Coronary heart disease and cardiovascular autonomic neuropathy in the elderly diabetic

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Abstract

Diabetes and old age come together to increase the frequency and severity of coronary heart disease. Often clinically nearly silent, symptoms frequently manifest dramatically, to such an extent that the question of screening should be raised, as in younger subjects. Preventing these manifestations relies on better management of the cardiovascular risk factors and obtaining good blood glucose control, but here progress remains necessary, which also requires adapting to the older patient’s clinical and psychological condition. Cardiovascular autonomic neuropathy is a frequent degenerative complication in diabetics, particularly in the oldest subjects. The most severe types have serious clinical consequences, thus a higher mortality factor, but the mechanisms remain poorly understood. As for coronary heart disease, the therapeutic tools have expanded these last few years and should be thought out in relation to the geriatric evaluation, with the objective of improving these patients’ quality of life. Therefore, a necessary distinction should be made between subjects who have aged successfully, whose management, ultimately, differs little from younger subjects, and frail elderly individuals for whom exploratory techniques and treatment should be adapted.

Résumé

Coronaropathie et neuropathie végétative cardiaque du diabétique âgé.

Le diabète et l’âge se conjuguent pour majorer la fréquence et la gravité de la maladie coronaire. Souvent cliniquement peu bruyante, la symptomatologie se révèle fréquemment de façon dramatique si bien que la question du dépistage se pose comme chez les sujets plus jeunes. La prévention de ces manifestations repose sur une meilleure prise en charge des facteurs de risque cardiovasculaire et sur l’obtention d’un bon équilibre du diabète. En ce domaine, des progrès doivent être réalisés mais nécessitent également de s’adapter à l’état clinique et psychique des diabétiques âgés. La neuropathie autonome cardiaque constitue une complication dégénérative fréquente chez le diabétique, en particulier chez les sujets les plus âgés. Les atteintes les plus sévères ont des conséquences cliniques graves et constituent un facteur de surmortalité, mais les mécanismes en cause sont encore mal compris. En matière de coronaropathie, les armes thérapeutiques se sont nettement enrichies ces dernières années et doivent être raisonnées en fonction de l’évaluation gériatrique dans le but d’améliorer ainsi la qualité de vie de ces malades. Ainsi, une nécessaire distinction doit être faite entre les sujets qui ont bien réussi leur vieillissement, dont la prise en charge diffère en définitive peu de celle des sujets plus jeunes, et les vieillards fragiles pour lesquelles les techniques d’exploration et de traitement méritent d’être adaptées.

Key words: Diabetes; Coronary heart disease; Cardiovascular autonomic neuropathy; Elderly

Mots clés : Diabète ; Coronaropathie ; Neuropathie autonome ; Sujet âgé

Few chapters concerning diabetes of the elderly subject appear as important and as complex. The high prevalence of cardiac complications in this population and their multiple facets attest to the interest in this topic. As is often the case, scientific data is lacking in this area since the large studies exclude seniors who are too old, because of the high risk of
excessive mortality. However, all clinicians can testify to the questions generated by the suspicion or the onset of a cardiac complication in this type of patient. Is it reasonable to screen for coronary heart disease? Should investigations be pushed further? Does an aggressive treatment carry the risk of being more dangerous than effective? These are some of the questions that diabetologists encounter daily. The responses that will be advanced herein should be based on data from the literature, unfortunately often disappointing, and on collaboration with experienced and commonsensical cardiologists.

1. Epidemiology of the cardiac manifestations in elderly diabetics

Few studies are available other than the ENTRED (Echantillon National Témoin RÉPrésentatif des personnes Diabétiques) study, which investigated 10,000 diabetic subjects randomly selected among those eligible for the French national health insurance system. More than half of the diabetics were over the age of 65 years and nearly 25% were older than 75. Within the total diabetic population, 17% presented a coronary heart disease (CHD) documented by angina, myocardial infarction (MI), or a revascularization procedure. As expected, the prevalence of CHD increased regularly with age and the duration of diabetes, surpassing 25% after the age of 85 [1]. These results are even more significant given that the response rate of subjects normally decreases with age. Similar statistics were noted in the ECODIA (Economie du DIAbète) study, in which more than 50% of the subjects were aged over 65, even though the methodology was different [2]. In NHANES (National Health and Nutrition Examination Survey), the prevalence of CHD turns out to be higher, affecting one-fourth of North American diabetics aged from 20 to 74 years. The mediocrity of these results, despite the wide range of ages, is accounted for by the particularly high level of vascular risk in these patients [3]. The high level of risk is shown in prospective studies by the observation of a particularly poor prognosis in elderly diabetics who present with CHD, and this increases with the duration of diabetes [4].

Mortality rates at 5 years for subjects over 65 years of age in the PAQUID (Personnes âgées QUID) study are higher in diabetics (30% vs. 20.3% in nondiabetics). However, this excess mortality seems more related to an increase in neoplastic diseases than to vascular events [5, 6].

Diabetes also appears to be an element that favors the progression toward congestive heart failure in elderly diabetic subjects [7]. Therefore, in this prospective study on 2737 subjects who were 81 ± 9 years old, congestive heart failure was noted after 43 months in 39% of diabetics, whereas this disease was only recorded in 23% of nondiabetics.

2. Coronary heart disease in the elderly diabetic patient

Age and diabetes combine their effects to give CHD particular severity, making it the leading cause of death in diabetics. Management of CHD has, however, evolved over the last few years, so that the fatalism surrounding its discovery in elderly patients is no longer justified today. Without succumbing to excessive activism, we should provide diabetics with the best chances possible of preventing acute accidents whose consequences are always devastating. The data available on the subject are extrapolated from the knowledge acquired in younger patients in that coronary disease in the elderly diabetic has not been the subject of specific studies. This explains that the management strategies reflect more the practices in use than evidence-based medicine.

2.1. Position of the problem

Type 2 diabetes accounts for 95% of 150 million cases of diabetes in the world. Diabetics have a 2- to 3-fold higher risk of developing CHD than nondiabetics [8]. One patient out of two will die of cardiovascular disease, coronary disease being the leading culprit. In a population of men aged 52–74 years followed up for 10 years, compared to healthy subjects of the same age, the adjusted risk of coronary death was 2.82 in the diabetic, 2.12 in patients with angina, 3.91 in patients with a history of MI, and 8.93 in diabetic and coronary patients. The risk increases with the duration of diabetes, meaning that elderly diabetic patients pay a higher price for CHD [4]. The risk related to CHD is higher in female diabetics than in male diabetics, which seems to be partly related to a discrepancy in disease management [9]. Finally, in cases of MI, the risk of death is higher in the diabetic than in the nondiabetic [10].

The role of age intervenes by increasing the duration of exposure to diabetes and by favoring the appearance of co-morbidities, which increases the morbidity and mortality during coronary events. Thus, mortality at the 35th day after a MI increases from 4.6% before 55 years of age to 16.1% between 65 and 74 years and to 25% beyond 75 years [11]. Of the co-morbidities favored by age, the development of atherosclerosis and calcifications of the large arterial trunks, which interfere with possible interventions, as well as the aggravating role of kidney failure, should be underscored [12,13]. All of these elements explain that the elderly diabetic presents a particularly high risk for cardiovascular disease.

2.2. The influence of diabetes on the anatomy of the elderly subject’s arterial system

The prevalence of coronary lesions is higher in the diabetic patient than in the nondiabetic patient. In an autopsy study, the prevalence of high-grade coronary lesions in elderly, male, healthy diabetics with no coronary symptoms was 81% vs. 84% in nondiabetic coronary subjects of the same
age. The prevalence was slightly lower in elderly diabetic women, approximately 70% [14].

The angiographic data show that compared to nondiabetic subjects, diabetic patients present more diffuse and more severe coronary lesions with more lesions of the common trunk, multivessel lesions, and diffuse arterial lesions. In addition, the lesions are more calcified, the arterial lumen of the arterial segments adjacent to occluded or stenosed vessels is smaller, and occlusive lesions are more severe.

In addition to the wide spread of atherosclerosis, diabetics present with a higher number of plaques that are rich in lipids and at risk of rupturing. In angioscopy, during episodes of unstable angina, more fissured plaques and more thrombi are observed [15]. The arterial system is less capable of developing collateral vessels and of remodeling, which, in the nondiabetic subject at the beginning of coronary disease, contributes to maintaining lumen caliber and arterial flow.

2.3. Symptoms of coronary heart disease

CHD in the elderly diabetic patient responds to the usual physiopathological pattern that distinguishes, on the one hand, stable chronic heart failure related to non evolving stenosing coronary lesions and, on the other hand, acute coronary syndromes with or without persistent ST-segment elevation which reflect evolving coronary lesions with plaque rupture and more or less complete and durable coronary occlusion, that can lead to myocardial necrosis and its complications.

Unlike younger subjects and nondiabetic subjects, these events are often silent and manifest at the stage with complications: congestive heart failure or sudden death.

2.3.1. Silent myocardial ischaemia

2.3.1.1. Clinical presentation. Silent myocardial ischaemia (SMI) can be isolated (type 1) or can occur in a patient with a known coronary disease (type 2 or 3). Type 1 SMI is particularly important to screen for because it is the only expression of a disease with potentially serious consequences. It is defined as an electrocardiographic anomaly (and/or scintigraphic and/or echocardiographic), silent and transitory, observed with a stress in subjects whose resting electrocardiogram (ECG) is normal. It concerns 20%–36% of diabetics [16, 17]. Its prevalence is higher in elderly diabetic patients [17, 18]. In a French multicenter study, it affected 36% of a population of type 2 diabetics who had no known coronary disease. This percentage increased to 44% in subjects aged more than 60 years. Its presence seems more related to diabetes duration than to the presence of classical cardiovascular risk factors. It is predictive of the onset of cardiac events, particularly after the age of 60, with a Hazard ratio = 2.89 [17].

SMI, which is particularly frequent and has a poor prognosis in the older diabetic, is problematic in its screening, which only makes sense if beneficial treatments can be proposed to the patient. The data in the literature only respond to this question imperfectly, even though some studies point toward a beneficial effect of interventions for the elderly diabetic. For these reasons, the French recommendations on screening for silent ischaemia in diabetics, consider that it is worthwhile searching for SMI in the elderly diabetic: “The group of experts has no elements available enabling to provide a definition of a maximum age limit beyond 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 patient's physiological age” [19].

2.3.1.2. Traditional SMI screening. The screening modalities are based on a group of tests that should be used depending on their expected profitability, how invasive they are, and their cost, when the patient’s physiological age and their condition make them reasonable. The objective of these explorations is to demonstrate the myocardial ischaemia and to screen for the responsible coronary lesions.

- **Resting ECG:** Its predictive value is low. It can be normal, even when established coronary lesions are present. It should be interpreted in relation to reference documents. The demonstration of signs of ischaemia or a necrotic scar should motivate additional investigations, particularly if these anomalies did not exist on previous examinations. The same is true for the appearance of a left-branch block. A Holter recording, which has low sensitivity and low specificity, is no longer recommended for screening.

- **Exercise test:** It is rarely feasible in the elderly diabetic. Its diagnostic value is closely related to the ability to perform a maximal exercise test. A conclusion cannot be drawn from a submaximal test except in cases of early positivity.

- **Myocardial perfusion scintigraphy:** This test should be associated with an exercise and/or a drug provocation test. Since exercise tests are rarely feasible in elderly patients, pharmacological tests including an injection of dipyridamole are preferred. Its sensitivity is on the order of 80%, for a specificity of 5%. A positive result makes it possible to situate and quantify the compromised myocardial area. A perfusion defect greater than 20% is highly predictive of the onset of major cardiac events. It is possible to observe perfusion defects when there are no coronary lesions, in cases of left-branch block or myocardial hypertrophy. A negative test is associated with a low risk of a major cardiac event in the diabetic patient (1%–2%). This test is therefore an excellent tool to investigate the elderly diabetic patient.

- **Stress echocardiography:** This examination aims to demonstrate segmentary systolic kinetics impairment during physical or pharmacological stress. Performing this test during exercise can rarely be done in the older
patient, as the use of pharmacological products, such as high-dose dobutamine perfusion, is often poorly tolerated at this age.

2.3.1.3. The place of morphological tests. Demonstrating myocardial ischaemia as soon as it involves a sufficiently extended myocardial territory (>10% on scintigraphy) warrants undertaking a coronaryarography to demonstrate the coronary artery stenosis responsible and possibly to decide for an intervention. In the rare cases where the resting ECG demonstrates signs of myocardial ischaemia in an extended area, this examination should be done at once. Elderly diabetics are particularly exposed to the nephrotoxicity of iodinated contrast media, thus it is also indispensable to prevent this complication.

This evaluation strategy may evolve in the near future because of the noninvasive examinations that are coming to the forefront: computed tomography (CT) and magnetic resonance imaging (MRI). Coronary CT can calculate a calcic score, which reflects coronary atheroma and can screen for high-risk patients [20]. Visualization of the large coronary trunks is now possible but requires an injection of an iodinated contrast medium. However, its use is not as easy as in younger and nondiabetic subjects [21]. MRI contributes to similar information by providing complementary information on the quality of the heart muscle. It is likely that these techniques will eventually replace diagnostic coronaryography and will stand in for the functional MRI examinations. Classical coronaryography will then only be practiced for interventional purposes.

2.3.2. Stable angina

Stable angina is defined by painful symptoms or heaviness in the chest that always appears for the same level of exercise and disappears when the exercise is stopped, evolving with no change for more than two months. These symptoms, which can be more or less disabling, are not frequently encountered in the elderly diabetic patient, but can be associated with SMI. They indicate the existence of more or less severe occlusive coronary lesions. The progression is related to the patient’s condition and background, left ventricular function, the spread of coronary lesions, and the severity of the myocardial ischaemia. Age and diabetes place these patients at high risk, with annual mortality greater than 2%, whereas it is on average less than 1% in nondiabetic patients [22, 23]. Managing these patients requires clinical assessment, exercise test when possible, echocardiography, and possibly coronaryography evaluation if intervention is considered. The decision for intervention is based on the severity of the symptoms, the response to medical treatments, the possible history of MI, the existence of signs of congestive heart failure, and the patient’s condition [23].

2.3.3. Acute coronary syndromes

The term “acute coronary syndrome” designates a set of situations that depends on a common physiopathological process, made up of coronary atheroma plaque erosions and/or ruptures associated with different degrees of thrombotic and embolic phenomena that cause a more or less complete and more or less durable occlusion of one or several coronary arteries. Depending on the type of anatomic lesions, clinical expression can be unstable angina, nontransmural MI, or transmural MI. This graduation defines situations of increasing severity, potentially progressive, calling for urgent care. From an operational point of view, the current classification opposes acute coronary syndromes with persistent ST-segment elevation and acute coronary syndromes with no persistent ST-segment elevation. The existence of an ST-segment elevation is the expression of transmural ischaemia and its persistence beyond 30 min defines infarction being constituted.

2.3.3.1. Unstable angina. Unstable angina is expressed as a de novo angina, a crescedo angina, or a resting angina. De novo angina corresponds to angina pectoris that has been in place for at least two months. Crescendo angina designates the progression of stable angina whose symptoms are worsening with more frequent attacks that are more severe and occurring at a lower level of exercise. Resting angina corresponds to symptoms occurring spontaneously that can last up to 20 min. These different entities are characterized by chest pain associated with episodes of ST-segment elevation, more or less persistent ST-segment reduction, an inversion of the T waves or their flattening. Patients presenting ECG abnormalities without pain (silent ischaemia) can be included in this category. These are highly serious situations, with a 6-month mortality of 12% in the general population in Europe [24]. This explains why these patients should be urgently treated in an intensive care unit. In the OASIS (Organization to Assess Strategies for ischaemic Syndromes) registry that prospectively evaluated the management of acute coronary syndromes in six Western countries, 20% of patients hospitalized for unstable angina were diabetic; the main clinical factors prognostic of death were a history of congestive heart failure, age, and the presence of diabetes. Being diabetic gives a risk comparable to the risk of a nondiabetic subject who is 10 years older [25]. These elements underscore the harmful effects of this disease in the elderly diabetic.

Chest pain is rarely absent in patients, except for subjects who are old and for diabetics, which deprives them of the possibility of screening and exposes them to a delayed diagnosis and complications.

The clinical examination is most often normal. Its purpose is to search for the extracardiac causes of the pain, nonischaemic causes for the cardiac pain (pericarditis, etc.), aggravating extracardiac causes, signs of hemodynamic instability, and left ventricle dysfunction.
ECG changes are the key elements of the diagnosis. This test can be difficult to interpret in patients who have a pacemaker or in cases of preexisting left-branch block. Ideally, the recording during an acute syndrome should be compared to the reference recording. ST-segment elevation greater than 1 mm in two or more contiguous derivations is highly suggestive in this context, as is an inversion of the T waves in derivations with predominating R waves. Episodes of transitory left-branch block can be observed during an acute episode. ST-segment elevation indicates transmural ischaemia caused by coronary artery occlusion; its persistence designates progression toward MI. Finally, a normal ECG does not exclude the diagnosis.

A rise in the biochemical markers of myocardial necrosis – troponin I or T, myoglobin, CK-MB – is observed in one-third of cases. The cardiac specificity of troponin makes it the reference marker. In cases of myocardial necrosis, elevation begins 3-4 h after the symptoms begin and persists for two weeks. If myocardial necrosis is suspected, it is indispensable to repeat the dosage of troponin 6-12 h after the patient is hospitalized and after each episode of severe pain. False-positive results can be observed in cases of kidney failure. The threshold value to consider depends on the determination kit. Myoglobin is not a specific marker of myocardium, but an early rise (1-2 h after symptoms begin in cases of myocardial necrosis) makes it a useful diagnostic tool.

To start up the most appropriate treatment, the risk of progression toward MI of these patients should be assessed. This assessment takes into account the clinical presentation, the ECG modifications, the changes in the necrosis, inflammation, and thrombosis markers, the presence of cardiovascular risk factors, the patient’s condition, and the angiographic data. Advanced age and diabetes immediately place these patients at high risk.

Managing these patients aims to control blood glucose levels, treat myocardial ischaemia, fight against the thrombotic process, and possibly propose revascularization. This last objective requires that coronaryography be undertaken beforehand. This procedure is relatively serious and aggressive; the decision must be made on a case-by-case basis. The current recommendations do not establish a population or age limit beyond which such procedures would be considered unwarranted [24, 26].

2.3.3.2. Myocardial infarction. MI corresponds to myocyte necrosis secondary to prolonged myocardial ischaemia. It is diagnosed based on high levels of myocardial necrosis markers (troponin T and I, myoglobin, CK-MB) in a clinical context of myocardial ischaemia. It demonstrates the occlusion of a coronary artery. Nearly 25% of patients presenting MI are diabetic. Its presentation and diagnosis depend on where it is located and how extensive it is.

This is a medical emergency. The diagnosis for revascularization at the initial phase typically depends on the existence of intense chest pain lasting more than 20 min, resistant to nitrates, readily accompanied by pallor and sweating. The ECG, even if it was done early, is rarely normal. It typically shows the appearance of ST-segment elevation in several consistent derivations or the appearance of a left-branch block. Symptoms are far from always being characteristic in elderly and diabetic subjects. The pain can be dull or totally absent. Changes in the ECG can be unremarkable, so that one must not hesitate to repeat the ECG in case of doubt. The dosage of the myocardial markers provides a late confirmation, so much so that one must not wait for their results to affirm a diagnosis of MI and undertake reperfusion treatment. Performing an early echocardiography in a patient suspected of MI can be very useful, showing the existence of segmental wall kinetics impairment well before necrosis sets in. These abnormalities should, however, be interpreted with the patient’s history and the current context in mind.

The atypical nature and the symptoms in elderly diabetics explain why the diagnosis can be totally unrecognized; it is then made retrospectively when evidenced by necrotic scar tissue on the ECG or on an echocardiography. The disease can also be revealed at the stage of complications by manifestations of congestive heart disease. The prognosis is particularly poor in diabetics, with mortality double that of nondiabetics.

Management in the acute phase requires optimizing blood glucose control. From a cardiological point of view, management aims to relieve the patient, fight against ischaemia and thrombosis, and obtain reperfusion as rapidly as possible when this option is appropriate [27]. This attitude poses the same problems as those in unstable angina.

2.3.4. Complications

Complications include congestive heart failure and death. Congestive heart failure of the diabetic patient responds to multiple mechanisms, with CHD playing a central role. This disease has been the subject of a specific article in this issue.

The diabetic who has had myocardial infarction is a patient at high risk for death. This excess mortality persists even if the patient is revascularized and seems more dependent on congestive heart failure than on cardiac rhythm disorders, which also challenges the possible arrhythmogenic effect of the cardiovascular autonomic neuropathy [28].

2.4. Treatment

Treating CHD in the elderly diabetic patient is confronted with a large number of problems related to the patient’s condition and background, co-morbidities, and particularly kidney failure, which limits the possibilities of using certain treatments and exposes the patient to frequent detrimental events. The challenge consists in giving these patients the best chances possible without exposing them to iatrogenic complications.

We will describe the different interventions possible before issuing practical recommendations. Treatment of the
ischaemic cardiopathy is part of the management of the underlying diabetes, whose treatment modalities are well standardized [22, 23]. This means optimizing the blood glucose control and using appropriate cardiological treatments.

2.4.1. Treating the diabetes

The usual antidiabetic treatments and their associated blood glucose control have modest effects on how the macroangiopathy evolves, particularly CHD, as shown by the UKPDS (United Kingdom Prospective Diabetes Study). A trial using pioglitazone conducted in type 2 diabetics aged from 36 to 75 years, with a high cardiovascular risk, followed up for 35 months as a mean, on an optimal preventive treatment for cardiovascular complications showed a nonsignificant reduction in the main primary endpoint, the proportion of patients reaching an event within a pre-established composite list of seven distinct events (death from any cause, nonfatal MI including silent MI, stroke, acute coronary syndrome, leg amputation, coronary revascularization, or revascularization of the leg), but a significant reduction in the time to main secondary endpoint (a composite list including death from any cause, nonfatal MI excluding silent MI, or stroke). For the authors of this study, these results can be applied to all type 2 diabetics [31]. If these data are confirmed, they can contribute substantially to the prevention of CHD. It should be noted that using pioglitazone is contraindicated in cases of congestive heart failure or in patients with a history of congestive heart failure.

In the acute phase of a coronary event (unstable angina, MI) or during an interventional procedure or surgery, optimizing blood glucose control is of major importance in terms of cardiovascular prognosis [30, 32, 33]. The objective in these situations is to normalize blood glucose levels while preventing hypoglycaemia, which can always be troublesome in older subjects. Because of the contraindications related to the prescription of oral sulfonylureas at this age, insulin should be preferred.

2.4.2. Secondary cardiovascular prevention

Secondary cardiovascular prevention aims to prevent the onset of new cardiovascular events in patients presenting a patent coronary atheroma. This means observing the rules of a healthy lifestyle and controlling the cardiovascular risk factors [34]. The recommendations for a healthy lifestyle are not specific and include fighting obesity and a sedentary lifestyle as well as smoking cessation. Applying these recommendations is difficult in older subjects and the limited benefit that can be expected should not lead to altering these patients’ quality of life.

- Controlling hypertension in elderly subjects should be done with caution. This practice is beneficial until the age of 80 in preventing stroke and to a lesser degree in coronary disease. Beyond 80 years of age, a meta-analysis confirms the benefit in preventing stroke, but an increase in mortality is observed, which raises the question of whether lowering the elderly patient’s blood pressure (BP) too much does not aggravate the coronary disease [35]. The objectives should therefore be measured and lowering BP should be progressive. One must be particularly sure that the treatment does not induce or aggravate orthostatic hypotension. All the therapeutic classes can be used. Nevertheless, a preference should be given to angiotensin converting enzyme inhibitors (ACEIs) or angiotensin II receptor antagonists (ARA-IIs) when the patients’ renal function allows their use. Their cardiovascular protective properties go beyond their BP effect, as shown by the subpopulation of diabetics in the HOPE (Heart Outcomes Prevention Evaluation) study treated with ramipril administered at the target dose of 10 mg [22]. The dose administered is important because the same product administered at a dose of 2.5 mg did not show a beneficial effect. It should be emphasized that the use of medications blocking the renin-angiotensin system may induce severe kidney failure and hyperkalemia in older diabetics, especially since these patients have a preexisting alteration of their renal function, are on diuretics, or are dehydrated. The use of these medications should respect the contraindications formulated by the French Summary of Products Characteristics (AMM) and require regular monitoring of the ionogram and kidney function.

- The advantages of managing dyslipidemia in secondary cardiovascular prevention using statins is well established up to the age of 80. The objective is first and foremost to lower LDL cholesterol to below 1 g/l. The benefit of simvastatin treatment at a dose of 40 mg has been well demonstrated in diabetic subjects [36]. Statins adverse drug reaction profile does not seem to vary between elderly and younger subjects. There have been no studies providing information in subjects over the age of 80. In this population, decisions should be made on a case-by-case basis [37]. It should also be noted that the early use of statins in acute coronary syndromes does not modify the short-term prognosis [38]. The use of fibrates, once proposed for diabetics, did not show a beneficial effect in a recent study and is not warranted given the efficacy of statins [39].

2.4.3. Treatment of acute events

The main objective of treating acute events is to shelter the patient from the consequences of myocardial ischaemia, to fight against thrombotic phenomena, and if necessary provide myocardial revascularization.

2.4.3.1. Anti-ischaemic treatments. Anti-ischaemic treatments are mainly represented by nitrate vasodilators and related derivatives, beta-blockers, and calcium channel blockers.

- The nitrate vasodilator and derivatives are a purely symptomatic treatment for ischaemic episodes and pulmonary edema. Their long-term prescription does not modify prognosis. They are given intravenously during acute coronary syndromes, orally and intermittently.
during treatment of angina pectoris, or over the long term as second-line anti-ischaemic treatment. They should be used with caution in the elderly diabetic patient because of the risk of low blood pressure.

- The beta-blockers are a heterogeneous class of drugs. Some compounds have characteristics of β-adrenergic selectivity, partial agonist effects, anti-oxidant properties, that modify their pharmacological effects and their adverse reaction profiles. All show anti-ischaemic and antihypertensive effects, some of them are adapted to the treatment of congestive heart failure. They have been accused of masking the symptoms of hypoglycaemia and of hampering its correction in the diabetic patient by interfering with the adrenergic counter-regulatory mechanisms. This remains at the root of an unwarranted underuse in the diabetic patient. Their harmful effects should be taken into account, but should not rule out drugs that provide well-documented and effective anti-ischaemic protection, whether it is in the acute situation or as a long-term course of myocardial ischaemia treatment [40, 41]. Adverse drug reaction profile is variable and should be regularly monitored in the older patient. Certain compounds can be responsible for pronounced asthenia, hypotension, and bradycardia, and can aggravate the symptoms of peripheral arterial disease. As far as possible, preference should be given to selective beta-1-blockers while closely monitoring blood glucose level to prevent hypoglycaemic episodes.

- The calcium channel blockers can be used in treating stable angina, and in second-line therapy for unstable angina. They have no place in the acute phase of MI. Their tolerance is good and poses no problems to the elderly diabetic patient.

2.4.3.2. Antithrombotics. The use of antithrombotic treatments is a major step forward in managing ischaemic heart disease. The disadvantage is a risk of hemorrhage, which limits their use in older subjects. Finally, their use responds to precise rules [23, 24, 26, 27].

- Anticoagulants: anti-vitamin Ks are not usually used after acute coronary syndrome. Associated with aspirin, they have been shown to be effective in reducing cardiovascular events but at the price of an excess risk of hemorrhage; their use is therefore not advised for the elderly diabetic patient. Unfractionated heparin can be used during acute coronary syndromes in association with aspirin. Low-molecular-weight heparins (LMWHs), in particular enoxaparin, are indicated during acute coronary syndromes in association with other anti-thrombotics. They should be used cautiously in older diabetics because of a risk of hemorrhage that is difficult to predict. Generally speaking, LMHW use requires rigorous precautions in older patients. They are contraindicated in case of severe renal failure (creatinine clearance lower than 30 ml/min according to the Cockcroft formula).

- Platelet aggregation inhibitors: they consist mainly in aspirin, clopidogrel, and the antiglycoproteins (Gp) IIb/IIIa. These products strongly inhibit platelet aggregation by acting on different pathways. They can be used alone or in association. They expose the patient to a risk of hemorrhage that is not insignificant and is difficult to predict in older and very old subjects, particularly when they are used in association with each other or associated with anticoagulants.

- Aspirin inhibits the aggregation of platelets by blocking cyclo-oxygenase. Notwithstanding its cardiovascular preventive effects, it comes with an excessive risk of hemorrhage, which implies using it at low doses in situations where the benefits outweigh the risk. This is the case in the elderly diabetic in the situation of secondary cardiovascular prevention and during acute coronary syndromes (unstable angina and MI). The recommended dosage is 75 mg/day. It is not necessary to systematically combine aspirin with a proton-pump inhibitor over the long-term. Its use in primary prevention of CHD is therefore debatable in the older diabetic.

- Clopidogrel inhibits platelet aggregation by blocking the adenosine diphosphate (ADP) route. It is indicated at a dose of 75 mg/day in secondary cardiovascular prevention in patients with a history of MI. In acute coronary syndromes (unstable angina, nontransmural infarction, and transmural infarction), this drug is indicated combined with aspirin, in a 300-mg loading dose, followed by a 75-mg/day maintenance dose to be continued for 9-12 months. Whatever the context (unstable angina or stable angina), clopidogrel is prescribed for angioplasty when a stent is placed. The current trend is to begin treatment before the procedure and continue it for at least 6 months. It is very important not to interrupt treatment during this 6-month period because of the risk of thrombosis brought on by the stent. The consequences of this disadvantage must be weighed, particularly if surgery is planned in the short term.

- The anti-Gp IIb/IIIa inhibit platelet aggregation by blocking the activation of the corresponding receptors. Use of these drugs is only possible within the context of acute coronary syndromes in patients who are candidates for angioplasty, for short periods of time, intravenously, and in association with other anti-thrombotics. Their use in diabetics is an elective indication. It has reduced 30-day mortality, whereas its use in the nondiabetic has not changed the prognosis [42]. On the other hand, their use increases the risk of hemorrhage, to a varying degree depending on the study. A recent investigation showed that pretreatment with eptifibatide in high-risk patients (subjects over 75 years of age, diabetics) who are candidates for planned coronary angioplasty, very significantly improves the prognosis, with a nearly 50% reduction in death and infarctions at 30 days and 1 year, with no significant increase in the risk of hemorrhage in the group treated [43].
Thrombolytics: they are only used in the context of a MI in the acute phase. The earlier the treatment is administered, the more beneficial its effect is. These drugs are responsible for strokes, which increase with age to more than 10% beyond the age of 75 [11]. The real benefit for aged patients remains under debate, to such an extent that in the absence of precise data, it seems reasonable not to propose them to elderly diabetic patients.

2.4.4. Myocardial revascularization

Myocardial revascularization in the aged diabetics poses particular problems related to, other than the patient’s susceptibility, the distribution of the lesions, the narrowing of the arterial system, the importance of calcification, and the tendency toward restenosis after angioplasty [44]. Despite the progress made over the past few years, the results are less optimistic than in nondiabetics and their future is less favorable. Two types of methods can be used: percutaneous angioplasty and bypass surgery.

2.4.4.1. Contribution of percutaneous coronary angioplasty.

Age, as well as the co-morbidities that the older diabetic patient presents, increase the operative risk, whereas they have a lesser effect on angioplasty results. For this reason, this method seems to be particularly advantageous for these patients, but performed alone, the results are disappointing. Therefore, in a post-hoc analysis of the diabetic subgroup, the BARI (Bypass Angioplasty Revascularization Investigation) study [45] showed excessive 5-year mortality for angioplasty compared to surgery (35.5% vs. 19.0%). However, a difference was shown for patients who had had saphenous vein grafts or mammary artery bypass. Only these patients had a more favorable prognosis than those with angioplasty. These results differ noticeably from what is observed in the general population where there is no difference between the two procedures in terms of long-term survival.

A whole series of technical developments has advanced these results. The use of stents has improved the permeability of bypasses but has left open the problem of restenosis. The use of active stents has solved this problem. Finally, more recently the use of the anti-Gp IIb/IIIa has again improved prognosis.

The future of these patients compared to nondiabetics is being debated. In a retrospective study using sirolimus-eluting or paclitaxel-coated stents, no difference was noted in terms of clinical and angiographic results at nine months between a group of diabetics and a group of nondiabetics with a mean age of 61 years [46]. Another retrospective study on patients with similar characteristics treated with sirolimus-eluting stents showed substantially different results, with more events in the diabetic patients [47].

2.4.4.2. Bypass surgery. Diabetes and age are factors of poor prognosis in coronary surgery, as is a change in cardiac function and hemodialysis. In a cohort study on 42,663 diabetics, with a mean age of 65 years, surgically revascularized in 1997 in a group of 434 North American hospitals, excess early mortality appeared in diabetics (3.7%) compared to nondiabetics (2.7%). The causes of death were mainly cardiac, but with no difference between the two groups. On the other hand, the diabetics presented an excess of neurological events, kidney failure, and infections.

A more recent study specifies the long-term outcome of these patients and the part played by surgical technique. In a cohort study comparing 467 diabetics with 664 nondiabetics, with a mean age of 62 years, presenting with surgically revascularized CHD, early postoperative mortality was comparable between the two groups and was not different depending on whether the patients had had one or two mammary bypass surgeries. Ten-year survival was slightly better in the nondiabetics (79.5%) than in the diabetic patients (76.8%) (P=0.06). In diabetics, 6-year survival was not different depending on whether they had had one or two mammary bypass operations; however, 10-year survival was better in the subgroup that had had such operations (80.2% vs. 75.4%, P=0.046). In this study, age was a factor in excessive mortality in the diabetic patients having undergone surgery [48].

When surgery and coronary artery angioplasty are compared, the first studies [45] showed a better result with surgery in multivessel CHD diabetic patients. This benefit was less clear in patients at high surgical risk such as older patients and did not take into account the contribution of the anti-Gp IIb/IIIa. The BARI-2 study currently underway should answer to this question.

It therefore seems that diabetic patients present a moderate excess surgical risk compared to nondiabetics and lower rates of survival. This risk is higher in the subgroup of elderly diabetics. The comparison between surgery and interventional procedures that initially favored surgery may change as these latter techniques evolve, particularly for older diabetics [49]. In any case, angioplasty revascularization will be preferred whenever possible, with surgery reserved for extreme situations that are otherwise inaccessible.

3. Cardiovascular autonomic neuropathy of the older diabetic patient

Cardiovascular autonomic neuropathy (CAN) of the older diabetic is a frequent complication [50]. Investigating this disease poses a certain number of problems stemming from its nature and the role of aging.
3.1. Position of the problem

The description of CAN is less simple than it may seem: this disease remains silent for a long time and it manifests clinically late, which explains that its prevalence depends to a large degree on the stage at which it is diagnosed and therefore the sensitivity of the diagnostic methods used. Age itself is a factor of deterioration of the autonomic nervous system (ANS), such that it is difficult in the older diabetic patient to differentiate what stems from the diabetes and what is caused by aging [51, 52].

There have been no studies establishing its prevalence in the elderly diabetic. In the general population, prevalence varies from 7.7% to 90%, depending on the diagnostic methods used [50]. Beyond these numbers, this disease can be considered, at least at the subclinical stage, the most frequent degenerative complication. The crux of the matter lies in establishing the consequences.

3.2. Natural history, pathogenesis

ANS involvement is frequent during diabetes and appears early. It is even more frequently encountered as these patients age. Its presence is significantly associated with macroangiopathy, particularly renal disease, and with obesity in type 2 diabetics. However, it is not correlated with the presence of macroangiopathy [53].

The longest fibers are the first ones affected, which explains why involvement starts with the parasympathetic system, with sympathetic involvement coming later.

The consequences remain subclinical for a long time. Clinical expression is capricious and only appears at an advanced stage of denervation.

Aging produces harmful effects of the same type on the ANS. It is therefore responsible for a lower parasympathetic response to stimuli, whereas the sympathetic response remains preserved [51, 52].

Hypotheses on the pathogenesis of the disease refer to metabolic disorders of the nerve fibers, ischaemic mechanisms related to vasoconstriction phenomena related to activation of protein kinase C and accumulation of free radicals, autoimmune phenomena, and a deficit in growth factors and neurohormonal factors [50].

3.3. Diagnosis

The diagnostic methods used to demonstrate CAN have greatly evolved over the past few years. In the 1970s, DJ Ewing was the first to propose a battery of tests to evaluate the reflex response of the cardiovascular system to stimuli that brought into play the parasympathetic and sympathetic systems, involving variations from heart rate (HR) to deep breathing, moving from a supine position to an orthostatic position, and the Valsalva maneuver, and variations in BP [54]. These tests, the reference method, have standardized the diagnostic approach to CAN. In clinical practice, they are often used in a dissociated or partial manner, which modifies the method’s sensitivity, removing some of its interest. They have the disadvantages of requiring good cooperation on the part of the patient and being relatively long to implement, with the result that they are difficult to use with the older diabetic.

Other methods were later developed such as the dosage of plasma catecholamines and the analysis of heart rate (HR), indirect evaluation methods. Positron emission tomography (PET), which is the first method to specify the type and extension of cardiac sympathetic involvement, and MIBG (I^{123}-meta-iodobenzylguanidine) scintigraphy, which evaluates sympathetic activity in vivo by measuring postganglionic, presynaptic noradrenaline release [55]. These different methods, except for the analysis of HR variation, remain research methods. Heart rate variation analysis is widely used and is based on the fact that the HR is modulated by high-frequency oscillations (HF, 0.18–0.40 Hz) depending on breathing, which is a marker of parasympathetic activity, and low-frequency oscillations (LF, 0.03–0.15 Hz), which are in part influenced by the sympathetic nervous system. The LF/HF ratio is a good indicator of vagosympathetic equilibrium. This method has the advantage of being easy to implement with a Holter recording. The results of this recording generally correlate well with Ewing tests [56], but they have the disadvantage of not discriminating borderline situations. This method cannot be used in patients with arrhythmia, in particular subjects with auricular fibrillation, which considerably reduces its potential in older diabetics.

3.4. Consequences

The consequences of CAN depend on the severity of the denervation and the patient’s condition and susceptibility associated with the disease. Subclinical neuropathy screened through the above-mentioned tests should be distinguished from clinically expressed CAN. The existence of CAN is a factor of excess cardiovascular mortality, but several doubts remain on the relation between the severity of the neuropathy and the excess mortality as well as on the causal mechanisms [55].

3.4.1. Subclinical neuropathy

At the subclinical stage, CAN is manifested through permanent tachycardia with a decrease in sinus variability, a change in the sensitivity of the baroreflex with an increase in BP variability. Detection of these anomalies is based exclusively on the above-mentioned tests. It is probable that the excess risk associated with CAN progresses with increasing severity of the disorder, but it is difficult to establish the condition at an early stage. It is possible that intensive treatment could slow down progression [57]. Therefore, the importance of CAN seems to attest to the increase in cardiovascular mortality in older diabetics presenting orthostatic hypotension [58]. Finally, the need to place a pacemaker
seems greater in elderly diabetics and this may be related to the more frequent existence of myocardial ischaemia but also to CAN [59].

### 3.4.2. Clinical neuropathy

When it is expressed clinically, CAN is responsible for intolerance to exercise, abnormalities in BP regulation with possible orthostatic hypotension symptoms, silent myocardial ischaemia, an excess of major cardiovascular events, and excess mortality [50]

- Intolerance to exercise may result from the diabetic’s lower capacity for accelerating the HR and a reduction in myocardial contractile capacity [60]. It is particularly difficult to isolate the role played by CAN in symptoms that are so frequent in the elderly subject and whose causes are often multifactorial.

- Abnormalities in BP regulation are detected at best by ambulatory BP measurement. Typically, this test demonstrates the BP’s variability and an inversion of the BP’s nycthemeral rhythm, with nighttime values higher than daytime values. The severity of the abnormality is directly correlated with the seriousness of the patient’s CAN [61]. Inversion of the nycthemeral rhythm is frequently associated with nephropathy. When the kidney disease is advanced, certain patients can present manifestations of orthostatic hypotension, reflecting sympathetic denervation. At a minimum, orthostatic hypotension involves discomfort, but it can also be responsible for angina symptoms and loss of consciousness. It is immediately associated with episodes of nighttime hypotension.

- Silent myocardial ischaemia (SMI) is a frequent complication of diabetes in the elderly subject. The silent nature of the myocardial ischaemia may be furthered by autonomic denervation. In a 12-study meta-analysis, CAN in a diabetic subject confers a highly significant excess risk for SMI compared to the healthy diabetic patient (RR = 1.96, CI95 [1.53–2.51], P < 0.001) [50].

- The relation between the existence of CAN and the onset of major cardiovascular events was evaluated in two prospective studies with small sample numbers. These studies observed the occurrence of a fatal or non-fatal cardiovascular event such as angina, MI, congestive heart failure, tachycardia or resuscitated ventricular fibrillation, and myocardial revascularization in diabetic subjects with or without CAN. The results are at the limit of significance and indicate that the presence of CAN confers an excess risk between 2.2 and 3.4 [62, 63].

- Fifteen studies on 2900 diabetics under care for 1-16 years showed excess mortality in diabetics presenting with CAN compared to those who did not have CAN, with an excess risk ranging from 0.91 to 9.20. These studies were part of a meta-analysis that estimated the excess risk at 2.14 [50]. The reasons for this excess mortality are being debated. The role of different mechanisms has been suggested such as the autonomic control of breathing with a reduction in the sensitivity to hypoxia or a lower sensitivity to hypoglycaemic episodes. Finally, an excess of sudden death caused by arrhythmia disorders could be related to a parallel progression in microvascular complications. Excess sudden death due to arrhythmia may be favored by a lengthening of the QT interval, whose duration reflects the neurovegetative influences that are exerted on the heart. Several studies have shown a relation between the duration of the QT interval and the severity of CAN [64, 65]. Diabetics also present an increase in QT dispersion, but the relation between this abnormality and CAN remains under debate [65]. However, the responsibility of CAN as such in the excess mortality of diabetics is not unanimously admitted. In the Rochester Diabetic Neuropathy Study, the investigators showed that all patients who died suddenly, diabetics and non-diabetics, presented severe CHD or a left ventricular dysfunction. They suggested that the neuropathy could be, at most, a contributor but not an independent cause of death [66].

CAN is a frequent degenerative complication in diabetics, in particular in the oldest subjects. Since age itself has harmful effects on autonomic function, these effects cannot be dissociated from the role of diabetes. CAN is not a monomorphous entity and presents in varying degrees of seriousness, which are poorly accounted for in the literature. The consequences of subclinical involvement, which is the most frequent, deserve to be more clearly detailed. The most severe involvement has serious clinical consequences and is a factor of excessive mortality whose causal mechanisms remain poorly understood.

### 4. Management of the disease – practical considerations

The objective of management for the elderly diabetic is to shield the patient from the complications of cardiac involvement and prevent the onset of new handicaps by being the most effective and the least aggressive possible. It is not possible to define a standardized treatment since elderly subjects can vary so much in their attitude and physiological condition. It is not useful, for example, to propose aggressive investigations to patients who do not wish to take advantage of myocardial revascularization.

#### 4.1. Objectives

The essential treatment objectives of cardiac manifestations in diabetic patients include improving the vital prognosis, but even more in elderly subjects, acting on their symptoms and quality of life. There have been no studies investigating this particular case of the elderly diabetics, and as a result we have no choice but to transpose the knowledge gained from
studies on younger subjects. Improvement in quality of life should be assessed based on specific scales, but also on the regression of symptoms and the decrease in the frequency of hospitalizations. Nutritional recommendations should be more flexible than in young subjects because of the risk of denutrition and hyponatremia related to a diet with low salt intake and the use of diuretics. Close monitoring is therefore indispensable, both on compliance and the importance of the symptoms, which are essential conditions for maintaining an acceptable quality of life.

4.2. Evaluation of the elderly diabetic

Evaluation of the diabetic’s condition should take the following into account: the risk level the patient is exposed to in the immediate future and the possibilities for treatment depending on the patient’s cognitive state, the existence of comorbidities, the quality of the arterial system, the existence of kidney failure, and the risk factors related to diabetes. This evaluation includes precise questioning, a complete clinical examination, and a minimum of complementary examinations: the usual blood and urine chemistry analyses, resting ECG, cardiac echography, echo-Doppler of the supra-aortic trunks, the aorta, and the arteries of the lower limbs.

Questioning the patient should target most particularly a history of ischaemic heart disease, congestive heart disease, and high blood pressure. The clinical examination assesses the patient’s general condition, the intellectual functions, the severity of the angina episodes when they exist, the hemodynamic state, and the possible presence of another visceral disease.

Beyond the habitual risk factor parameters, two elements are of a particular importance:
– The existence of renal failure has a negative cardiovascular prognosis [67]. It is very frequently encountered in these patients, but it must be emphasized that the Cockcroft evaluation tends to overestimate its severity in elderly subjects [68]. Renal failure makes iodated tests more difficult, in particular coronarography, and limits the use of certain drugs such as drugs acting on the renin-angiotensin system and low-molecular-weight heparins. Finally, renal failure can worsen rapidly, and can itself pose complex problems;
– The quality of the peripheral arteries, notably with advanced atheroma, a highly calcified arterial system, or the presence of an aorta aneurysm, causes the frequent problems that expose the patient to complications during hemodynamic explorations, interventional procedures, and surgery.

4.3. The different scenarios

4.3.1. When there is no serious handicap in patients less than 80 years old

Management should follow the same recommendations as for younger subjects.

– Screening for silent ischaemia with a preference for Technetium Myocardial Perfusion Scintigraphy (TMPS). When TMPS shows extended ischaemia (>10% of the myocardia), revascularization should be discussed after coronary imaging;
– Screening for CAN is useful and should include at least the search for orthostatic hypotension;
– Patients presenting with stable CHD should have an annual evaluation. For those with incapacitating angina or extended ischaemia, a revascularization procedure should be discussed;
– Patients presenting with acute coronary syndrome should be managed in a specialized facility. Attaining blood glucose control as close to perfect as possible is indispensable and most often requires insulin therapy. The possibility of revascularization will always be decided according to the risk for constitutive MI and with the patient’s condition in mind. It will be preceded by a coronarography, and generally angioplasty will be preferred.

4.3.2. In patients presenting a severe handicap or advanced age

– Systematic screening for silent ischaemia no longer seems warranted;
– In cases of incapacitating angina or acute coronary syndrome, a purely medical approach is preferable because of the high level of iatrogenic consequences in interventional procedures in these patients.

4.3.3. In all diabetics

As soon as the CHD is established, the usual anti-ischaemic treatment should be started, associated with aspirin, a statin, and possibly an ACEI if the blood pressure level and the renal status permit it. During acute episodes, good glycaemic control is essential.

5. Conclusion

Cardiac complications are particularly frequent, taking on a wide variety of forms in elderly diabetic patients. The armamentarium has been greatly enriched over the last few years, which has limited the consequences and thus improved the quality of life of these patients, so that a wait-and-see attitude is no longer valid. Prevention of these manifestations is based on better management of the cardiovascular risk factors and better control of blood glucose. In this area, progress still needs to be made, but this also requires adapting to the clinical and psychological condition of the elderly diabetic. A necessary distinction should be made between subjects who are aging successfully and whose management differs little, in the end, from younger subjects, and the frail elderly for whom exploratory techniques should be nuanced.
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