DOI 10.51231/2667-9507-2021-001-01-60-74

Myocardial Ischemia and Diabetes Mellitus. Approaches and Recommendation

Puel J.[1], Valensi P.[2], Vanzetto G.[1], Lassmann-Vague V.[2], Monin J.-L.[1], Moulin P.[2], Ziccarelli C.[3], Mayaudon H.[2], Ovize M.[1], Bernard S.[2], Van Belle E.[1], Halimi S.[2]

[1]French Society of Cardiology, Paris, France

[2]Association for the study of diabetes and metabolic diseases, Paris, France

[3]National College of French Cardiologists, Paris, France

Abstract

The outlook epidemiological auguring an increase considerable the number of subjects with diabetes and cardiological problem during diabetes, and the recent progress registered in the explorations and the treatment of coronary are necessary for to continue research. Since long been recognized as a factor of risk vascular age, the diabetes can be regarded as a genuine vascular disease in because of the frequency and in the severity. The share growing, observed and expected, of the population of diabetics, whose prognosis life is dominated by the complication's coronary up the diabetes mellitus among the priorities of health public in France. The specific features of diabetic coronary artery disease, marked by the often-insidious nature of its development, place silent myocardial ischemia (IMS) and possible atheromatous involvement of the epicardial coronary artery trunks at the center of the diagnostic and therapeutic approach. The progress, drug and instrumentals, the treatment of the inadequacy coronary lead naturally to reconsider the treatment, and therefore the screening early to IMS in the aim of reducing the morbidity and the mortality heart of patients with diabetes.

KEY WORDS: treatment, new treatment approaches, clinical trials

Introduction

The interest prognostic and therapeutic potential of the identification of the crumb ischemyocardial in the diabetic symptom has not yet been the subject of extensive studies prospective multicentre enabling of to this day of the pipes to keep clear and formal, common to diabetics, cardiologists and general practitioners [1-5]. It is therefore in a field diagnostic and therapeutic still controversial and in the absence of evidence strong, that the group of work has attempted to bring the consensual answers to questions that control the search for a possible ischemic myocardium in a diabetic asymptomatic. Our goals were researches in this areal. Find a) the potential therapeutic benefit of an early diagnosis of IMS; b) the most appropriate examinations for carrying out this screening; c) the developments after the search for an IMS.

It is to go to work wearing specifically on the cohorts limited diabetics usually type 2 or from more extensive studies dedicated to coronary artery disease in which the diabetic does represent feel that a subgroup casual than the group of work has tried to write these recommendations. These codes of good practice not would know be formal and will be later the subject of evaluating prospective bringing the two disciplines. These recommendations are essentially on the diabetes of the type 2.

The diabetes mellitus is an entity defined by its phenotype biological marked by an upper glucose or equal to 1.26 g / L (7 mmol / L) observed twice after 8 hours of fasting in a subject apparently healthy. The current etiopathogenic classification distinguishes [6]:

- the diabetes of the type 1 response to a destruction of origin the most often autoimmune, the cells pancreatic officials usually a deficiency of insulin absolute.
  This diabetes affects preferentially in subjects aged of less than 40 years and requires the implementation in road early one insulin;
- the diabetes of the type 2, more frequent and affecting the subjects more aged, characterized by the association variable of a resistance to the action of insulin and a deficiency of insulin secretion;
- exceptionally, the diabetes knows other causes, genetic by default to the function of cells or of the action of insulin, pancreatic, endocrine, toxic and infectious.

This new classification also defines two clinical and biological situations likely to bring into play type 2 diabetes:

- hyperglycemia moderate close of intolerance to glucose, defined by a glyceryl crumb to fasting placed between 1.10 and 1.26 g / L which exposes also the risk vascular and can evolve to diabetes mellitus in 50% of cases about [7];
- the syndrome metabolic, into which fits typically the diabetes of the type 2, and which, according to the National Cholesterol Education Program [8, 9], is defined by the association of at least three of the following criteria: an abdominal obesity (waist circumference > 102 cm in man and 88 cm in the female), of triglycerides “1.5 g / L, an HDL cholesterol < 0.4 g / L in humans and 0.5 g / L at the woman and 135 mmHg for the systolic and” 85 mmHg for the diastolic.

The frequency of diabetes is in constant progression. The projections of the WHO pre see the doubling of the population of diabetics in 2025, notably by reason of the increase

of diabetes in the country by way of development [10] In France, today, the population of diabetics is estimated at 2 million and a half with a prevalence of 90% approximately of diabetes of the type 2. The number of diabetics undetected is estimated between 300 000 and 500 000 subjects, or 15 to 25% of all of the diabetic population. In addition, the number of individuals with abdominal adiposity excessive, conducive to the development of a diabetes of the type 2, is considered around 10 million.

Two to three times more frequent than in the subject not diabetic, [11] the complications cardiovascular make the prognosis of diabetes and contribute to shorten the expectation of life of a diabetic for 8 years for the subjects of 55 to 64 years [12]. The death of a subject with diabetes is of natural cardiovascular in approximately 65 to 80% of the cases [13,14]. The accidents heart, and more parcularly myocardial infarction (MI), are more common and more severe in the diabetic than in the non-diabetic [15,16]. After a procedure of myocardial revascularization, cardiac events are more numerous in the diabetic. In the register American of the NHLBI, the survival estimated at 9 years after an angioplasty coronary nary, by balloon the most often, is of 68% in the diabetics against 83.5% among non-diabetics [17]. The share of diabetic in the activity of the services of cardiology is growing. Their proportion in the population of patients hospitalized for MDI can reach 33% [18]. It is 20 to 30% in one of the coronary subjected to an exploration angiographic [19]. The diabetes is well for a long time recognized as a factor of risk cardiovascular sys – independent [20,21]. Classically, the coronary mortality of a non-coronary diabetic is identical to that of a non – diabetic coronary artery patient [22]. The most recent observations, although correcting this assertion by a less pessimistic conclusion, confirm well as the risk cardiovascular (RCV) of a diabetic is greater than that of a subject non – diabetic [23,24].

The specific anatomical, functional and biological are the severity of the coronary ropathie of diabetic. Although that aspect morphology of lesions will be no separate, infiltration parietal is more diffuse, more distal and more calcified in the subject diabetic as in evidenced the comments coronarographic [25] and as it confirms the findings autopsy [26]. The dysfunction endothelial, who participates in all the stages of the development of atherosclerosis, is worse in the diabetic by the hyperglyce – crumb and insulin resistance [27]. With the disorders of hemostasis related to platelet aggregability [28] and the imbalance in the balance fibrin-training-fibrinolysis [29] character – tics of diabetes, the dysfunction endothelial renders account of the evolution accelerated the process atheromatous in the diabetic. The disorders of hemostasis and the dysfunction endothelial contribute also to abnormalities in the microcirculation that, in the absence of a breach of trunks epicardial, can make account of IMS [30]. The neuropathy heart is common in diabetics and explains in large part the character often silent in ischemia myocardial [31].

Silent myocardial ischemia

The alteration transient of the perfusion myocardial as well as the disorder consecutive pro – visional of the function and of the activity of the muscle heart, developed in the absence of pain chest or of any equivalent angina, is a definition pathophysiologic theory of IMS, whose clinical assertion is naturally less formal. Under the circumstance's clinics, it is agreed to distinguish three kinds of IMS: Type 1 in the subjects asymptomatic without antecedent clinic of coronary artery disease; Type 2 in the patients asymptomatic with history of heart attack of myocardium; Type 3 in the coronary angina who also of episodes of IMS [32]. Clinically, the IMS to the type 1 is defined as an abnormal electrocardiographic (and/ or scintigraphy and /or echocardiography), silent and transient, observed at the occasion of a stress in the subjects which the electrocardiogram of rest is strictly normal.

The IMS of the type 1 is more frequently observed in the diabetic than in the diabetic non in a ratio of 2 to 6 according to the series [33]. In the diabetic, the prevalence IMS varies widely from 10 to 30% depending on the mode of pre-screening of individuals and according to the acuity of screening [34,35]. It is more frequent in diabetics with two other cardiovascular risk factors and can then be noted in a third of cases [36,37]. This great variability underscores the low rentability of a screening systematic of IMS in any diabetic and puts into light the need for a selection prior rigorous of patients to go to the assessment of the overall RRS each diabetic.

Premonitory of the occurrence of secondary cardiovascular events, IMS is a factor of poor prognosis [38]. In fact, in the studies devoted to the follow-up of diabetics, it appears that IMS is regularly associated with the risk of occurrence of a major coronary accident [39-42]. After 60 years, several studies have shown that the risk relating to occur later an event cardiac major is 3.2 times higher in the diabetic with an IMS that among the diabetic without IMS [40,42].

The correspondence between the IMS and the (or the) stenosis (s) coronary (s) angiographic (s) significant stage (s) is unclear and not compulsory. In fact, in the short series reported, coronary angiographic exploration of an IMS reveals the presence of one or more angiographic strictures equal to or greater than 70% in 30 to 60% of cases [36,42]. The alteration of the reserve coronary secondary to the microangiopathy intramyocardique, the disturbance of the vasomotor by dysfunction endothelial and the disorder of the hemostase can associate to render account of this discrepancy functional and angiographic in the diabetic. However, it seems that the prognosis of IMS is closely dependent on the existence or not of angiographic coronary stenosis. Indeed, two French studies have recently shown that the presence of significant stenosis is a strong predictor of major cardiac events at 2 and 3.5 years in patients with IMS, while patients with abnormal scintigraphy but without coronary stenosis have a prognosis similar to that of subjects without IMS [16,42]. The discovery of IMS justified, reasonable today, the research of coronary stenoses by the practice of a coronary angiography in the respect of the rules of own safety in this type of examination in a diabetic.

The severity of the prognosis Heart of diabetes should lead to take to load the diabetic asymptomatic in a logic of prevention secondary.

More frequent in the diabetic than in the non-diabetic, IMS is a factor of poor prognosis, promonitoire of the occurrence of events Cardiac major.

The prevalence of IMS is high when other vascular risk factors are associated with diabetes.

An IMS can appear without reaching the big trunks coronary epicardial. However, the prognosis of IMS is dependent on the presence of angiographic coronary stenosis.

The search of the IMS does should not be systematic in the diabetic. It should be guided by the assessment of the overall cardiovascular risk of each diabetic.

The discovery of an IMS justifies the practice of a coronary artery exploration while respecting the safety rules specific to diabetic patients.

By its high prevalence and its potential prognostic severity, IMS Center ‘s approach diagnosis and therapy in the diabetic symptoms. Point of encounter natural between the diabetologist and the cardiologist, IMS led to question first on the benefit therapeutic potential of a screening early, then on selecting suitable for diabetics at risk cardiovascular high under a such research of same as on the choice of examinations appropriate and finally on the strategies diagnosis and to follow the gaze of the results of this screening.

Stenosis and atheromatous lesion – current data

The relationship between on the one hand angiographic coronary stenosis greater than or equal to 70%, and on the other hand ischemia myocardial and the prognosis in the long term are long established. Prognostic index, defined from the follow large cohorts of patients anginal stable or asymptomatic, oppose, according to the severity of the infringement angiographic, the patients with low and high risk myocardial. If the risk of coronary mortality at 5 years is estimated at 7.5% for the monotrunk patient without involvement of the anterior ventricular, this same risk is evaluated at 40% for the intravascular coronary artery (obviously with an involvement of the anterior ventricular) [43,44]. These data angiographic and scalable have chaired the development of treatments of revascularization surgery and interventional [43-45].

In vivo, the progress of the exploration morphological, functional and organic of atheroma allow a better understanding of the evolution of the process atherosclerotic sclerotic. Discontinuous, the development of atherosclerosis combines the phases of stability and instability governed by the degree of vulnerability of lesions atheromatous. The plate atheromatous is the seat constant an activity histological and biochemical which involved either in the stable, or at the destabilizing. Rich in material lipid-cell and poorly contained by a fibrous cap slender, vulnerable lesions are threatened with instability and exposed to the risk of the cracking and to erosion with formation of a thrombus endoluminal more or less occlusive [46,47]. Multifactorial, the determinism of the instability of the plaque vulnerable based on of many mechanisms dent interdependent of natural mechanical (the burden of heart lipid-cell), biological (metalloproteases Teases), vasomotor (dysfunction endothelial), hemodynamics (strengths of shear) and inflammatory [48,49]. These factors of instability

of the plate atheromatous are exacerbated by the diabetes. There is no parallel between the qualitative character of the vulnerability of the plaque and the quantitative character of the angiographic stenosis.

Some comments coronarographic suggest that the plaque unstable, responsible sand of a syndrome coronary acute, will determine not of stenosis significant. In fact, coronary angiography, occasionally practiced before the establishment of an IDM, show that the artery coronary, responsible for the necrosis, not present initially as angiographic lesions less than 50% in 60% of cases [50,51]. The low volume of the unstable lesion and the phenomenon of parietal remodeling render account in these cases, the character bit stenosing of objectified abnormalities in the coronary angiography [52]. In addition, in the framework of a syndrome coronary acute, the observation ultrasound endovascular show that the plates unstable are multiple in 75% of cases [53]. It thus appears that the phenomenon of lesional instability can be multifocal and diffuse and that, although a single plaque can cause acute coronary syndrome, many other lesions can remain asymptomatic in however, remaining exposed to the risk of an evolution either paroxysmal by an acute or subacute occlusion, or insidious with the development of an angiographic stenosis of a scarring nature.

The complexity of the development of the process atheromatous makes good account of the difficulties of screening clinic for atherosclerosis coronary and explains the limits of functional and morphological explorations. In asymptomatic diabetic lesion parietal atherosclerotic little or no significant, but potentially vulnerable by reason in particular of the dysfunction endothelial and the disorder of hemostasis specific of diabetes, cannot cause IMS to the effort and can also escape to coronary angiography. The value of diagnostic of these exams, which put the day preferentially of stenosis coronary fixed and tight, is therefore not categorical. The floor of lesions not stenotic at risk high instability, by the resonance magnetically nuclear tick, intravascular ultrasound, thermography, palpograhie and OCT (optical coherence tomography) still belongs to the field of research clinical. In the practice clinic, it is therefore less of detecting the lesions atherosclerotic risk of instability that identify the topics to RCV high. In addition, a cardio – logical assessment only explores the instant of a progressive and unpredictable disease: either quiescent, paroxysmal or insidiously stenosing. The predictive value of the tests, when they are negative, is therefore not formal, and by therefore the evaluations cardiologiques complementary must be repeated in the monitoring of a diabetic at risk in the research of evolution silent stenosis.

At plane therapeutic, the knowledge more thoroughly the mechanisms of installations ion and evolution of atheroma gives all its meaning to measures of pre – vention, pharmacological and dietary, who can participate in to many ways complementary to the stabilization preventive and curative of the vulnerable plaque.

The dissemination and the seat of stenosis coronary angiographic define the high and the low risk myocardique.

However, the progressive severity of atherosclerosis depends as much on the instability of the lesions as on the severity of the strictures.

The lesions not stenotic, potentially unstable, can escape the explorations functional and mortal phologiques.

The diagnostic and predictive value of stress tests and coronary angiography is therefore not categorical.

However, the installation of a stenosis can be done on the fashion insidious evaluation cardiology complement commentary will be repeated in the monitoring of a diabetic at risk.

It is more significant and helpful to identify the subjects at risk as to detect the lesions atheromatous potentially unstable and stenotic.

Potential therapeutic benefit

The advantages therapeutic a screening early and systematic of IMS are not yet formally demonstrated in the diabetic. They are suggested by the results of therapeutic interventions applied to diabetic patients with a coronary disease clinically proven and well in subjects asymptomatic Sou put at risk atheromatous, diabetic or not diabetic. The profit potential is based on three measures therapeutic potential: the setting in implementing a treatment anti-ischemic, the strengthening of measures to prevent cardiovascular and in need, the practice of an act of revascularization.

Anti-ischemic treatment

The setting in the day of IMS can and must lead to the implementation in road a treatment medi – anti-ischemic early camenteux. In asymptomatic coronary patients and with an IMS study ACIP has already demonstrated the effectiveness of a treatment anti-ischemic on the reduction of the severity and the number of episodes of ischemia sicious and, at this time, has confirmed the superiority of blockers on the inhibitor's calcium [54]. In patients with coronary artery disease, the efficacy of blockers is alsoproven. In the BIP study, the risk of cardiac mortality in diabetics was significantly reduced by 44% in the group of patients receiving a B-blocker [55]. This effect positive is more marked the waning of an IDM and in the presence of an alteration moderation ESR of the function ventricular left [56].

Reinforcement of preventive measures

The discovery of an IMS places the diabetic in a logic of secondary prevention. The precocity of the diagnosis may lead to the setting in work early and reinforced measures lifestyle modifications and therapy with a control more strictly the fac – tors of risk associated with the prescription agents' drug which have already proved their effectiveness in the field of the prevention.

The statins have accumulated a large amount of evidence in favor of their efficacy in the diabetic. In the field of the prevention side, the big trials have proven the efficacy of a lower treatment of cholesterol with, for 5 years, a reduction of 55% of the risk related events coronary major in the diabetic hyper cholesterol treated by simvastatin in the study 4S [57] and of 25% in the diabetic normo cholesterol put under pravastatin in testing CARE [58]. In a population of 5 963 diabetics, HPS confirmed these results with a reduced significantly by 22% of the risk relative, identical to that observed in the cohort of patients non diabetics [59]. With a reduction of the risk relating to 33%, the benefit is also noted in the group of 2912 diabetic symptoms. This gain prognostic is registration what that are the kind of diabetes, its length and the quality of its control glycemic, which that are age and the sex and finally what as are the levels initial of the pressure arterial (PA), the cholesterol total and the LDL-cholesterol (LDL-C). Although having attracted less testing, the fibrates have also proven their efficiency in secondary prevention in the diabetic [60].

In the diabetic with two other factors of risk as in the coronary out, the threshold of interventions is set to 1.3 g/L of LDL-C to the Affrays with a value target of 1 g/L for the latest European recommendations [61].

The control participates also to improve the prognosis vascular. In the trial, the decrease of pressure systolic and diastolic of respectively 10 and 5 mmHg is associated with a reduction of 5% to 8 years of risk absolute occurrence of an accident vascular brain or a death of vascular origin [62].

Other studies devoted to the prognosis and the treatment of hypertensive report of results similar in the subgroup of diabetic patients [63].

Thus, in the diabetic hypertensive, a PA less to 130/80 mmHg is currently defined as the goal to reach in the past recommendations [61,64]. A square privileged must be reserved for angiotensin converting enzyme as recommendation ADA, especially in the diabetic with a proteinuria or an alteration of the function ventricular left [65]. This class drug has actually proven its effectiveness in the diabetic. In the suites immediate of IDM, the 6 weeks was significantly more low in the diabetic treated by lisinopril (8.7 against 12.4% in the group placebo) in the trial [66]. Among the diabetics who already had an accident cardiovascular or accusing one other factor of cardiovascular risk, the ramipril decreases significantly from 25% in 4 years the risk related to occurrence of a cardiovascular event in the subgroup of diabetics in the study [67].

Recently, testing EUROPA has confirmed the effectiveness of perindopril, associated to a B-blocker, in the reduction of risk vascular in the coronary steady with, in the population of diabetics, a trend favorable that reaches however not the threshold significance [68].

Aspirin, in the meta-analysis of several trials comparative, has also proven effective in the reduction of risk vascular as well in the diabetic than in the non-diabetic [69]. Among the diabetics suffering a retinopathy and who have no signs of coronary artery disease, the prescription of aspirin is associated with a reduction of 15% in 7 years of risk relative to occurrence of an IDM [70].

Recently, testing EUROPA has confirmed the effectiveness of perindopril, associated to a B-bloquant, in the reduction of risk vascular in the coronary steady with, in the population of diabetics, a trend favorable that reaches however not the threshold significance [68].

Aspirin, in the meta-analysis of several trials comparative, has also proven effective in the reduction of risk vascular as well in the diabetic than in the non-diabetic [69] Among the diabetics suffering a retinopathy and who have no signs of coronary artery disease, the prescription of aspirin is associated with a reduction of 15% in 7 years of risk relative to occurrence of an IDM [70].

The presence of achieving blood clinic, peripheral, coronary or cerebral, the clopidogrel is revealed more effective than aspirin in the subgroup of patients with diabetes CAPRIE with a reduction of 2.1% absolute risk annual occurrence of a major arterial event [71].

The control strict and attentive to the blood sugar is involved also to improve the vascular diabetic prognostic tic. In the aftermath of an IDM, DIGAMI the trial showed that the recourse to insulin, since the phase of hospital until the third month of development to a minimum, allowing a reduction of the mortality of 29% at 1 year [72]. Finally, in the UKPDS trial which recruits asymptomatic type 2 diabetics, it appears that any increase in the level of glycated hemoglobin (HbA1c) of 1% above the threshold of 6.2% is accompanied at 10 years an exaggeration of 11% of the risk coronary [73].

The affirmation of IMS may well lead to a decision in support strict and continues the RRS overall by the setting in game of medications tailored to each case. At the high vascular risk men and having an IMS affirmed by an exercise test positive, these measures attentive engaged to reduce significantly the mortality cardio vascular from 61% to 7 years [74] In diabetic type 2, with albuminuria micro, a decision in support therapeutic aggressive (control glycemic strict control blood pressure at the level of 135/80 mmHg and prescription of statin and aspirin) reduces the risk vascular to 7 years of 50% with respect to the treatment conventional and casual of factors of risk associated [75].

Myocardial revascularization

The discovery of IMS and the setting in evidence of coronary artery disease with coronary stenosis tight and commanding a wide territory myocardial may lead to consider a gesture of revascularization. Without testing specifically dedicated to the revascularization of diabetic, including asymptomatic, and the fact of the constant evolution of methods surgical and interventional, the principle even of the revascularization and its terms are still controversial. The major trials have however allowed to identify some lines guidelines helpful in making therapeutic vis-à-vis of ischemic myocardium in the diabetic.

At the coronary stable efficiency of revascularization surgery has been proven in the group of patients at high risk myocardial having a stenosis of the trunk com – mon left a damage multivessel involving the first segment of the IVA and alteration of the function ventricular left [76]. Among the patient's single vessel at low risk myocardial, a revascularization with angioplasty will affect not notable – lies the risk of occurrence of an event cardiac major, but it improves significantly the become functional, especially in the presence of a breach of the IVA proximal male [77].

In the stable coronary artery, the efficacy of surgical revascularization has been proven

in the group of patients at high myocardial risk with stenosis of the left common trunk, multivascular involvement involving the first segment and an alteration of left ventricular function [76]. In monotronic patients with low myocardial risk, revascularization by angioplasty does not appreciably influence the risk of a major cardiac event, but it significantly improves the functional outcome, especially in the presence of a disease of the heart [77]. In coronary patients, trials tend to demonstrate the superiority of myocardial revascularization over anti-ischemic medical treatment alone. Although lacking in power, the study [78] demonstrated in subjects revascularized by bypass surgery a reduction in subclinical ischemic manifestations and above all a significant reduction in mortality at one year (0 against 1.6% in the group treated with anti-ischemic agents).

In multivascular diabetics selected for revascularization, the results of large comparative trials argue in favor of the surgical option [79]. At 7 years, the trial [80] reported lower mortality in the group treated with surgery (24.5 versus 44% in the balloon angioplasty group) with a clearer benefit in subjects revascularized by the artery. internal breast. The stent is not enough to bridge the gap between angioplasty and surgery. In the trial, the mortality at one year was 6.3% in the “stent” group compared to 3.1% in the “surgery” group in diabetics [81]. However, the registers recruiting less selected populations of diabetics do not show significantly different long-term results between the 2 methods [82]. Thus, the choice of revascularization in multivascular diabetics remains open and is based, on a case-by-case basis, on an assessment of the etiological context, in particular with age and associated pathologies, and on the analysis of coronary artery lesions.

When the indication for angioplasty is retained and the angiographic conditions are favorable, placement of a stent should be preferred. The risk of restenosis, particularly high in diabetics [83], is significantly reduced by the implantation of a stent [84] to reach, in the best case, a threshold identical to that of non-diabetic patients [85]. Finally, the results obtained with active stents seem promising today, and if they are confirmed, will lead to facilitating angioplasty in diabetics and possibly broadening the indications for revascularization in these patients [88]. In the population of diabetics in the study (26% of the total number), the rate of new supported coronary revascularization was 22.3% in the “inactive stent” group and 6.9% in the “inactive stent” group the sirolimus “covered stent” group [89].

Reference

1. Passa Ph, Drouin P, Issa-Sayegh M et al. Coronaries et diabète. Recommandations de l’Alfédiam. Diabete 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 exercise testing. J Am Coll Cardiol 1997; 30: 260-315.

5. ANAES. Recommandations pour la pratique clinique. Suivi du patient diabétique de type 2 à l'exclusion du suivi des complications. Janvier 1999. WWW.anaes.fr.
6. American Diabetes Association. Report of the expert committee on the diagnosis and classification of diabetes mellitus. Diabetes Care 1998; 21: S5-S19.
7. Saydah SH, Loria CM, Eberhardt MS et al. Subclinical states of glucose intolerance and risk of death in the 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 syn – drome 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, Benjamin IJ, 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; 1.6: 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 Heart 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 3 266 patients scheduled for coronary angiography. Am Heart J 2003; 145: 285-9.
20. Kannel WB, McGee DL. Diabetes and cardiovascular disease. The Framingham study. JAMA 1979; 241: 2035-8.
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. BMJ 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 – dependent diabetes. J Am Coll Cardiol 1996; 27: 567-74.
28. Knobler H, Savion N, Shenkman et al. Shear-induced platelet adhesion and aggregation on sub endothelium 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 persistance. Circulation1998; 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. BMJ 1990; 301: 92-5.
34. Langer A, Freeman MR, Josse RG et al. Detection of myocardial ischemia in diabetes mellitus. Am J Car – diol 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. Diabetology 2000; 43: 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. Diabetology 2000; 43
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 mil-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 vulnera – bility. Circulation 2002; 105: 939-43.
53. Rioufol G, Finet G, Ginon I et al. Multiple atherosclerotic plaque rupture in acute coronary syndroms; 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 and al. Diabetic patients and beta-blockers after acute myocardial infarction. Eur Heart J 1990; 1143-50.
57. Pyörälä K, Persen T, Kjeksus J. 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. Bene – fit 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 5963 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.
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) randomized 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: S23-S31.
66. Zuanetti G, Latini R, Maggioni AP et al. Effect 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: randomized double-blind, placebo-controlled, multicenter trial (the EUROPA study). Lancet published online September 1st, 2003.
69. Antiplatelet trialist's collaboration. Collaborative overwiev of randomized trials 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. ETDRS Investigators. 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-year results from randomized trials by the coronary artery bypass trialist collaboration. Lancet 1994; 344: 1116-21.
77. Blumenthal 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 revascularization. J Am Coll Cardiol. 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 revascular-

ization 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 followimg 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.