93-95]. Age and duration of diabetes often being superimposed factors, the group defined the first selection criterion for inclusion in a screening program for SMI as age > 60 years or duration of diabetes > 10 years.

Further evaluation of the overall cardiovascular risk refines the selection process for identifying high-risk diabetics. Cumulating risk factors increases the cardiovascular risk and it is recognized that smoking, hypertension, and dyslipidemia contribute as much as the glycemic disorder to accelerated development of atherosclerosis. The MRFIT study demonstrated that the annual number of cardiovascular deaths per 10,000 subjects progressed from 20 deaths for diabetics with no associated risk factor to 80 for diabetics with at least two other risk factors [21]. Furthermore, these cofactors are often associated with diabetes. Prevalence of hypertension and/or dyslipidemia is much higher in diabetics than in non-diabetics of the same age [21, 96]. Although not listed as identified risk factors in the early large-scale epidemiology studies, occurrence of a major cardiovascular event before the age of 60 years in a first-degree relative should also be considered as an associated risk factor [3, 97].

Considering that the likelihood of a positive screening test should be high, the expert group proposed screening for SMI among asymptomatic diabetics aged over 60 years or presenting diabetes for more than 10 years who have at least two associated risk factors. This option falls within the category of class IIb recommendations (divergent opinion) described by the ACC/HA [4]. For information, these selection criteria lead to retaining asymptomatic diabetic subjects whose risk of a coronary event at 10 years is ≥ 30% in men and ≥ 24% in women [98]. For this selected population, the relative risk of a coronary event at 10 years is 2.3-fold higher than in diabetics with no other risk factor. It is clear that this measurement of risk, which issues from the Framingham

stratifications, is not systematically applicable to the French population of diabetics whose risk is lower. The most recent estimates of cardiovascular risk established by the European Society of Cardiology distinguished high- and low-risk countries. In the low-risk countries, including France, the risk of cardiovascular death at 10 years is 18% in diabetic men and 16% in diabetic women aged 60 years whose systolic pressure is 180 mmHg and whose total cholesterol level is ≥ 3 g/l [61]. This evaluation is only an estimate and must of course be modulated by the severity of each of the risk factors.

In type 1 diabetes, recommendations for SMI screening are based on the three following criteria: age over 45 years, diabetes treated for more than 15 years, and presence of at least two other risk factors. Finally, SMI screening is recommended in subjects who plan to resume intense sports activities after the age of 45 years [4].

Peripheral vascular disease and diabetic nephropathy

Clinical or infraclinical peripheral vascular disease is a factor of poor prognosis in the asymptomatic diabetic subject. Heart disease is the cause of death in the majority of subjects in this category [100]. The prevalence of scintigraphic SMI, which has exceeded 50% in certain series, is higher than in the diabetic subject without peripheral vascular disease [101, 102]. In the Cardiovascular Health Study of a population of 1,343 asymptomatic diabetic patients, the relative risks of death at six years, of a major coronary event, and of myocardial infarction in diabetics with peripheral vascular disease were respectively 1.5-, 1.99- and 1.93-fold that found in diabetics of the same age free of peripheral vascular disease [103]. In a French study, the risks of death and coronary events were 23% and 57.5% in patients with arteriopathy of the lower limbs and SMI with or without diabetes [104].

Microalbuminuria, observed in approximately 25% of all diabetics, is also a factor of poor prognosis which doubles the risk of early death [105]. The prognostic significance is the same as a 30% risk of death at 10 years measured from the Framingham Study. Association of SMI and microalbuminuria is particularly threatening in this situation since the risk of a major cardiovascular event at 5 years is 60% [106]. Since micoralbuminuria can be variable and sometimes corresponds to proteinuria, the severity of diabetic nephropathy and its prognostic significance are also highly variable. The level of albuminuria should be considered when screening for SMI.

Thus, whatever the patient's age or the duration of diabetes, it is recommended to search for SMI in patients with asymptomatic type 2 diabetes who exhibit vascular lesions involving the large extracardiac vessels with loss of at least two pulses on the lower limbs or a vascular murmur corresponding to ultrasound-evaluated stenosis of at least 30%, or isolated proteinuria or microalbuminuria (30-300 mg/24 hr or 20-200 mg/l observed in two urine samples) associated with two other classical risk factors.

Since there is no strong evidence of a relationship between SMI and retinopathy, alterations of the retina alone cannot be retained as a determinant element in the screening strategy.

Other factors and markers of cardiovascular risk

Other factors or markers of cardiovascular risk have also been described. Sufficient evidence has not however been accumulated to enable large-scale risk stratification. Markers of inflammation (fibrinogen and ultrasensitive CRP), blood glucose control by HbA_{1c} assay, and serum homocysteine are biological markers of risk but remain too variable for integration into a strategy of annual evaluation of risk in the asymptomatic diabetic subject. Functional or morphological anomalies such as acceleration of the pulse wave, exaggerated intima-media thickness, left ventricle hypertrophy, cardiac autonomic neuropathy, and coronary calcifications have real predictive value and are strong markers of diffuse atherosclerosis. They are associated with recognized risk factors and are generally found in patients who already have clinically patent arterial disease [36, 39, 41, 107-111]. Most of the complementary explorations allowing confirmation of these anomalies are not readily available for large-scale screening and are generally employed for sophisticated scientific research projects rather than clinical stratification of cardiovascular risk.

Screening tests

These tests are designed to search for SMI in the asymptomatic diabetics selected for screening and to make the diagnosis of coronary lesions. These examinations are also used to establish the prognosis and evaluate the risk of a vascular event.

Resting electrocardiogram

The predictive value of the resting electrocardiogram is very limited. Certain asymptomatic diabetic patients display a normal resting ECG despite the presence of multivessel coronary artery disease [112]; the incidence remains to be determined because coronary angiography is not indicated solely on the basis of this electrocardiographic situation. An annual ECG, as recommended earlier [5] cannot screen for SMI.

In the event of an abnormal resting ECG, the prognostic value is however well defined [113, 114] and should trigger further investigations.

– An abnormal tracing which is only minimally suggestive of SMI, for example intraventricular conduction disorders or anomalous repolarization evoking left ventricle hypertrophy, incite to search for myocardial ischemia using myocardial scintigraphy or stress electrocardiography; an exercise test is not useful here because the electrocardiographic result cannot be properly interpreted.

– An abnormal tracing strongly suggestive of myocardial ischemia, for example a Q wave signaling necrosis or a T

wave signaling subepicardial ischemia, noted on at least three contiguous leads and in the absence of electrical left ventricle hypertrophy, should lead to more invasive exploration. For the expert group, first-intention coronary angiography is warranted especially when the abnormal tracing occurs during the follow-up of a diabetic whose prior ECGs were normal.

The 24-h electrocardiogram is only minimally sensitive and non-specific and has not been included in the latest recommendations [1-3]. Screening for SMI depends on function tests.

Exercise tests

Although the sensitivity and specificity of the exercise test could be better, this examination has been validated for coronary stenosis screening of asymptomatic patients with a high myocardial risk (multivessel disease and stenosis of the left common coronary) who are able to perform the test and do not present repolarization anomalies on the resting ECG. In the diabetic, the small series which have been reported demonstrate sensitivity in the 50-67% range with a satisfactory specificity to the order of 75% with significant positive and especially negative predictive values (46% and 87% respectively) [115-117]. Although the exercise test can lack reliability in recognizing single-vessel disease with minimal myocardial risk, it is conversely a high-performance test for recognizing diabetic subjects free of major myocardial risk which would compromise their long-term prognosis.

In correctly selected populations, the exercise test is a low-cost exploration that can be used as an effective first-intention screening test. The results can be divided into the following categories.

– Negative maximal exercise test (heart rate reaching 200 bpm minus age). The negative predictive value is close to 90% and, consequently, the probability of severe coronary artery disease is very low [118]. This result is a marker of good long-term prognosis [117]. There is no need to perform a myocardial scintigraphy, which would only add minimal prognostic information [119].

– A strongly positive exercise test with ST depression > 2 mm for a threshold of < 75 W or presenting criteria of serious rhythmic or hemodynamic disorders. In this situation, the risk of coronary disease is high and coronary angiography is indicated.

– Minimally positive or doubtful exercise test. The positive predictive value of a positive exercise test conducted beyond 75 W with no criteria of gravity is weak, approximately 45% [115, 116]. In this situation, coronary angiography, which could only reveal a low myocardial risk in less than half of the patients is not recommended as a first-intention exploration. A second functional text (scintigraphy or echocardiogram) is however indicated to provide certain complementary prognostic information.

– Submaximal exercise test. The duration of the exercise test is a powerful predictive factor. The inability to exercise for more than 440 seconds is associated with a high risk of coronary events (116 Rubler). In diabetics with two other vascular risk factors who cannot perform an exercise test, the annual rate of major cardiac events is 6- to 7-fold higher than in the same subjects who are able to complete a negative test [116, 41]. Second-intention functional tests with drug-induced stress are strongly recommended in this situation.

Myocardial perfusion scintigraphy

Widely available in France, Technetium Myocardial Perfusion Scintigraphy (TMPS) provides optimal evaluation of coronary artery disease. Combined with an exercise and/or drug provocation test, TMPS can confirm the presence of myocardial ischemia, map the territory involved, and determine its severity; it can also be used to assess residual myocardial viability after myocardial infarction and, when performed with synchronized ECG, to evaluate global, segmentary, and left ventricular function.

In the diabetic subject, the diagnostic performance of TMPS is less satisfactory than in the non-diabetic subject. In the different series reported which used variable selection and evaluation criteria, the sensitivity of the test varies form 80-90% with a specificity of 75-90% and positive and negative predictive values of 50-87% and 85-95% respectively [36, 115, 120, 121]. The imperfect diagnostic results are related to the possible presence of left ventricle hypertrophy, endothelial dysfunction, or altered microcirculation which can induce perfusion disorders even in the absence of coronary stenosis.

The usefulness of TMPS results for its strong negative predictive value. In the general population of subjects exposed to vascular risk or presenting clinically patent coronary artery disease, the annual rate of death and/or myocardial infarction is less than 1% when the TMPS is normal [122-124]. The prognostic value of TMPS is also proven in the diabetic population (with or without symptoms). At two years, the rate of major cardiac events was correlated with the TMPS results in a large North American series recruiting 1,271 diabetics: the annual risk was 1-2% when the test was normal and 3-4% when the test was weakly positive but 7% when the test was strongly positive [125]. TMPS also provides strong discrimination in the asymptomatic diabetic population. At five years, the rate of cardiac events was significantly higher when the TMPS was abnormal (19.2% *versus* 1.9%) in a recent series of 735 diabetic patients free of clinical signs of coronary artery disease [126]. At three years, the risk of major cardiac events in another series of 180 asymptomatic diabetics was 3, 10, and 31% for a normal, weakly positive, or strongly positive TMPS respectively [127].

TMPS provides quantitative and qualitative information. Abnormal perfusion involving more than 20% of the left ventricle mass is highly predictive of a major cardiovascular event [41, 123]. Thus the TMPS is considered abnormal when the perfusion disorder involves at least 10% of the left ventricle mass. Finally, the presence of a reversible defect is preferentially associated with significantly increased risk of a cardiovascular event and the presence of an irreversible defect is predictive of a high risk of cardiac death [128].

Summarizing, in 80 to 85% of asymptomatic diabetics with other cardiovascular risk factors, a normal or subnormal (perfusion disorder involving less than 10% of the left ventricle mass) TMPS can confirm the absence of coronary artery disease amendable by revascularization and has a good negative predictive value close to 95% for occurrence of major cardiac events at two years. Conversely, a perfusion anomaly involving more than 10% of the left ventricle mass is associated with a 3- to 7-fold greater cardiovascular risk [125, 126]. Thus coronary angiography can be recommended after a positive or weakly positive TMPS if more than 10% of the left myocardial mass is involved in the perfusion disorder.

The excellent negative predictive value of TMPS takes into account the rare false negatives observed in some patients who have what is termed a "balanced" triple-vessel disease. Study of pulmonary isotope uptake together with an analysis of the left ventricle dilatation and function during exercise can in general detect these relatively exceptional cases of false negatives [129-131]. Inversely, a left bundle branch block can produce a false positive exploration. In this situation, a dipyridamole provocation test enables better performance than the exercise provocation test and stress echocardiography is more discriminating than TMPS [132, 133].

Stress echocardiography

A more recent development, stress echocardiography, explores segmentary systolic kinetics. The drug-induced stress is generally triggered with high-dose dobutamine during this second-intention exploration in patients unable to perform an exercise test or who had a doubtful test. Performed by an experimented operator, stress echocardiography presents an interpretation problem in 5-10% of the cases due to poor echogenicity in certain subjects.

The diagnostic performance of the test is satisfactory. In a series of 55 asymptomatic diabetics who underwent coronary angiography due to an abnormal stress echocardiography, the sensitivity of the method reached 81% for a specificity of 85% and 82% diagnostic precision [134]. The prognostic value of stress echocardiography is also satisfactory [135]. A 3-year follow-up of a population of 563 asymptomatic diabetics demonstrated a significant difference in the rate of major cardiac events to the order of 2% after a negative stress echocardiography and 12% after a positive stress echocardiography [136].

Although few studies have been conducted, stress echocardiography appears to provide diagnostic performance and prognostic value equivalent to TMPS. The choice between these two second-intention functional explorations depends on the patient's echocardiographic characteristics, operator experience, and technical availability.

Screening cost

The following cost schedule is applied by the French Health Insurance Fund (schedule codes in parenthesis) for the different examinations:
– exercise test (K40): 76.8€,
– exercise TMPS plus redistribution (Zn255 + radioactive product 225 + K40): 520.05€,
– dipyridamole TMPS plus redistribution (Zn225 + radioactive product 225 + K8.5): 459.57€,
– transthoracic echocardiography (K50): 94.5€,
– coronary angiography plus ventriculography (K150 + Z300): 687€,
– the relationship between exploration costs and therapeutic benefit has not been established because a detailed medico-economic analysis of SMI screening has not been performed to date. Nevertheless, the cost/effectiveness ratio of strategies based on scintigraphy appears to be better than that of strategies centered on coronary angiography indicated because of doubtful exercise test results [137]. The cost of screening cannot be the decisive factor but should be taken into consideration in the context of large-scale screening.

Screening and follow-up strategy (Table IV)

An annual check-up for the asymptomatic diabetic subject includes an attentive physical examination and a resting ECG. Laboratory tests search for lipid disorders and evaluate renal function. Together, these results allow defining the overall cardiovascular risk for each diabetic subject and orient the screening strategy. These clinical findings also enable recognizing subjects with patent peripheral arterial disease and identifying rare cases where the electrocardiographic results indicate probable coronary artery disease.

History taking must be conducted with care in order to confirm the absence of symptoms. Exercise-induced angina as well as claudication and angina-equivalent manifestations (thoracoabdominal pain and dyspnea) must be clearly ruled out. Their presence, particularly if recent and exercise-related,

Table IV

– Discovery of a formally described type of ischemia on the resting ECG warrants further exploration with first-intention coronary angiography.
– An exercise test constitutes a first-intention screening examination.
– TMPS and stress echocardiography are to be performed in the following circumstances:
  – Weakly positive exercise test conducted beyond 75 W.
  – Doubtful exercise test
  – Negative very submaximal exercise test lasting less than 440 seconds.
  – Incapacity for exercise.
  – Invalidating arteriopathy of the lower limbs.
  – Non-ischemic anomalies on the resting ECG (complete LBBB, WPW, electrostimulation, ST depression > 1 mm at rest [4, 99]).

should, depending on the clinical presentation, lead to further extracardiac explorations and/or search for myocardial ischemia. A minute physical examination of the clinically assessable arteries is necessary. Since the absence of pedal pulses can be a normal finding, the diagnosis of lower limb arteriography is based on absence of at least two distal pulses including at least one posterior tibial pulse. Determination of the systolic pressure index, by measuring the blood pressure from the arm and the ankle, lacks specificity in diabetic patients because of the possibility of a mediacalcinosis. Discovery of a vascular murmur, particularly at the cervical level, requires ultrasound confirmation to determine its atheromatous nature. Blood pressure should be measured in optimal conditions with, if needed, a second measurement 24 hours later. After this annual clinical, biological, and electocardiographic check-up, three situations can be described based on the level of cardiovascular risk and the ECG data *(Fig. 1)*.

Low cardiovascular risk

Further search for SMI is not indicated, but the cardiovascular risk may change and should be re-evaluated annually. Patients with a low cardiovascular risk should undergo an annual check-up in order to re-evaluate prognosis and search for new risk factors as well as to identify insidious recent developments related to peripheral arterial disease and/or an ECG anomaly.

High cardiovascular risk (Table III, Fig. 2)

It is recommended to search for SMI. If the resting ECG is normal, an exercise test should be conducted to guide further management [138]. A negative maximal exercise test is in favor of good prognosis; an annual check-up is indicated and possibly a new functional evaluation three years later. A strongly positive exercise test with a threshold under 75 W warrants prescription of a coronary angiography due to the high probability of underlying coronary artery disease. In the event of a doubtful exercise test, which is submaximal or weakly positive (see chapter on explorations), or the presence of nonspecific repolarization disorders on the resting ECG, the functional exploration should be completed with TMPS or stress echocardiography. The choice between these two explorations is essentially guided by the technical facilities available and operator experience [139]. Coronary angiography is indicated if one of these explorations is positive.

Ischemia on the resting ECG

Irrespective of the risk level or the results of the physical examination, the presence of an ischemic disorder on the resting ECG, a Q wave signaling necrosis and/or negative T wave indicating subepicardial ischemia on at least three contiguous leads, is indicative of the need to discuss the usefulness of coronary angiography if electrical left ventricle hypertrophy is absent. Although there remains some controversy concerning the indication for coronary angiography after symptomatic non-complicated myocardial infarction (class II indication in the SFC guidelines) [140], the expert group recommends this exploration for asymptomatic diabetics who present an ischemic disorder on the resting ECG. In this functional situation, the advent of silent electrocardiographic anomalies formally identified as signs of ischemia cannot affirm the stabil-

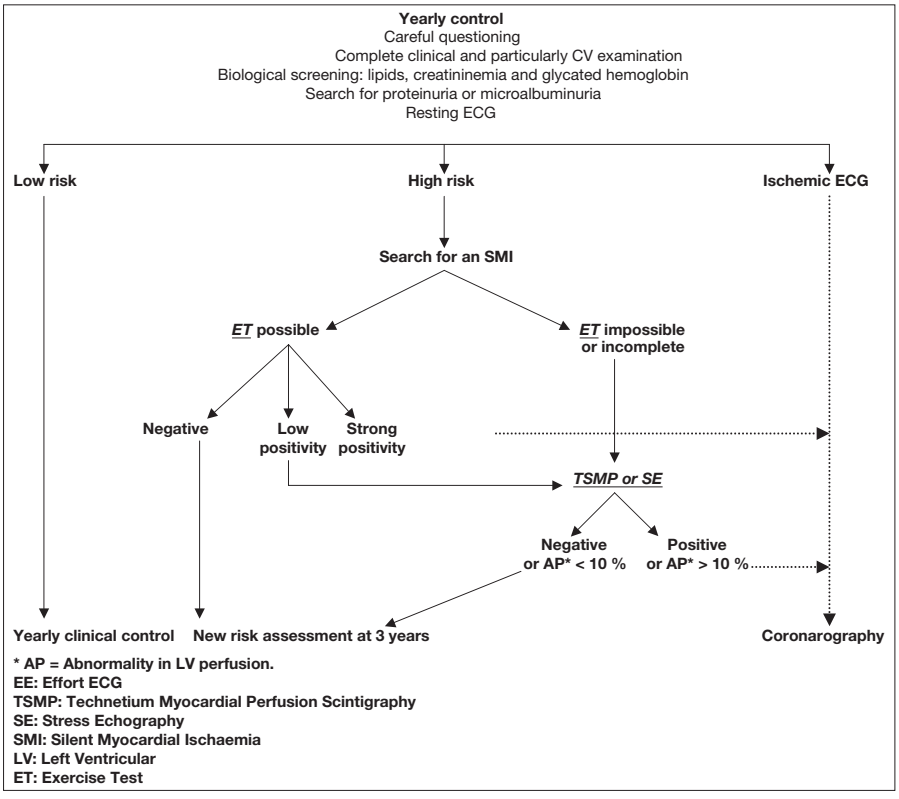

Figure 1

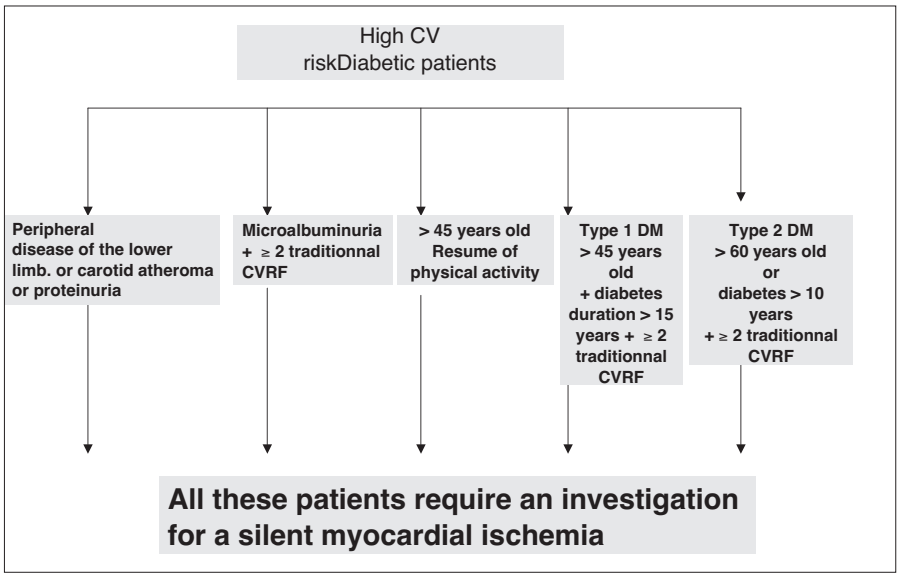

Figure 2

ity of the underlying coronaropathy and constitute an argument in favor of its progression. The probability the large epicardial vessels are involved is high. Angiography can thus enable recognizing lesions causing a high cardiovascular risk and guide revascularization interventions. The risk of coronary angiography conducted under conditions of proper hydration and minimal use of contrast agents is low.

Irrespective of the orientation provided by the initial stratification, patients should undergo an annual check-up for physical examination, laboratory tests, and electrocardiogram. There are no elements available to the expert group enabling a definition of an age limit above which screening for SMI is no longer indicated for high-risk asymptomatic diabetic subjects. If such a limit does exist, it will be defined on an individual basis taking into consideration the physiological age.

Conclusions

Ideally, the screening strategy for SMI should enable identifying subjects whose cardiovascular risk could be compensated for by an at least equivalent therapeutic benefit. The relationship between the measured risk and the expected benefit has not been established. In more practical terms, screening is essentially designed to identify asymptomatic diabetic subjects who might present angiographically significant coronary lesions, specifically multivessel or left common coronary stenosis, for which revascularization interventions have proven efficacy.

More restrictive than the preceding, these guidelines are based on uncertainties. They attempt to resolve the need for efficacy and sobriety by screening the subjects most at risk and by using the most appropriate examinations, thus avoiding useless research. Although they may be ignored and although new, equally uncertain, protocols may have to be drawn-up, these recommendations must be assessed in depth within the framework of a large prospective registry regrouping Diabetologists and Cardiologists. The observations in such a registry, enriched by the supply of new investigational methods such as non-invasive angiography and the development of new, validated, medicinal or interventional means of treatment, will permit the updating of these guidelines on far more solid bases.

References

1. Passa Ph, Drouin P, Issa-Sayegh M, *et al.* Coronaires et diabète. Recommandations de l'Alfediam. Diabetes Metab, 1995, 21, 446-51.
2. American Diabetes Association. Consensus development conference on the diagnosis of coronary artery disease in people with diabetes. Diabetes Care, 1998, 21, 1551-9.
3. Grundy SM, Howard B, Smith S *et al.* Prevention conference VI. Diabetes and cardiovascular disease. Circulation, 2002, 105, 2231-9.
4. Gibbons RJ, Balady GJ, Beasley JW, *et al.* ACC/AHA guidelines for exercice testing. JACC, 1997, 30, 260-315.
5. Suivi du patient diabétique de type 2 à l'exclusion du suivi des complications. Recommandations ANAES. Diabetes Metab, 1999, 25 (Suppl.2), 1-64.
6. American Diabetes Association. Report of the expert committee on the diagnosis and classification of diabetes mellitus. Diabetes Care, 1998, 21 (Suppl), S5-19.
7. SaydahSH, Loria CM, Eberhardt MS, *et al.* Subclinical states of glucose intolerance and risk of death in US. Diabetes Care, 2001, 24, 447-53.
8. Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in adults. Executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in adults (adult treatment panel III). JAMA, 2001, 285, 2486-97.
9. The European Group for the Study of Insulin Resistance (EGIR). Frequency of the WHO metabolic syndrome in European cohorts, and an alternative definition of an insulin resistance syndrome. Diabetes Metab, 2002, 28, 364-76.
10. King H, Aubert RE, Herman WH. Global burden of diabetes, 1995-2025: prevalence, numerical estimates and projection. Diabetes Care, 1998, 21, 1414-31.

11. Saydah SH, Eberhardt MS, Loria CM, Brancati FL. Age and the burden of death attributable to diabetes in the United States. Am J Epidemiol, 2002, 156, 714-9.

12. Gu K, Cowie CC, Harris MI. Mortality in adults with and without diabetes in a national cohort of the US population, 1971-1993. Diabetes Care, 1998, 21, 1138-45.

13. Grundy SM, BenjaminIJ, Burke GL, *et al.* Diabetes and cardiovascular disease: a statement for healthcare professionals from the American Heart Association. Circulation, 1999, 100, 1134-46.

14. American Diabetes Association. Consensus statement: role of cardiovascular risk factors in prevention and treatment of macrovascular disease in diabetes. Diabetes Care, 1993, 19 (2 Suppl), 72-8.

15. Melchior T, Kober L, Madsen CR, *et al.* Accelerating impact of diabetes mellitus on mortality in the years following an acute myocardial infarction. TRACE Study Group. Trandolapril Cardiac Evaluation. Eur Heat J, 1999, 20, 973-8.

16. Cosson E, Guimfack M, Paries J, *et al.* Prognosis for coronary stenoses in patients with diabetes and myocardial ischemia. Diabetes Care, 2003, 26, 1313-4.

17. Kip KE, Faxon DP, Detre KM, *et al.* Coronary angioplasty in diabetic patients. The National Heart, Lung and Blood Institute percutaneous transluminal coronary angioplasty registry. Circulation, 1996, 94, 1818-25.

18. Chen J, Radfort MJ, Wang Y, Krumholz HM. Care and outcome of elderly patients with acute myocardial infarction by physician specialty: the effects of comorbidity and functional limitations. Am J Med, 2000, 108, 460-9.

19. Tauber G, Winkelmann BR, Schleifer T, *et al.* Prevalence, predictors, and consequences of unrecognized diabetes mellitus in 3266 patients scheduled for coronary angiography. Am Heart J, 2003, 145, 285-9.

20. Kannel WB, Mc Gee DL. Diabetes and cardiovascular disease. The Framingham study. JAMA, 1979, 241.

21. Stamler J, Vaccaro O, Neaton JD, Wentworth D. Diabetes, other risk factors, and 12-years cardiovascular mortality for men screened in the multiple risk factor intervention trial. Diabetes Care, 1993, 16, 434-44.

22. Haffner SM, Lehto S, Rönnemaa T, *et al.* Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. N Engl J Med, 1998, 339, 229-34.

23. Evans JMM, Wang J, Morris AD. Comparison of cardiovascular risk between patients with type 2 diabetes and those who had had a myocardial infarction: cross sectional and cohort study. B Med J, 2002, 324, 939-42.

24. Becker A, Bos G, de Vegt F, *et al.* Cardiovascular events in type 2 diabetes: comparison with nondiabetic individuals without and with prior cardiovascular disease. 10-year follow-up of the Hoorn Study. Eur Heart J, 2003, 24,1406-13.

25. Vlietstra RE, Kronmal RA, Lie JT, *et al.* Factors affecting the extend and severity of coronary artery disease in patients enrolled in the coronary artery surgery study. Atherosclerosis, 1982, 2, 208-15.

26. Goraya TY, Leibson CL, Palumbo PJ, *et al.* Coronary atherosclerosis in diabetes mellitus: a population-based autopsy study. J Am Coll Cardiol, 2002, 40, 946-53.

27. Williams SB, Cusco JA, Roddy MA, *et al.* Impaired nitric oxide-mediated vasodilatation in no-insulin-dependant diabetes. J Am Coll Cardiol, 1996, 27, 567-74.

28. Knobler H, Savion N, Shenkman, *et al.* Shear-induced platelet adhesion and aggregation on subendothelium are increased in diabetic patients. Throm Res, 1998, 90, 181-90.

29. Sobel BE, Woodcock-Mitchell J, Schneider DJ, *et al.* Increased plasminogen activator inhibitor type 1 in coronary artery atherectomy specimens from type 2 diabetes compared with nondiabetic patients: a potential factor predisposing to thrombosis and its persistence. Circulation, 1998, 97, 2213-21.

30. Nitenberg A, Ledoux S, Valensi P, *et al.* Impairment of coronary microvascular dilatation in response to pressor-induced sympathetic stimulation in type 2 diabetic patients with abnormal stress thallium imaging. Diabetes, 2001, 50, 1180-5.

31. Maser RE, Mitchell BD, Vinik AI, *et al.* The association between cardiovascular autonomic neuropathy and mortality in individuals with diabetes: a meta-analysis. Diabetes Care, 2003, 26, 1895-901.

32. Cohn PF. Should silent ischemia be treated in asymptomatic individuals? Circulation, 1990, 82(Suppl II), 149-54.

33. Koïstinen MJ. Prevalence of asymptomatic myocardial ischemia in diabetics subjects. Br Med J, 1990, 301, 92-5.

34. Langer A, Freeman MR, Josse RG, *et al.* Detection of myocardial ischemia in diabetes mellitus. Am J Cardiol, 1991, 67, 1073-8.

35. Milan study on atherosclerosis and diabetes (MiSAD) group. Prevalence of unrecognized silent myocardial ischemia and its association with atherosclerotic risks factors in noninsulin-dependent diabetes mellitus. Am J Cardiol, 1997, 79, 134-9.

36. Valensi P, Sachs RN, Lormeau B, *et al.* Silent myocardial ischemia and left ventricular hypertrophy in diabetic patients. Diabetes Metab, 1997, 23, 409-16.

37. Janand-Delenne B, Savin B, Habib G, *et al.* Silent myocardial ischemia in patients with diabetes. Who to screen. Diabetes Care, 1999, 22, 1396-400.

38. Weiner DA, Ryan TJ, Parsons L, *et al.* Significance of silent myocardial ischemia during exercise testing in patients with diabetes mellitus. A report from coronary artery surgery study (CASS) registry. Am J Cardiol, 1991, 68, 729-34.

39. Valensi P, Sachs RN, Harfouche B, *et al.* Predictive value of cardiac autonomic neuropathy in diabetic patients with or without silent myocardial ischemia. Diabetes Care, 2001, 24, 339-43.

40. Valensi P. Predictive value of silent myocardial ischemia in diabetic patients. Influence of age. Diabetologia, 2000, 43 (Suppl 1), A61.

41. Vanzetto G, Halimi S, Hammoud T *et al.* Prediction of cardiovascular events clinically selected high-risk NIDDM patients. Diabetes Care, 1999, 22, 19-26.

42. Janand-Delenne B, Labastie N, Savin B, *et al.* Poor prognosis of silent myocardial ischemia: a two years follow-up of 203 diabetic patients. Diabetologia, 2000, 43, suppl 1.L.

43. Mark DB, Nelson CL, Califf R, *et al.* Continuing evolution of therapy for coronary artery disease. Initial results from era of coronary angioplasty. Circulation, 1994, 89, 2015-25.

44. Mock MB, Rinqvist I, Fischer L, *et al.* Survival of medically treated patients in the Coronary Artery Surgery Study (CASS) Registry. Circulation, 1982, 66, 562-8.

45. Murphy ML, Hultgren HN, Detre K, *et al.* Treatment of chronic stable angina. A preliminary report of survival data of the randomized Veterans Administration Cooperative Study. N Engl J Med , 1977, 297, 621-7.

46. Fuster V, Badimon JJ, Chesebro JH. The pathogenesis of coronary artery disease and the acute coronary syndromes. N engl J Med, 1992, 326, 242-50, 310-8.

47. Falk E, Shah P, Fuster V. Coronary plaque disruption. Circulation, 1995, 92, 657-71.

48. Libby P. Current concepts of the pathogenesis of the acute coronary syndromes. Circulation, 2001, 104, 365-72.

49. Davies MJ. The composition of coronary artery plaque. N Engl J Med, 1997, 336, 1312-3.

50. Little WC, Constantinescu M, Robert J, *et al.* Can coronary angiography predict the site of a subsequent myocardial infarction in patients with mild-to-moderate coronary artery disease? Circulation, 1988, 78, 1157-66.

51. Ojio S, Takatsu H, Tanaka T, *et al.* Considerable time from the onset of plaque rupture and/or thrombi until the onset of acute myocardial infarction in humans. Circulation, 2000, 102, 2063-9.

52. Varnava AM, Mills PG, Davies MJ. Relationship between coronary artery remodeling and plaque vulnerability. Circulation, 2002, 105, 939-43.

53. Rioufol G, Finet G, Ginon I, *et al.* Multiple atherosclerotic plaque rupture in acute coronary syndromes; a three-vessels intravascular ultrasound study. Circulation, 2002, 106, 804-8.

54. Knatterud GL, Bourassa MG, Pepine CJ, *et al.* Effects of treatment strategies to suppress ischemia in patients with coronary artery disease: 12-week results of the Asymptomatic Cardiac Ischemia Pilot (ACIP) study. J Am Coll Cardiol, 1994, 24, 11-20. Erratum in: J Am Coll Cardiol, 1995, 26, 842.

55. Jonas M, Reicher-Reiss H, Boyko V, *et al.* Usefulness of beta-blocker therapy in patients with non-insulin-dependent diabetes mellitus and coronary artery disease. Am J Cardiol, 1996, 77, 1273-7.

56. Kjekshus J, Gilpin E, Cali G, *et al.* Diabetic patients and beta-blockers after acute myocardial infarction. Eur Heart J, 1990, 11, 43-50.

57. Pyörälä K, persen TR, Kjeksus J, *et al.* Cholesterol lowering with simvastatin improves prognosis of diabetic patients with coronary artery disease: subgroup analysis of the Scandinavian simvastatin survival study. Diabetes Care, 1997, 20, 614-20.

58. Sacks FM, Tonkin AM, Craven T, *et al.* Coronary heart disease in patients with mow LDL-Clolesterol. Benefit of pravastatin in diabetics and enhanced role for HDL-Cholesterol and triglycerides as risk factors. Circulation, 2002, 105, 1424-8.

59. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5,963 people with diabetes: a randomized placebo-controlled study. Lancet, 2003, 361, 2005-16.

60. Rubins HB, Robins SJ, Collins D, *et al.* Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high density lipoprotein cholesterol. N Engl J Med, 1999, 341, 410-8.

61. Conroy RM, Piörälä K, Fitzgerald AP, *et al.* Estimation of ten-years risk of fatal cardiovascular disease in Europe: the SCORE Project. Eur Heart J, 2003, 24, 897-1003.

62. UK Prospective Diabetes Study (UKPDS). Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. BMJ, 1998, 317, 703-13 (Erratum BMJ, 1999, 318, 29).

63. Hansson L, Zanchetti A, Carruthers SG, *et al.* Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. Lancet, 1998, 351, 1755-62.

64. Chobanian AV, Bakris GL, Black HR, *et al.* The seventh report of the joint committee on prevention, detection, evaluation and treatment of high blood pressure. JNC 7 report. JAMA, 2003, 289, 2560-72.

65. American Diabetes Association: Standards of medical care for patients with diabetes mellitus (Position statement). Diabetes Care, 1998, (Suppl. 1), S23-S31.

66. Zuanetti G, Latini R, Maggioni AP, *et al.* Effetc of the ACE inhibitor lisinopril on mortality in diabetic patients with acute myocardial infarction. Circulation, 1997, 96, 4239-45.

67. Heart outcomes prevention evaluation (HOPE) study investigators. Effect of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. Lancet, 2000, 355, 253-9.

68. The European trial on reduction of cardiac events with perindopril in stable coronary artery disease investigators. Efficacy of perindopril in reduction of cardiovascular events in patients with stable coronary artery disease: randomised double-blind, placebo-controlled, multicenter trial (the EUROPA study). Lancet published online September 1, 2003.

69. Antiplatelet trialist's collaboration. Collaborative overview of randomized trails of antiplatelet therapy I. Prevention of death, myocardial infarction and stroke by prolonged antiplatelet therapy in various categories of patients. BMJ, 1994, 308, 71-2, 81-106.

70. ETDRSInvestigators. Aspirin effects on mortality and morbidity in patients with diabetes mellitus. JAMA, 1992, 268, 1292-300.

71. Bhatt DL, Marso SP, Hirsch AT, *et al.* Amplified benefit of clopidogrel *versus* aspirin in patients with diabetes mellitus. Am J Cardiol, 2002, 90, 625-7.

72. Malmberg K, Ryden L, Eferdic S, *et al.* Randomized trial of insulin-glucose infusion followed by subcutaneous insulin treatment in diabetes patients with acute myocardial infarction (DIGAMI Study); effect on mortality at 1 year. J Am Coll Cardiol, 1995, 26, 57-65.

73. Turner RC, Millns H, Neil HAW, *et al.* Risk factors for coronary artery disease in non-insulin dependent diabetes mellitus: United Kingdom Prospective Diabetes Study (UKPDS: 23). BMJ, 1998, 316, 823-8.

74. Okin PM, Prineas RJ, Grandits G, *et al.* Heart rate adjustment of exercise-induced ST-segment depression identifies men who benefit from a risk factor reduction program. Circulation, 1997, 96, 2899-904.

75. Gaede P, Vedel P, Larsen N, *et al.* Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. N Engl J Med, 2003, 348, 383-93.

76. Yusuf S, Zucher D, Peduzzi P, *et al.* Effect of coronary artery bypass graft surgery on survival: overview of 10-years results from randomised trials by the coronary artery bypass trialist collaboration. Lancet, 1994, 344, 1116-21.

77. Blumenthal RS, Cohn G, Schulman SP. Medical therapy *versus* coronary angioplasty in stable coronary artery disease: a critical review of the literature. J Am Coll Cardiol, 2000, 36, 668-73.

78. Rogers WJ, Bourassa MG, Andrews TC, *et al.* Asymptomatic cardiac ischemia pilot (ACIP) study: Outcome at 1 year for patients with asymptomatic cardiac ischemia randomized to medical therapy or revascularisation. JACC, 1995, 26, 594-605.

79. Mak K, Faxon DP. Clinical studies on coronary revascularization in patients with type 2 diabetes. Eur Heart J, 2003, 24, 1087-103.

80. BARI investigators. Seven-years outcome in the Bypass Angioplasty revascularization Investigation (BARI) by treatment and diabetic status. J Am Coll Cardiol, 2000, 35, 1122-9.

81. Abizaid A, Costa MA, Centemero M, *et al.* Clinical and economic impact of diabetes mellitus on percutaneous and surgical treatment of multivessel coronary disease patients. Insight from the Arterial Revascularization Therapy Study (ARTS) trial. Circulation, 2001, 104, 533-8.

82. Feit F, Brooks MM, Sopko, G, *et al.* Long-term clinical outcome in the Bypass Angioplasty Revascularization Investigation Registry. Circulation, 2000, 101, 2795-802.

83. Van Belle E, Abolmaali K, Bauters C, *et al.* Restenosis, late vessel occlusion and left ventricular function six months after balloon angioplasty in diabetic patients. J Am Coll Cardiol, 1999, 34, 476-85.

84. Elezi S, Kastrati A, Pache J, *et al.* Diabetes mellitus and the clinical and angiographic outcome after coronary stent placement. J Am Coll Cardiol, 1998, 32, 1866-73.

85. Van Belle E, Bauters C, Hubert E, *et al.* Restenosis rate in diabetic patients. A comparison of coronary stenting and balloon angioplasty in native coronary vessels. Circulation, 1997, 96, 1454-60.

86. Marso SP, Lincoff AM, Ellis SG, *et al.* Optimizing the percutaneous interventional outcomes for patients with diabetes mellitus. Results of EPISTENT (Evaluation of Platelet IIb/IIIa Inhibitor for Stenting Trial) Diabetic substudy. Circulation, 1999, 100, 2477-84.

87. Bhatt DL, Marso SP, Lincoff AM, *et al.* Abciximab reduces mortality in diabetics following percutaneous coronary intervention. J Am Coll Cardiol, 2000, 15, 922-8.

88. Morice MC, Serruys PW, Sousa JE, *et al.* A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. N Engl J Med, 2002, 346, 1773-8.

89. Moses JW, Leon MB, Popma JL, *et al.* Sirolimus-eluting stent *versus* standard stent in patients with stenosis in a native coronary artery. N Engl J Med, 2003, 349, 1315-23.

90. Sever PS, Dahlof B, Poulter NR, *et al.* ASCOT investigators. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA); a randomised controlled trial. Lancet, 2003, 361, 1149-58.

91. Inoguchi T, Yamashita T, Umeda F, *et al.* High Incidence of silent myocardial ischemia in elderly patients with non insulin-dependent diabetes mellitus. Diabetes Res clin Pract, 2000, 47, 37-44.

92. Becker A, Bos G, de Vegt F, *et al.* Cardiovascular events in type 2 diabetes: comparison with non-diabetic individuals without and with prior cardiovascular disease. Eur Heart J, 2003, 24, 1406-13.

93. Hu Fb, Stampfer MJ, Solomon CG, *et al.* The impact of diabetes mellitus on mortality from all causes and coronary heart disease in women: 20 years of follow-up. Arch Intern Med, 2001, 161, 1717-23.

94. Faglia E, Favales F, Calia P, *et al.* Cardiac events in 735 type 2 diabetic patients who underwent screening for unknown asymptomatic coronary heart disease: 5-year follow-up report from Milan Study on atherosclerosis and diabetes (MiSAD). Diabetes Care, 2002, 25, 2032-6.

95. Cho E, Rimm EB, Stampfer MJ, *et al.* The impact of diabetes mellitus and prior myocardial infarction on mortality from all causes and from coronary heart disease in men. J Am Coll Cardiol, 2002, 40, 954-60.

96. Detournay B, Vauzelle-Kervroedan F, Charles MA, *et al.* Epidemiology, management and costs of type 2 diabetes in France in 1998. Diabetes Metab, 1999, 25, 356-65.

97. Myers RH, Kiely DK, Cupples LA, *et al.* Parental history is an independent risk factor for coronary artery disease. The Framingham study. Am Heart J, 1990, 120, 963-9.

98. Wilson PW, D'Agostino RB, Levy D, *et al.* Prediction of coronary heart disease using risk factor categories. Circulation, 1998, 97, 1837-47.

99. Gibbons RJ, Balady GJ, Bricker JT, *et al.* ACC/AHA 2002. Guideline update for exercise testing. Summary article. A report of American College of Cardiology/American Heart Association task force on practice guidelines (Committee to update the 1997 exercise testing guidelines). Circulation, 2002, 106, 1883-92.

100. Criqui MH, Langer RD, Fronek A, *et al.* Mortality over a period of 10 years in patients with peripheral arterial disease. N Engl J Med, 1992, 326, 381-6.

101. Nesto RW, Watson FS, Kowalchuk GJ, *et al.* Silent myocardial ischemia and infarction in diabetics with peripheral arterial disease: assessment by dipyridamole thallium-201 scintigraphy. Am Heart J 1990, 120, 1073-7.

102. Darbar D, Gillespie N, Main G, *et al.* Prediction of late cardiac events by dipyridamole thallium scintigraphy in patients with intermittent claudication and occult coronary artery disease. Am J Cardiol, 1996, 78, 736-40.

103. Kuller LH, Velentgas P, Barzilay J, *et al.* Diabetes mellitus. Subclinical cardiovascular disease and risk of incident of cardiovascular disease and all-cause mortality. Arterioscler Thromb Vasc Biol, 2000, 20, 823-9.

104. Ponsonnaille J, Fabry R, Chapou M, *et al.* Silent ischemic heart diseases in patients with peripheral arterial diseases. Screening and 5-year prognosis in a population of 418 patients. Arch Mal Cœur, 1991, 84, 1407-11.

105. Dinneen SF, Gerstein HC. The association of microalbuminuria and mortality in non-insulin-dependent diabetes mellitus: a systematic overview of the literature. Arch Intern Med, 1997, 157, 1413-8.

106. Rutter MK, Wahid ST, McComb JM, *et al.* Significance of silent ischemia and microalbuminuria in predicting coronary events in asymptomatic patients with type 2 diabetes. J Am Coll Cardiol, 2002, 40, 56-61.

107. Cruickshank K, Riste L, Anderson SG, *et al.* Aortic pulse-wave velocity and its relationship to mortality in diabetes and glucose intolerance. An integrated index of vascular function? Circulation, 2002, 106, 2085-90.

108. O'Leary DH, Joseph F, Polak JF, *et al.* For the cardiovascular health study collaborative group. Carotid artery intima media thickness as a risk factor for myocardial infarction and stroke in older adults. N Engl J Med, 1999, 340, 14-22.

109. Ridker PM, Buring JE, Cook NR, *et al.* C-Reactive protein, the metabolic syndrome, and risk of incident cardiovascular events. An 8-years follow-up of 14719 initially healthy American women. Circulation, 2003, 107, 391-7.

110. Maser Re, Mitchell BD, Vinik AI, *et al.* The association between cardiovascular autonomic neuropathy and mortality in individuals with diabetes: a meta-analysis. Diabetes Care, 2003, 26, 1895-901.

111. Hosoi M, Sato T, Yamagami K, *et al.* Impact of diabetes on coronary stenosis and coronary artery calcification detected by electron-beam computed tomography in symptomatic patients. Diabetes Care, 2002, 25, 696-701.

112. Paillole C, Ruiz J, Juliard JM, *et al.* Non-invasive identification of severe coronary artery disease in patients with long-standing diabetes mellitus. Eur J Med, 1992, 1, 464-8.

113. Scheidt-Nave C, Barrett-Connor E, Wingard DL. Resting electrocardiographic abnormalities suggestive of asymptomatic ischemic heart disease associated with non-insulin-dependent diabetes mellitus in a defined population. Circulation, 1990, 81, 899-906.

114. Kannel WB, Gordon T, Castelli WP. Electrocardiographic left ventricular hupertrophy and risk of coronary heart disease. The Framingham study. Ann Intern Med, 1970, 72, 813-22.

115. Paillole C, Ruiz J, Juliard JM, *et al.* Detection of coronary artery disease in diabetic patients. Diabetologia, 1995, 38, 726-31.

116. Rubler S, Gerber D, Reitano J, *et al.* Predictive value of clinical and exercise variable for detection of coronary artery disease in men with diabetes mellitus. Am J Cardiol, 1987, 59, 1310-3.

117. Gerson MC Khoury JC, Hertzberf VS, *et al.* Prediction of coronary artery disease in a population of insulin-requiring diabetic patients: results of an 8-years follow-up study. Am Heart J, 1988, 116, 820-6.

118. Koistinen MJ, Huikuri HV, Pirttiaho H, *et al.* Evaluation of exercise electrocardiography and thallium tomographic imaging in detecting asymptomatic coronary artery disease in diabetic patient. Br Heart J, 1990, 63, 7-11.

119. Cosson E, Paycha F, Paries J, *et al.* Selecting silent coronary stenosis with stratifying cardiac risk in patients with diabetes. ECG stress test or exercise myocardial scintigraphy. Diabetes Metab (in press).

120. Boudreau RJ, Strony JT, du Cret RP, *et al.* Perfusion thallium imaging of type 1 diabetes with end stage renal disease: comparison of oral and intravenous dipyridamole administration. Radiology, 1990, 175, 103-5.

121. Kumar R, Patel CD, Marwah A, *et al.* Detection of coronary artery disease by stress thallium scintigraphy in diabetic patients. Nucl Med Commun, 2001, 22, 287-9.

122. Machecourt J, Longere P, Fagret D, *et al.* Prognostic value of thallium-201 single-photon emission computed tomographic myocardial perfusion imaging according to extent of myocardial defect. J Am Coll Cardiol, 1994, 23, 1096-106.

123. Vanzetto G, Ormezzano O, Fagret D, Comet M, Denis B, Machecourt J. Long-term additive prognostic value of thallium-201 myocardial perfusion imaging over clinical and exercise stress test in low to intermediate risk patients: study in 1,137 patients with 6-year follow-up. Circulation, 1999, 100, 1521-7.

124. Hachamovitch R, Hayes S, Friedmann JD, *et al.* Determinants of risk and its temporal variation in patients with normal stress myocardial perfusion scans. Circulation, 2003, 41, 1329-40.

125. Kang X, Berman DS, Lewin HC, *et al.* Incremental prognostic value of myocardial perfusion single photon emission computed tomography in patients with diabetes mellitus. Am Heart J, 1999, 138, 1025-32.

126. Faglia E, Favales F, Calia P, *et al.* Cardiac events in 735 type 2 diabetic patients who underwent screening for unknown asymptomatic coronary heart disease: 5-year follow-up report from the Milan Study on Atherosclerosis and Diabetes (MiSAD). Diabetes Care, 2002, 25, 2032-6.

127. De Lorenzo A, Lima RS, Siqueira-Filho AG, Pantoja MR. Prevalence and prognostic value of perfusion defects detected by stress technetium-99m sestamibi myocardial perfusion SPECT in asymptomatic patients with diabetes mellitus and no known coronary artery disease. Am J Cardiol, 2002, 90, 827-32.

128. Giri S, Shaw LJ, Murthy DR. Impact of diabetes on the risk stratification using stress single-photon emission computed tomography myocardial perfusion imaging in patients with symptoms suggestive of coronary artery disease. Circulation, 2002, 105, 32-40.

129. Takeishi Y, Chiba J, Abe S, *et al.* Noninv asive identification of left main and three-vessel coronary artery disease by thallium-201 single photon emission computed tomography during adenosine infusion. Ann Nucl Med, 1994, 8, 1-7.

130. Romanens M, Gradel C, Saner H, *et al.* Comparison of 99mTc-sestamibi lung/heart ratio, transient ischaemic dilation and perfusion defect size for the identification of severe and extensive coronary artery disease. Eur J Nucl Med, 2001, 28, 907-10.

131. Lebtahi NE, Stauffer JC, Delaloye AB. Left bundle branch block and coronary artery disease: accuracy of dipyridamole thallium-201 single-photon emission computed tomography in patients with exercise anteroseptal perfusion defects. J Nucl Cardiol, 1997, 4, 266-73.

132. Tandogon I, Yetkin E, Yanik A, *et al.* Comparison of thallium-201 exercise SPECT and dobutamine stress echocardiography for diagnosis of coronary artery disease in patients with left bundle branch block. Int J Cardiovasc Imaging, 2001, 17, 339-45.

133. Elhendy A, van Domburg RT, Poldermans D, *et al.* Safety and feasibility of dobutamine-atropine stress echocardiography for the diagnosis of coronary artery disease in diabetic patients unable to perform an exercise stress test. Diabetes Care, 1998, 21, 1797-802.

134. Sozzi FB, Elhendy A, Roelandt JR, *et al.* Prognostic value of dobutamine stress echocardiography in patients with diabetes. Diabetes Care, 2003, 26, 1074-8.

135. Elhendy A, Arruda AM, Mahoney DW. Pronostic stratification of diabetic patient by exercise echocardiography. J Am Coll Cardol, 2001, 37, 1551-7.

136. Shaw LJ, Hachamovitch R, Berman DS, *et al.* The economic consequences of available diagnostic and prognostic strategies for the evaluation of stable angina patients: an observational assessment of the value of precatheterization ischemia. Economics of Noninvasive Diagnosis (END) Multicenter Study. J Am Coll Cardiol, 1999, 33, 661-9.

137. Gibbons RJ, Chatterjee K, Daley J, *et al.* ACC/AHA/ACP-ASIM guidelines for the management of patients with chronic stable angina: a report from the American College of Cardiology/American Heart Association task force on practce guidelines. J Am Coll Cardiol, 1999, 33, 2092-197 (Erratum, J Am Coll Cardio, 1999, 34, 314).

138. Schinkel AF, Bax JJ, Geleijnse ML, *et al.* Noninvasive evaluation of ischaemic heart disease: myocardiol perfusion imaging or stress echocardiography. Eur Heart J, 2003, 24, 789-800.

139. Delahaye F, Bory M, Cohen A, *et al.* Recommandations de la Société Française de Cardiologie concernant la prise en charge de l'infarctus du myocarde après la phase aiguë. Arch Mal Cœur, 2001, 94, 697-725.