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VIEWPOINT

Consensus on: Screening and therapy of coronary heart disease in diabetic patients

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Abstract The screening and best treatment for coronary heart disease in diabetic patients is still a matter of debate. For this reason the main Italian scientific societies dealing with diabetes and cardiovascular diseases have tried to finalize a document providing shared recommendations based on the available evidence on : 1) how and who to screen for coronary heart disease, 2) methodologies for the characterization of existing coronary heart disease 3) evaluation of the optimal treatment of cardiovascular risk factors and 4) appropriate revascularization procedures. For each of these points, the levels of evidence and strength of recommendations used in the Italian Standard of Care were adopted.
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Introduction

Mortality and morbidity from coronary heart disease (CHD) are significantly increased in diabetic patients [1]. Given the magnitude of the problem, beyond an intensive preventive approach through the optimal correction of all risk factors, it is necessary to try to make a very early diagnosis and implement the best possible treatment in patients with diabetes who already have CHD.

For this reason, several Italian scientific societies dealing with this issue have prepared a consensus document, based on available scientific evidence, giving indications on : 1) how and who to screen for coronary heart disease, 2) the optimal treatment of cardiovascular risk factors and 3) the best intervention therapy.

To this regard, it was decided to adopt the levels of evidence and strength of recommendations used in the

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Italian Standard of Care [2]. Here is a summary of this document, whose full version is available on the websites of the Italian Diabetes Society (SID) and the Italian Diabetologists Association (AMD)

A. Screening and diagnosis of asymptomatic CHD

1) when and in which asymptomatic diabetic patients should CHD be sought?

Recommendations

- Screening should be done only in patients with reasonable life expectancy and quality of life, especially if eligible for a possible revascularization (Level of Evidence VI, Strength of Recommendations B).
- The probability of silent CHD in the population tested must be sufficiently high to optimize the cost/benefit of screening (Level of Evidence VI, Strength of Recommendations B).
- The medical conditions listed in Table 1 help identify patients with sufficiently high probability of being affected with silent CHD (Level of evidence VI, Strength of Recommendation B)

Comments

To optimize screening, i.e. increasing the possibility of identifying patients with CHD, it is necessary that the *a priory* probability of CHD be high, with a value at least equal to 20% [3].

The guidelines published so far suggest various approaches to identify patients at high risk, based on either the evaluation of clinical and biochemical risk factors or the identification of subclinical atherosclerosis. It is interesting to note that the classic cardiovascular risk factors have a poor positive predictive power of an altered functional cardiac examination, because coronary risk factors and cardiovascular risk scores project risk over a long period of time, usually ten years. Therefore, if a patient has a 10-year coronary risk of 15%, this risk is reduced to 1.5% at one year and to 0.125% at thirty days from the calculation of the risk. Thus, in a patient with this level of coronary risk, the chances of identifying myocardial ischemia are certainly minimal in the short term. On the contrary, a severe atherosclerotic process involving other vascular districts indicates that the patient's arteries—presumably including the coronary arteries— have already suffered damage. This explains the stronger association of coronary perfusion defects with peripheral vascular disease, rather than with cardiovascular risk factors [4].

As there are no diagnostic algorithms of asymptomatic CHD adequately evaluated in controlled studies, any suggestion in this regard is based on expert opinion gained by inferences of studies stratifying coronary risk, and on consensus documents [5,6].

We believe that pre-test requirements sufficiently powerful to identify a population with high prevalence of silent CHD are those summarized in Table 1.

The decision to screen also patients with symptomatic or asymptomatic non coronary atherosclerosis is justified by the observation that the impairment of a vascular district often indicates a wider distribution, involving multiple vascular beds [7,8]. Using a coronary risk score, it is possible to consider the classical cardiovascular factors not only as continuous variables but also to integrate their prognostic value. The decision to adopt the "UKPDS risk engine" is based on the fact that it was calculated on a population with type 2 diabetes mellitus; moreover, it is the only algorithm that takes into account glycemic control expressed as glycated haemoglobin, and diabetes duration. For the reasons discussed above, there is need to increase the possibility of the actual presence of coronary artery disease based on the coexistence of a high risk score (>20%) and subclinical macrovascular damages, clinical microvascular/neuropathic lesions, and family history of premature coronary artery disease, unless the risk score is not very high (>30%).

The choice of subclinical macroangiopathy and clinical microangiopathy as diagnostic criteria is supported by the fact that they are not only independent risk factors as compared to those considered in the UKPDS engine, but also in relation to each other and this results in a multiplicative effect with greater probability of selecting

Table 1 High risk of silent CHD.

Patients who meet the criteria in at least one of the boxes below is at high risk of silent CHD	
Advanced non coronary macroangiopathy *Symptomatic* ▪ History of atherothrombotic events ▪ History of revascularization procedures *Asymptomatic* ▪ Peripheral vascular disease with ABI<0.9; ▪ Asymptomatic carotid stenosis >50% ▪ Aortic aneurysm	**Coronary risk score (UKPDS) > 20% at 10 y + at least one of the following conditions:** ▪ Atheromatous plaques causing ≥20% vessel lumen stenosis in any district ▪ Cardiac autonomic neuropathy ▪ Erectile dysfunction ▪ First degree family history positive for ischemic heart disease before age 55 y for men and 65 y for women.
Coronary Risk Score (UKPDS) > 30% at 10 y	**Coronary Risk Score (UKPDS) > 20% at 10 y + at least two of the following conditions:** ▪ GFR <60 ml/min for 1.73 m^2 ▪ Micro- or macroabluminuria ▪ Laser-treated or proliferating retinopathy

a population with high prevalence of silent ischemic heart disease.

It should be noted that the presence of possible ischemic equivalents (dyspnea, fatigue, positive Rose questionnaire, ECG diagnostic for probable or definite ischemia, positive echocardiography) rules out asymptomatic heart disease, and requires a more detailed diagnosis.

2) which test should be used to detect asymptomatic CHD?

Recommendations

- The presence of asymptomatic CHD should be investigated after a careful history and physical examination to exclude symptoms (including coronary heart disease equivalents such as dyspnea) or signs of heart disease, according to the flow chart shown in Fig. 1 (Level of Evidence VI, Strength of recommendation B).
- Second level tests should be functional tests able to detect a defect in myocardial perfusion under stress or stress echocardiography (Level of Evidence: I, Strength of recommendation A).
- The evidence of high risk for cardiac mortality (Table 2), as revealed by functional tests, is an indication for a coronary arteriography (Level of Evidence VI, Strength of recommendation B).
- The evidence of low-intermediate risk of cardiac mortality (Table 2) must be evaluated case by case with respect to the indications of a coronary arteriography (Level of Evidence VI, Strength of recommendation B).

Comments

The purpose of screening for asymptomatic CHD is to identify subjects with myocardial ischemia. This means that it is not sufficient to identify subjects with potentially very high coronary risk using morphological imaging techniques, even the most advanced, such as the coronary calcium score or coronary arteriography by computed tomography, but it is necessary to document the presence of stress-inducible myocardial ischemia with functional tests [9]. In fact, the finding of coronary artery stenosis is insufficient as indication for revascularization in the absence of symptoms or evidence of a significant perfusion defect [9]. To this regard exercise ECG, echocardiography with exercise or pharmacological stress, SPECT with exercise or pharmacological stress, PET with stress test or pharmacological stress, the Stress Cine MRI are suitable diagnostic tools.

Although poorly sensitive, the first examination should be a resting ECG, given its feasibility and low cost. This examination is able to identify prior necrosis, a left bundle branch block, ventricular ripolarization abnormalities suggestive of myocardial ischemia. The presence of Q waves or ST segment changes have been significantly associated with the detection of high-risk SPECT [4].

A positive finding requires further investigations by means of baseline echocardiography. An abnormal segmental wall motion or depressed left ventricular function, provides the basis for the implementation of functional stimulation. However, a normal baseline ECG and possibly echocardiography does not rule out further investigations on the basis of the criteria listed above. The simplest and least expensive test available to screen for inducible ischemia in asymptomatic diabetic patients is exercise ECG testing. This implies that the patient is able to perform sufficient effort to achieve the necessary heart rate and has no ECG changes at baseline (left bundle branch block or intraventricular conduction delay with QRS$>$0:12 s, ventricular preexcitation, ST segment depression $>$ 1 mm), which may limit its interpretation. A variable percentage of diabetic patients, as many as 30% in one study [10], is ineligible or cannot perform a diagnostic test. The alternative in these cases is an imaging technique with pharmacological stress. In the presence of a Duke score ≤ -11 at exercise ECG the patient is a candidate for coronary

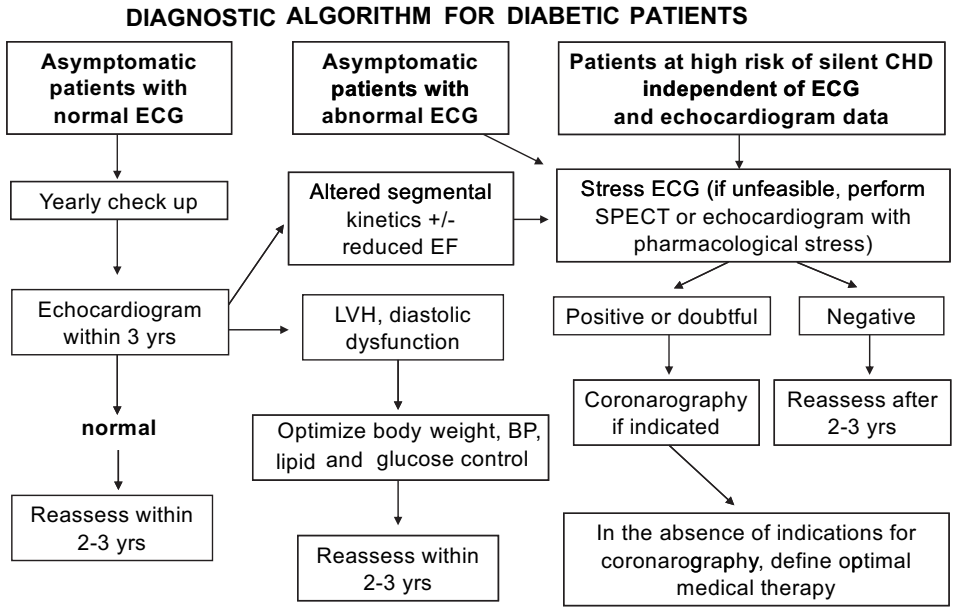


Figure 1 Diagnostic algorithm for diabetic patients.

Table 2 Criteria for the definition of patient's risk on the basis of cardiovascular tests.

High risk patients (mortality/year >3%)
1. Resting left ventricular ejection fraction <35%
2. High risk stress test (Duke score ≤ −11)
3. Severe left ventricular dysfunction during exercise (FE ≤ 35%)
4. Large perfusion defects, especially involving the anterior region, during stress testing
5. Multiple medium-sized perfusion defects
6. Extensive perfusion defects not amenable to correction, during stress testing
7. Medium severity perfusion defects during stress testing, with left ventricular dilation or thallium-201 lung uptake
8. Altered kinetics in more than two segments during Echo-stress with low dose dobutamine (≤10 mg/kg/min) or with heart rate <120 b/m
9. Evidence of extended ischemic damage at Echo-stress.
Intermediate risk patients (Mortality/year 1−3%)
1. Left ventricular resting ejection fraction between 35 and 49%
2. Intermediate risk stress test (Duke score between −11 and 5)
3. Medium severity perfusion defects without left ventricular dilation or thallium-201 lung uptake.
4. Mild ischemia at echo-stress with abnormal wall kinetics only with high dose dobutamine and involving only two segments.
Low risk patients (Mortality/year <1%)
1. Low risk stress test (Duke score ≥ 5)
2. No or small perfusion defects at resting or under stress
3. No wall kinetics alterations or no modifications of resting small wall kinetics alterations during echo-stress

angiography [9]. In the presence of less pronounced abnormalities, the decision to proceed to coronary angiography will be evaluated on a case by case basis.

Exercise or pharmacological stress echocardiography/SPECT are the more advanced diagnostic tests routinely used to detect myocardial ischemia. In terms of sensitivity and specificity the two tests are substantially similar and therefore the choice of one over the other depends primarily on local protocols and availability.

Considering the radiological risk associated with the implementation of radionuclide imaging techniques [11] and that the screening should be repeated periodically, the use of echocardiography is, in this view, preferable.

Fig. 1 summarizes the diagnostic flow chart suggested for diabetic patients with suspected silent coronary heart disease.

3) is it useful to search for silent CHD in diabetic patients?

Recommendations

- It is necessary to search for silent CHD in diabetic patients to identify those at high risk of cardiac death (>3% per year) (Table 2), as they may benefit from coronary revascularization (Level of Evidence VI, Strength of Recommendation B).
- In the presence of intermediate risk (annual mortality between 1 and 3%) (Table 2) revascularization is indicated only in case of three-vessel disease (not involving the common trunk) (Level of Evidence VI, Strength of Recommendation B).
- In all other situations, the indication for coronary revascularization is considered inappropriate or questionable (Table 2) (Level of Evidence VI, Strength of Recommendation B).

Comments

The joint guidelines of the American Societies of Cardiologists and Cardiac Surgeons consider coronary revascularization in asymptomatic subjects only in the presence of a stress test indicative of high risk and maximum drug therapy [9]. Patients are considered at high risk (yearly mortality ≥ 3%) in the presence of the criteria listed in Table 2.

In the presence of intermediate risk (annual mortality between 1 and 3%) (Table 2) revascularization is indicated only in the case of three-vessel disease (not involving the common trunk). In all other situations, the indication for coronary revascularization is considered inappropriate or questionable.

B. Control of cardiovascular risk factors in diabetic patients with CHD

Since this issue is extensively dealt with in the Italian Standard of Care and other guidelines, here we report only the main recommendations (for full recommendations and comments see the SID-AMD websites).

General recommendation

- An intensive multifactorial intervention aimed at optimizing all cardiovascular risk factors through appropriate lifestyle changes and drug therapy should be implemented in diabetic patients with or without CHD (Level of Evidence II, Strength of Recommendation A).

Comments

Intervention studies in patients with and without diabetes with stable coronary artery disease have recently shown that intensive medical therapy aimed at optimizing all the

cardiovascular risk factors, and which includes β-blockers and/or ACE inhibitor, is as effective as revascularization procedures, in terms of both total mortality and new cardiovascular events [12,13].

The goals to be reached for cardiovascular risk factors are :

LDL cholesterol <100 mg/dl (if possible <70 mg/dl)

Plasma Triglycerides <150 mg/dl.

HDL cholesterol > 40 mg/dl in men and >50 mg/dl in women.

Blood pressure <130/80 mmHg.

HbA1C <7% or 7–8% in patients with longstanding diabetes and/or comorbidities.

How to reach the goals?

Recommendations

Lipids

- In diabetic patients with stable CHD lipid-lowering drug therapy (primarily statins) should be prescribed, in addition to lifestyle changes, regardless of their LDL cholesterol values, unless they are already included in the target level (Level of Evidence I, Strength of recommendation A).
- In patients with optimal levels of LDL cholesterol, but with hypertriglyceridemia and/or low HDL cholesterol, therapy with fibrates/niacin/n3 fatty acids may be considered possibly in combination with statins (in case of fibrates, the association with gemfibrozil should be avoided) (Level of Evidence II, Strength of recommendation B).
- In diabetic patients with acute coronary syndrome (ACS), in the absence of specific contraindications, "intensive care" with high-dose statins (mainly atorvastatin) should be started as soon as possible (within 1–4 days) regardless of baseline LDL-C values, and continued for at least 6 months (Level of Evidence I, Strength of Recommendation A).
- In diabetic patients with stable CHD or ACS undergoing PCI, a loading dose of statins (i.e. atorvastatin 80 mg 12 h before and 40 mg immediately before the procedure) can be taken into consideration (Level of Evidence II, Strength of Recommendation B).

Blood pressure

- The primary objective is to achieve the desired therapeutic effects regardless of the antihypertensive drug used (Level of Evidence I, Strength of Recommendation A).
- It is often necessary to combine two or more antihypertensive drugs at doses able to achieve the therapeutic goals, and the association should always include an ACE inhibitor or an angiotensin II receptor antagonist (Level of Evidence II, Strength of Recommendation B).
- In diabetic subjects with cardiovascular disease the use of an ACE inhibitor, unless contraindicated, should be considered to reduce the risk of cardiovascular events (Level of Evidence I, Strength of Recommendation A).
- In diabetic patients with previous myocardial infarction the use of a beta-blocker, unless contraindicated, should be considered to reduce morbidity and mortality (Level of Evidence I, Strength of Recommendation A).

Blood glucose

- Insulin therapy is the therapy of choice to control hyperglycemia during acute coronary syndrome or periprocedural revascularization, both in the presence and absence of a history of diabetes mellitus (Level of Evidence I, Strength of Recommendation A), with glycemic goals between 140 and 180 mg/dl (Level of Evidence II, Strength of Recommendation B).
- The blood glucose lowering treatment strategy to be recommended in the follow-up of post-acute care of diabetic patients with ACS, in the absence of specific studies, is based on the general principles that specific contraindications for any drug be taken into account and that extremely intensive interventions associated with high risk of hypoglycaemia be avoided (Level of Evidence VI, Strength of Recommendation B).

Antiplatelet therapy

- The use of aspirin (75–162 mg/day) is recommended in all patients with a history of cardiovascular events. For patients with documented allergy to aspirin the use of clopidogrel at a dose of 75 mg/day is recommended (Level of Evidence I, Strength of Recommendation A).
- After ST elevation myocardial infarction (STEMI) early treatment with aspirin at a dose of 162–325 mg/day in the absence of contraindications is recommended. The addition of 75 mg/day clopidogrel to aspirin for at least 14 days is also suggested, regardless of whether fibrinolytic therapy was done (Level of Evidence I, Strength of Recommendation B).
- In diabetic patients with unstable angina and non ST myocardial infarction (NSTEMI), the administration of antiplatelet treatment with aspirin (initial dose 162–325 mg/day, maintenance dose 75–162 mg/day) should be started as early as possible after the onset of symptoms and must be maintained indefinitely (Level of Evidence I, Strength of Recommendation A).
- In patients who have to undergo revascularization, antiplatelet therapy with aspirin and clopidogrel (load dose followed by maintenance dose, except for surgical revascularization) should be started before the procedure (Level of evidence I; strength of recommendation A).

C. revascularization procedures

1) indications for coronary revascularization in diabetic patients with acute coronary syndrome

Recommendations

- Mechanical reperfusion by percutaneous coronary intervention (PCI) is the first choice treatment for revascularization in diabetic patients with acute myocardial infarction (AMI) (Level of Evidence I, Strength of Recommendation A).

2) indications for coronary revascularization in diabetic patients with stable CHD

Choosing between PCI and coronary by-pass (CABG)

Recommendations

- In patients with stable CHD, coronary revascularization with PCI or CABG did not increase survival compared to traditional drug therapy (Level of Evidence II, Strength of Recommendation A).
- Diabetic patients with stable CHD and optimally controlled cardiovascular risk factors benefit from coronary revascularization only if the extent of the lesions is an indication to treatment with coronary by-pass (Level of Evidence II, Strength of Recommendation A).
- Patients with stenosis involving the left main trunk of the left coronary artery or the three main coronary vessels, associated with normal or reduced left ventricular function, should preferably undergo CABG (Level of evidence I, Strength of Recommendation A).
- In patients with critical stenosis involving a single coronary vessel, PCI is generally the method of choice (Level of Evidence VI, Strength of Recommendation B)

Comments

In THE COURAGE study [12], carried out in a general population with stable CHD, early revascularization by PCI in diabetic patients, combined with intensive medical treatment, was not more effective than the continuation of intensive medical treatment alone on the incidence of death and nonfatal myocardial infarction. It is important to note that all the patients in this study underwent very intensive medical treatment.

The BARI study, a prospective randomized study aimed to analyze the benefits of continued intensive medical care compared to coronary revascularization by PCI or CABG in patients with type 2 diabetes mellitus and stable coronary artery disease, showed a benefit in terms of lower incidence of major cardiovascular events (combined endpoint including death, AMI and stroke, mainly driven by the reduction in the incidence of AMI) only among subjects who underwent CABG compared with medical therapy (absolute reduction of 8.1%) [13].

Choice between drug-eluting stents (DES) and bare-metal stents (BMS)

Recommendations

- In patients with type 1 and type 2 diabetes it is preferable to use DES compared to BMS because the former significantly reduces the number of new revascularization (Level of Evidence II, Strength of Recommendation A).

Comments

Several studies have compared DES to BMS in the subgroup of diabetic patients and revealed that DES were associated with 80% reduction of restenosis during the first year of follow-up [14,15]. However, diabetes mellitus remains a negative prognostic factor for restenosis, despite the use of DES. There are no studies of sufficiently long duration, i.e., exceeding three years, comparing DES to BMS. Therefore, longer-term results are warranted to definitely establish the advantage of DES over BMS.

3) prevention of thrombosis after coronary revascularization

Recommendations

- In case of coronary angioplasty, initiate therapy with aspirin and clopidogrel (600 mg plus 75 mg/day), preferably 2 h before the procedure, (Level of Evidence II, Strength of Recommendation A).
- In patients with acute coronary syndromes, not pretreated with clopidogrel, prasugrel can be used (60 mg bolus + 10 mg/day) at the time of revascularization and continued for 1 year (Level of Evidence II, Strength of Recommendation A).
- Chronic therapy with aspirin and thienopyridine (clopidogrel or prasugrel) reduces the risk of cardiovascular events after angioplasty (Level of Evidence I, Strength of Recommendation A).
- The administration of periprocedural glycoprotein IIb/IIIa inhibitors (abciximab) reduces stent thrombosis and reinfarction in patients undergoing primary angioplasty and can be considered useful, at least in selected patients (Level of Evidence II, Strength of Recommendation A).

Comments

Treatment with aspirin and clopidogrel started at the time of angioplasty was able to prevent stent thrombosis [16]; in addition, the maintenance of this treatment reduces the risk of major cardiovascular events [17].

The same treatment modalities associated with the use of drug-eluting stents are recommended in patients with diabetes [18].

Diphosphate adenosine receptor antagonists (ADP) (thienopyridines), like clopidogrel, could prevent late complications of stent thrombosis, particularly in patients with diabetes [19,20]. This treatment should be continued for 12 months when PCI is performed with DES.

Pre-treatment with a loading dose of 600 mg clopidogrel 2 h before the intervention is considered the golden standard in diabetic patients.

In a recent trial, prasugrel (CS-747, LY640315), a thienopyridine antiplatelet agent considered of third generation, has shown increased activity and less variability in the pharmacological effects compared to clopidogrel, with consequent clinical benefits in terms of intra-stent thrombosis [21], especially in diabetic patients [22].

A recent metanalasis has showed that the use of Gp IIb/IIIa inhibitors (abciximb) reduces reinfarction and mortality in patients undergoing primary angioplasty [23].

4) follow-up of coronary restenosis in diabetic patients

Recommendations

- All diabetic patients should undergo a functional imaging diagnostic test 6 months after PCI or CABG (Level of Evidence II, Strength of Recommendation A).

Comments

Exercise testing is widely used in the cardiovascular evaluation of patients with diabetes after a cardiovascular event or after therapeutic interventions such as PCI. However, data from two meta-analyses [24,25] show that the stress test has low power to highlight restenosis and myocardial ischemia with a sensitivity of 46% and a specificity of 77%. The use of a radionuclide stress test significantly increases the sensitivity to 87% and specificity to 78%, while stress echocardiography increases the sensitivity and specificity to 63% and 87%.

Although exercise testing has the advantage of being available in different centers at lower cost, greater accuracy obtained by functional imaging tests provides significant advantages in patients at high risk of restenosis, with the added benefit that it can also be performed in patients with ECG of doubtful interpretation and unable to perform physical exercise.

Appendix

Members of the Italian Intersociety Consensus Group:

SID Study Group on Diabetes and Atherosclerosis: Pier-Marco Piatti (Coordinator), Angelo Avogaro, Giovanni Anfossi, Diego Ardigo, Saula Vigili de Kreutzenberg, Sandro Inchiostro, Angela Albarosa Rivellese, Mariella Trovati, Sabina Zambon, Ivana Zavaroni
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