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Expert consensus

Risk stratification and screening for coronary artery disease in asymptomatic patients with diabetes mellitus: Position paper of the French Society of Cardiology and the French-speaking Society of Diabetology

Évaluation du risque et dépistage de la maladie coronaire chez le patient diabétique asymptomatique. Consensus de la société française de cardiologie et de la société francophone de diabétologie

Paul Valensi [a,1], Patrick Henry [b,2,*], Franck Boccara [c], Emmanuel Cosson [d,e], Gaetan Prevost [f], Joseph Emmerich [g], Laura Ernande [h], Dany Marcadet [i], Elie Mousseaux [j], François Rouzet [k], Ariane Sultan [l,m], Jean Ferrières [n], Bruno Vergès [o], Eric Van Belle [p,q,r]

[a] *Unit of Endocrinology Diabetology Nutrition, AP-HP, Jean Verdier hospital, CINFO, CRNH-IdF, Paris 13 University, Sorbonne Paris Cité, Bondy, France*
[b] *Department of Cardiology, Inserm U942, Lariboisiere Hospital, Assistance Publique - Hôpitaux de Paris, University of Paris, Paris, France*
[c] *AP-HP, Hôpitaux de l'Est Parisien, Hôpital Saint-Antoine, Department of Cardiology, Sorbonne Université-Inserm UMR S_938, Centre de Recherche Saint-Antoine, Paris, France*
[d] *AP-HP, Avicenne Hospital, Paris 13 University, Sorbonne Paris Cité, Department of Endocrinology-Diabetology-Nutrition, CRNH-IdF, CINFO, Bobigny, France*
[e] *Paris 13 University, Sorbonne Paris Cité, UMR U557 Inserm/U11125 INRAE/CNAM/Université Paris13, Unité de Recherche Epidémiologique Nutritionnelle, Bobigny, France*
[f] *Department of Endocrinology, Diabetes and Metabolic Diseases, Normandie Univ, UNIROUEN, Rouen University Hospital, Centre d'Investigation Clinique (CIC-CRB)-Inserm 1404, Rouen University Hospital, 76000 Rouen, France*
[g] *Service de Médecine Vasculaire, Groupe Hospitalier Paris Saint-Joseph, Université de Paris, Inserm UMR1153-CRESS, 75674 Paris cedex 14, France*
[h] *Service des explorations fonctionnelles, Hôpital Henri Mondor, AP-HP et Inserm U955, Université Paris-Est Créteil, France*
[i] *Centre Coeur et Santé Bernoulli - Cardiologie du sport et Réadaptation Cardiaque, 3, rue Bernoulli, 75008 Paris, France*
[j] *Radiology Department, Hôpital Européen Georges Pompidou & Inserm U 970; Assistance Publique - Hôpitaux de Paris, University of Paris, French Society of Cardiovascular Imaging (SFICV), Paris, France*
[k] *Nuclear Medicine Department, Bichat Hospital, AP-HP Paris - Université de Paris, Laboratory for Vascular Translational Science, Inserm, UMR 1148, 75018 Paris, France*
[l] *Physiologie et Médecine Expérimentale du Coeur et des Muscles (PHYMEDEX), U1046 Inserm, UMR9214 CNRS, Université de Montpellier, 34295 Montpellier*
[m] *Département Endocrinologie, Nutrition, Diabète, Equipe Nutrition, Diabète, CHRU Montpellier, 34090 Montpellier, France*
[n] *Department of Cardiology and UMR Inserm 1027, Toulouse Rangueil University Hospital, Toulouse University School of Medicine, Toulouse, France*
[o] *Service Endocrinologie-Diabétologie, CHU Dijon - Inserm LNC-UMR 1231, Dijon, France*

Abbreviations: ABI, ankle-brachial index; ACCORD, Action to Control Cardiovascular Risk in Diabetes; ADA, American Diabetes Association; ADVANCE, Action in Diabetes and Vascular Disease: Preterax and Diamicron - Modified Release Controlled Evaluation; ARIC, Atherosclerosis Risk In Communities; AU, Agatston units; BARI 2D, Bypass Angioplasty Revascularization Investigation 2 Diabetes; BP, blood pressure; CAC, coronary artery calcium; CAD, coronary artery disease; CAN, cardiac autonomic neuropathy; CCTA, coronary computed tomography angiography; CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CMR, cardiac magnetic resonance; CV, cardiovascular; CVD, cardiovascular disease; EASD, European Association for the Study of Diabetes; eGFR, estimated glomerular filtration rate; ESC, European Society of Cardiology; FFR, fractional flow reserve; GLP-1 RA, glucagon-like peptide 1 receptor agonist; HAS, Haute Autorité de Santé (French National Authority for Health); HbA1c, glycated haemoglobin; HDL-C, high-density lipoprotein cholesterol; IMPROVE-IT, Improved Reduction of Outcomes: Vytorin Efficacy International Trial; JPAD, Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes; LDL-C, low-density lipoprotein cholesterol; LEADER, Liraglutide Effect and Action in Diabetes: Evaluation of CV Outcome Results; LGE, late gadolinium enhancement; Look AHEAD, Action for Health in Diabetes; LV, left ventricular; MACE, major adverse cardiovascular events; MESA, Multi-Ethnic Study of Atherosclerosis; METs, metabolic equivalents of the task; MI, myocardial infarction; NAFLD, non-alcoholic fatty liver disease; ORBITA, Objective Randomised Blinded Investigation With Optimal Medical Therapy of Angioplasty in Stable Angina; OSAS, obstructive sleep apnoea syndrome; PCSK9, proprotein convertase subtilisin/kexin type 9; PET, positron emission tomography; POPADAD, Prevention Of Progression of Arterial Disease And Diabetes; RAAS, renin-angiotensin-aldosterone system; SCOT-HEART, Scottish Computed Tomography of the Heart; SFD, Société Francophone du Diabète (Francophone Society of Diabetes); SGLT2, sodium glucose transporter-2; SMI, silent myocardial ischaemia; SPECT, single-photon emission computed tomography; T1D, type 1 diabetes; T2D, type 2 diabetes; UKPDS, UK Prospective Diabetes Study; VADT, Veterans Administration Diabetes Trial.

* Corresponding author.
E-mail address: patrick.henry@aphp.fr (P. Henry).
[1] French-speaking Society of Diabetology Chairperson.
[2] French Society of cardiology Chairperson.

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[p] Department of Interventional Cardiology for Coronary, Valves and Structural Heart Diseases, Institut Coeur Poumon, Centre Hospitalier Universitaire de Lille, Lille, France
[q] Inserm, U1011, Institut Pasteur de Lille, EGID, Lille, France
[r] Department of Medicine, Université de Lille, Lille, France

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Introduction

Diabetes is a chronic metabolic disease, characterized by elevated levels of blood glucose, which leads–over time–to serious damage to the heart, blood vessels, eyes, kidneys and nerves. The incidence of cardiovascular (CV) events is greater in people with diabetes compared to those without [1–4]. A large number of people with diabetes do not survive their first CV event and, if they do survive, their subsequent mortality rate is higher than for those without diabetes [5].

During recent decades, the risk of CV events has markedly decreased in patients with diabetes, but it remains higher than in the general population. CV risk associated with diabetes is heterogeneous. A risk stratification approach must be considered for each patient in order to define the need for additional investigations and the goals to achieve, and to adjust pharmacological treatments. Even if silent coronary disease is frequent in patients with diabetes, its detection in primary prevention is still debated. Several non-invasive screening tools have been proposed to detect coronary artery disease (CAD), and new screening methods with greater performances are now available. However, their prognostic value, cost-benefit ratio and the potential harms of such approaches must be carefully evaluated. While risk related to screening procedures and overtreatment should be avoided in patients with moderate risk, some additional investigations may be considered in high-/very high-risk patients, as the results may lead to better estimation of the risk and refinement of the goals and treatments. Moreover, in addition to the major role of glycaemic, lipid and blood pressure (BP) control in CV prevention, the recent CV outcome trials [6] have provided strong evidence in favour of the role of some new glucose-lowering drugs in the prevention of CV complications, in particular in patients with established atherosclerotic complications.

Regarding the assessment of asymptomatic patients, the latest French guidelines, published in 2004, already limited assessment of myocardial ischaemia to selected patients [7]. The American Diabetes Association (ADA) guidelines recommend not screening asymptomatic diabetes patients for silent CAD [8]. A risk stratification approach has recently been developed by the European Society of Cardiology (ESC) in collaboration with the European Association for the Study of Diabetes (EASD) [6]. This approach includes age, type and duration of diabetes, the number of associated risk factors and target organ damage. Indeed, carotid or limb arterial ultrasound study, coronary artery calcium (CAC) score and coronary computed tomography angiography (CCTA) can be proposed for a better assessment of CV risk.

This position paper proposes a consensus strategy defined by diabetologists, cardiologists and CV imagers in order to more precisely evaluate coronary risk; and proposes strategies according to risk level in asymptomatic diabetes patients in primary prevention.

Cardiovascular risk in patients with diabetes in primary prevention

Different types of diabetes and the diagnostic criteria for diabetes and prediabetes are shown in Supplementary data, Tables S1 and S2, respectively. CV risk is increased in both type 1 diabetes (T1D) and type 2 diabetes (T2D), although T1D has been less well studied, and the data in rare monogenic diabetes are scarce. Data from a meta-analysis of 37 prospective cohort studies among more than 400,000 individuals reported an increased adjusted relative risk of coronary mortality of 1.99 in men with diabetes and 3.12 in women with diabetes [2]. In a large survey performed in Finland with a mean 18-year follow-up, the adjusted hazard ratios for CV mortality were 3.6 in men with T1D, 13.3 in women with T1D, 3.3 in men with T2D and 10.1 in women with T2D, compared with individuals without diabetes [9]. In the Scottish Registry linkage study, men and women aged 20–39 years with T1D had 4.8- and 5.5-fold higher CV risks, respectively, than that of the general population, and the relative risk reached 3.1 and 5.0, respectively, among those aged 40–49 years [10]. For all CV outcomes, the relative risk is greater in T1D than in T2D, and in women than in men for both T1D and T2D. It is important to note that patients with T1D also have age-associated risk factors, including insulin resistance, similarly to patients with T2D.

In the Unites States, the rate of acute myocardial infarction (MI) declined by 68% between 1990 and 2010 [11]. Data from the Swedish National Diabetes Register showed that, between 1998 and 2012, deaths from CV disease (CVD) decreased by 42% among patients with T1D and 46% among patients with T2D [12]. Between 1984–1986 and 1995–1997, mortality from CAD decreased by approximately 50% in Norway, both in people with and without diabetes [4]. However, CV morbidity and mortality remained significantly higher in patients with diabetes. Indeed, in the United States, in 2010, the adjusted relative risk for acute MI was still 1.8 compared to people without diabetes [11]. Similarly, in Sweden, although CV risk declined between 2006 and 2013, the relative risk for MI remained significantly elevated (1.7) [13].

There is large heterogeneity for CV risk between diabetes patients depending on age, duration of diabetes and coexisting risk factors, including misunderstood risk factors such as the metabolic syndrome and chronic inflammatory state. Considering ethnicity and country income level is also important for the assessment of CV risk. For example, diabetes has emerged as a strong risk predictor of multivessel disease among Afro-Caribbean patients [14] and those from the Indian subcontinent [15]. It is now well documented that people from South Asia, North Africa and the Middle East remain at a higher risk for CV death after age and mortality standardization [16]. In addition to anatomical peculiar-

ities such as smaller coronary artery size described in Asian populations, numerous factors have been implicated, including tobacco exposure linked to income levels, worse metabolic control and access and adherence to CV treatments.

Particularities of coronary artery disease in diabetes patients

Severity and diffusion of coronary artery disease in diabetes patients

CAD is more severe, more extensive and more diffuse in individuals with versus without diabetes. The autopsy register of Rochester showed that, among patients aged over 65 years, the prevalence of high-grade and multivessel coronary lesions was similar in patients with diabetes but without antemortem CAD as in those without diabetes but with antemortem CAD [17]. Angiographic studies have shown that CAD in diabetes patients has a number of specificities, with more diffused lesions, more intermediate lesions, more calcification and pronounced damage on the distal coronary bed [18,19]. A decrease in coronary collateral formation in response to chronic myocardial ischaemia has also been described [20]. Vascular calcification is likely driven by specific diabetes-associated mechanisms with vascular smooth muscle cells undergoing osteogenic transformation.

Pathophysiology

The main pathophysiological mechanisms of atherothrombosis in patients with diabetes are illustrated Fig. 1.

Inflammation. The discovery of elevated tumour necrosis factor-α in adipose tissue as an inducer of obesity associated insulin resistance indicates that a subclinical inflammatory process underlies metabolic changes. Chronic inflammation associated with increased oxidative stress and abnormal macrophage functions has been incriminated in CAD associated with diabetes [21]. Major biochemical pathways–including the overproduction of reactive oxygen species, increased formation of advanced glycation end-products and activation of the receptor of advanced glycation end-products (RAGE), polyol and hexosamine flux, protein kinase C activation, and chronic vascular inflammation–are involved in diabetic macroangiopathy [22]. Strategies that focus on inflammatory risk are ongoing [23].

Endothelial dysfunction and reduced coronary reserve. Endothelial dysfunction is an early and ubiquitous marker of vascular disease in diabetes. Characterized by vasodilatation abnormalities, inflammation and a pro-thrombotic state, its pathophysiology remains complex [24]. Apart from hyperglycaemia, associated risk factors–but also insulin resistance and hyperinsulinemia–may contribute to endothelial dysfunction by increasing oxidative stress and decreasing nitric oxide bioavailability [25,26]. In clinical practice, microalbuminuria may be considered as a marker of endothelial dysfunction [27]. Endothelial dysfunction can also be assessed by the cold pressure test, flow-mediated dilatation, index of microcirculatory resistance in coronary arteries, positron emission tomography (PET) and cardiac magnetic resonance (CMR) imaging. Such an impairment is associated with a more than doubled incidence of CV events during 10 years of follow-up [28]. Using PET, a progressive decline in myocardial blood flow and myocardial flow reserve from insulin resistance to diabetes has been described [29,30]. Such an impairment appears to be reversible after improvement of glycaemic control [31]. Together, these results suggest that endothelial dysfunction should be considered as an early marker of vascular disease in patients without documented atherosclerotic lesions.

Thrombogenesis. Many coagulation abnormalities have been found among those with diabetes, including general coagulation and platelet aggregation abnormalities, as well as fibrinolysis im-

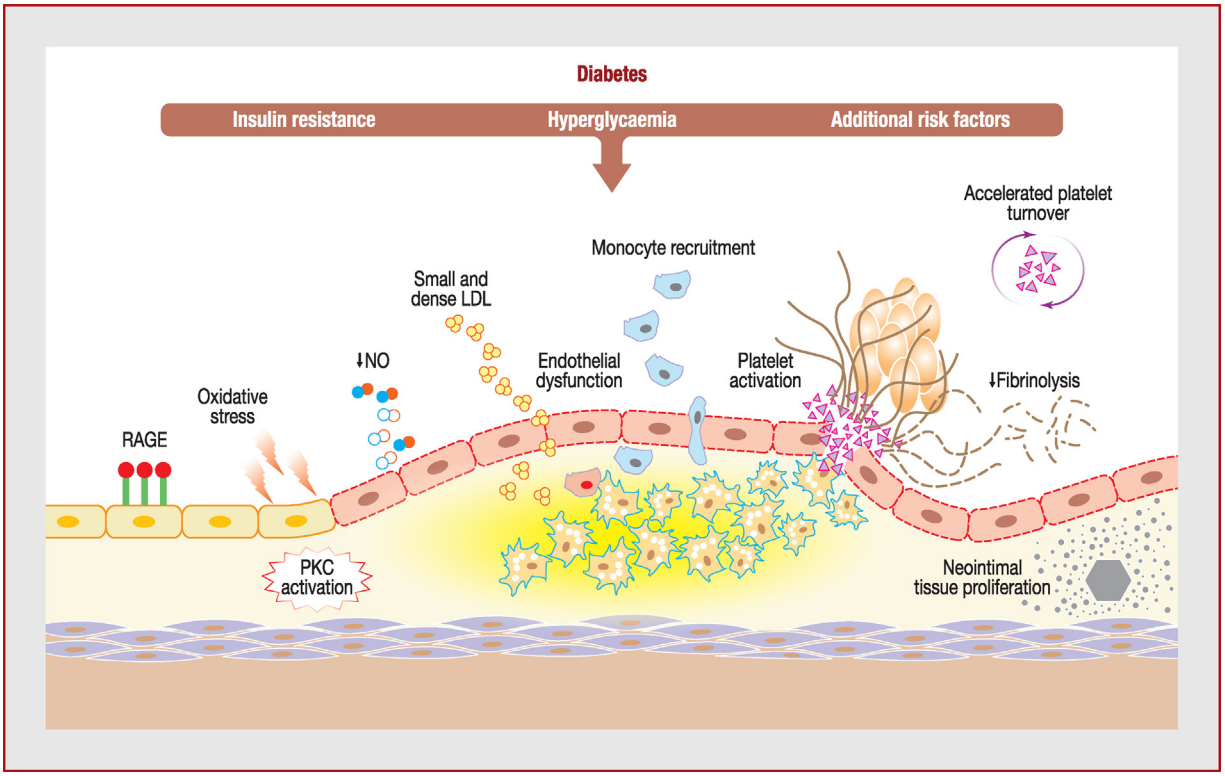

Figure 1. Main pathophysiological mechanisms of atherothrombosis in diabetic patients. LDL: low-density lipoprotein; NO: nitric oxide; PKC: protein kinase C; RAGE: receptor of advanced glycation end-products.

pairment (increase of plasma fibrinogen and plasminogen activator inhibitor-1 and reduction of tissular plasminogen activator levels) [32]. Hyperglycaemia, insulin resistance and metabolic-related disorders induce a prothrombotic state. RAGE ligands increase endothelial tissue factor expression. In addition, increased adherence and activation of platelets have been demonstrated. Finally, accelerated platelet turnover, with the generation of large, hyperactive platelets that induce an abnormal response to antiplatelet therapy (mainly aspirin), has recently been demonstrated in patients with diabetes [33,34]. Accelerated turn-over is probably linked to insulin resistance and atherosclerosis extension [35].

Particular clinical features of coronary artery disease in patients with diabetes

Acute coronary syndromes

Acute coronary syndromes usually arise from the rupture of vulnerable coronary plaque, with thrombus formation and occlusion of a coronary vessel. Several studies have demonstrated–using coronary optical coherence tomography–that coronary lesions of patients with diabetes are characterized by several features of plaque vulnerability, including a higher frequency of thin-capped fibroatheroma, a larger lipid core and the presence of microvessels and/or macrophages, suggesting coronary inflammation [36–38]. Diabetes is associated with increased plaque burden, healed plaque ruptures and positive remodelling, along with greater calcification in T2D [39].

Silent coronary artery disease in patients with diabetes

Silent myocardial infarction. Up to 50% of silent MIs are not detected at the time of onset, but are instead detected later during routine care, when CV symptoms occur or by cardiac imaging [40,41]. The prevalence of silent MIs among diabetic patients as detected by resting electrocardiogram (ECG) is around 4% and is markedly higher when using echocardiography, myocardial single-photon emission computed tomography (SPECT) or CMR [42]. In the Atherosclerosis Risk In Communities (ARIC) study, around 50% of all MIs were clinically silent, detected by ECG, with twice as many individuals having diabetes among those with silent or clinical MIs than among those without MI [43]. Many studies in patients with diabetes have assessed serial ECGs over several years and found that silent MIs detected by Q waves accounted for up to one third of all identified MIs (symptomatic and asymptomatic) [44]. However, the sensitivity and specificity of Q waves is questionable [45]. In patients with diabetes, unrecognized MIs detected by CMR have been linked with a 4-fold increased risk of major CV events and a 7-fold increased risk of mortality [46]. Heart failure has also been directly related to CAD in asymptomatic patients [47].

Asymptomatic myocardial ischaemia. Cohn proposed considering three separate populations of patients with silent myocardial ischaemia (SMI):

- totally asymptomatic individuals;
- asymptomatic patients who experienced MI;
- those with both symptomatic and asymptomatic ischaemic episodes [48].

We will focus on the asymptomatic primary prevention population. The prevalence of SMI among those with diabetes has been reported to range from 6% [49] to 35% [50]. Among patients with SMI, those who have significant CAD on angiography range from 35% [51] to 90% [52]. Ischaemia can be due, not only to CAD, but also due to functional changes, such as endothelial dysfunction [53], abnormal microcirculation and abnormal coronary reserve [54]. The presence of less painful myocardial ischaemia has been largely described in patients with diabetes and is associated with a worse prognosis [44,46].

The prevalence of SMI depends on several factors [55]:

- the sensitivity and specificity of the test performed. Performances to detect CAD are better for stress SPECT and stress echography than for ECG stress tests [56]. Also, the positive predictive value for CAD detection is higher when two tests are concordant [57];
- the number of CV risk factors, which changes the pretest probability and the positive and negative predictive values [49,50,58];
- the presence of target organ damage. Retinopathy [58], nephropathy [49,59], cardiac autonomic neuropathy (CAN) [60] and peripheral artery disease [57,58] are associated with a higher prevalence of SMI and CAD. Finally, CAC score and hypokinetic changes on echocardiography are also associated with SMI;
- the influence of care management. A large proportion of patients with SMI demonstrate resolution of ischaemia upon repeat stress imaging in relation with more intensive control of CV risk factors [61]. Similarly, the prevalence of SMI has been shown to decrease markedly over a 10-year period [62].

Evaluation of coronary risk in patients with diabetes

Risk factors and the principles for coronary risk stratification

T2D covers a wide spectrum, from the beginning of the disease without any organ damage to a severe disease with multiple chronic complications. Several CV risk factors are similar to those in individuals without diabetes, including age, family history of premature CV events, hypertension, smoking, elevated low-density lipoprotein cholesterol (LDL-C) and high waist circumference, and should be considered in patients with T1D and T2D [6,63]. Specific risk factors should also be considered in patients with diabetes: diabetes duration, glycated haemoglobin (HbA1c) level and target organ damage (both microvascular and macrovascular) [6]. Other clinical disorders including erectile dysfunction, obstructive sleep apnoea syndrome (OSAS) and non-alcoholic fatty liver disease (NAFLD) may also be associated with an increase in CV risk. Moreover, geographical area, socioeconomic status and the intensity of active prevention can dramatically change the risk. Thus, global risk calculators–such as 12 risk equations that were specifically developed in patients with diabetes [64]–cannot be applied to all patients with diabetes [65].

One innovation is that we now have access to specific investigations, such as coronary CT scans, which can provide interesting prognostic information [66,67]. It is then mandatory to distinguish newly diagnosed diabetes patients–for whom a usual risk calculator could be considered–and patients with a more advanced disease (e.g. diabetes duration of several years, patients with proteinuria)–for whom the CV risk is very difficult to estimate. In patients with a long diabetes duration, evidence of atherosclerosis may act as a risk modifier and shift patients to a very high risk level [67–69]. In 2019, the ESC/EASD diabetes, prediabetes and CVD guidelines recommended the use of risk modifiers such as the CAC score, the presence of carotid or femoral plaques or a low ankle-brachial index (ABI) [6]. The evidence of SMI also adds to the prediction of an event above and beyond routine assessment risk prediction [70]. For example, the risk of major cardiac events is higher when the defects on myocardial SPECT are

large [71]. The prognosis of SMI is worse when associated with target organ damage, in particular high CAC score or CAN [50,72].

Symptoms

It is mandatory to carefully check whether patients are actually free of symptoms suggestive of CAD–e.g. unexplained dyspnoea, chest discomfort and decreased functional capacity–which may be found in a large proportion of presumably asymptomatic patients [73]. The inability to accomplish an activity equivalent to 5 metabolic equivalents of the task (METs) (e.g. brisk walking) should be considered.

Diabetic microangiopathic complications

Several studies have suggested that diabetic microangiopathy is strongly associated with macrovascular disease. Microalbuminuria (20–200 mg/L) predicts both progression to overt diabetic nephropathy and CVD, including silent ischaemia. Moreover, decreased estimated glomerular filtration rate (eGFR; preferably by the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] equation) and macroproteinuria (> 200 mg/L) are independently associated with an increased CV risk [74]. Among patients with diabetes and chronic kidney disease (CKD)–defined by eGFR < 60 mL/min/1.73 m^2–the MI incidence rate was found to approach that among non-diabetic patients with a history of MI [75]. Among patients with CKD, major cardiac events actually account for almost 50% of total mortality [76]. CV risk is particularly high among patients with diabetes and end-stage renal disease. The Chronic Renal Insufficiency Cohort study showed that–among patients with CKD–diabetes, more marked insulin resistance and higher HbA1c level were among the main predictors of increased CAC [75]. In a study of 64 haemodialysis patients, including 12% with diabetes, CAC score was found to correlate with coronary flow velocity reserve evaluated by transthoracic Doppler echocardiography, and the patients with CAC score > 10 Agatston units (AU) had worse CV outcomes [77]. Altogether, the data show that–in patients with diabetes–those with eGFR < 30 mL/min/1.73m^2 or on haemodialysis are at very high CV risk, whereas in those with eGFR 30–60 mL/min/1.73m^2, CAC score measurement may reclassify some patients as very high risk.

Diabetic retinopathy is also a predictor of CV events, with a 2-fold increased risk for patients with severe retinopathy compared with those without retinopathy [78]. A significant relationship was also reported between retinopathy and CAC score [78].

CAN–defined by ≥ 2 abnormal cardiac reflex tests (among deep-breathing, lying-to-standing or Valsalva)–is a predictor of silent ischaemia and CV mortality [79]. In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, patients with baseline CAN were twice as likely to die as patients without CAN during 3.5 years of follow-up [80].

Frequently associated disorders

Erectile dysfunction and CVD share common pathophysiological features. Erectile dysfunction is strongly associated with endothelial dysfunction and the decrease of nitric oxide-induced vasodilation and smooth muscle relaxation in corpus cavernosum is well documented in diabetes. Erectile dysfunction can be interpreted as a very early manifestation of CVD, comparable to the detection of an atherosclerotic plaque. The impact of atherosclerosis on penile artery flow is higher than on the coronary arteries due to a smaller diameter [81]. Prospective studies have confirmed that erectile dysfunction predicts future CV events, and the CV risk in diabetes patients with erectile dysfunction is significantly increased [82]. Finally, some studies have suggested that erectile dysfunction could be the most effective predictor of silent CAD in patients with diabetes [59].

Studies have shown that OSAS is associated with increases in mortality and CV events [83,84]. Some studies suggest a bidirectional relationship between OSAS and diabetes, additive or synergistic effects for diabetic complications and a reciprocal enhancement in their impact on hypertension and CVD [85]. In addition, screening for OSAS seems justified in patients with diabetes, particularly to optimize BP control in cases of resistant hypertension and microvascular complications [86].

In individuals with NAFLD, CVD represents the leading cause of death, and accumulating data suggest that NAFLD is associated with an increased rate of incident CV events [87] (Supplementary data, Text S1). However, it is not clear whether it is appropriate to consider NAFLD *per se* as an independent risk factor for CVD and further prospective studies are needed to address the question of whether NAFLD should be used as a tool to better stratify CV risk [88] in patients with diabetes.

Resting electrocardiogram abnormalities

Resting ECG has a very poor negative predictive value, but a high positive predictive value for CAD. The presence of abnormal Q-waves (duration > 0.04 s and size > 1/3 compared to following R waves in two concordant leads) must be considered as a potential MI sequel even if left ventricular (LV) hypertrophy could be an alternative explanation. Abnormal negative T waves must also be considered as potential indicators of chronic myocardial ischaemia [89]. However, smooth negative T-wave abnormalities (typically in D1, aVL, V5 and V6 leads) are frequent in LV hypertrophy. Upward-pointing T waves were associated with a 5-fold greater risk of mortality [90]. Enlarged QRS, including left bundle branch block or a recent right bundle branch block, must also be taken into consideration, albeit they are less predictive of CAD. Atrial fibrillation is often linked with abnormal LV filling pressure or function and can be associated with CAD. Any ECG abnormality should lead to resting echocardiography as a first-line examination. Systematic ECG is cost effective and should be performed annually in patients with diabetes [44].

Holter ECG is not considered to be useful due to its low sensitivity for the detection of ischaemic episodes in patients without known CAD [51].

Biological risk modifiers

Control of traditional risk factors

In the Swedish National Diabetes Register, which included 271,174 patients with T2D matched with controls, patients were assessed according to the presence of five risk factors (HbA1c ≥ 7%, elevated LDL-C ≥ 2.5 mmol/l [≥ 97 mg/dL], albuminuria, smoking and BP ≥ 140/80 mmHg) [63]. The results showed a stepwise increased risk for acute MI with each additional variable not at target, and that elevated HbA1c and LDL-C were among the main risk drivers [63].

Biological risk modifiers not related to glycaemic control

Diabetes and the prediabetic state have been associated with subclinical myocardial necrosis that could be identified by troponin measurement [91]. Such an increase in troponin level is predictive of CV events. However, troponin increase is not necessarily related to CAD and may suggest associated abnormalities of the microvascular bed and/or a specific cardiomyopathy. Similarly, brain natriuretic peptide or N-terminal pro brain

natriuretic peptide are good markers of CV events in patients with T1D or T2D [92,93].

Inflammatory markers, mainly high-sensitivity C-reactive protein, have also been linked to an increased risk of CV events, mainly death and MI, particularly in patients with diabetes [94]. However, high-sensitivity C-reactive protein is not specific and cannot be used as such in daily practice.

Uric acid is associated with obesity and insulin resistance [95] and is also linked to poor CV prognosis in patients with diabetes [96]. However, lowering uric acid does not appear to change CV prognosis.

Non-coronary anatomical markers (peripheral arteries and myocardium)

Peripheral atheroma

CV risk prediction may be improved by adding an evaluation of atherosclerosis extension in peripheral arterial beds. In the REACH Registry cohort, atherosclerosis in two or more locations (lower extremities, carotid and/or coronary arteries) was associated with a risk of death related to CAD of 18% after 4 years of follow-up [97]. In patients with versus without diabetes, this risk was increased by 44% [97]. Thus, the presence of peripheral artery disease is a strong predictor of CAD [6]. Regarding the predictive value of carotid plaque in patients with asymptomatic T2D, it is not clear whether or not this is associated with increased CV risk [98]. The interest of carotid ultrasound as a marker of CAD in patients with diabetes has recently been demonstrated. Carotid stenosis between 50% and 69% combined with a diabetes duration of $\geq$ 10 years was associated with a doubled risk of fatal or non-fatal stroke and MI, and all-cause mortality [99]. Recent guidelines recommend to not consider intima-media thickness due to its weak specificity and reproducibility [6]. However, pulse wave velocity ($>$ 10 m/sec) is an excellent parameter reflecting arterial rigidity and CV risk, but is rarely assessed in clinical practice [100].

ABI and toe-brachial index are not only diagnostic tests for peripheral arterial disease, but also markers of systemic atherosclerosis. In patients with diabetes, ABI validity is debated due to frequent medial arterial calcification [101]. In T2D patients with microalbuminuria and no clinical features of CAD, a 2.5-fold risk of MI has been reported when ABI is $<$ 0.9 [102]. In clinical practice, an ABI $\leq$ 0.90 or $>$ 1.40 is associated, on average, with a 2- to 3-fold increased risk of total and CV deaths [103].

Echocardiography

Echocardiography in asymptomatic diabetes patients for screening purposes remains controversial. Diabetes is associated with a high coronary risk, but may also induce a specific cardiomyopathy [104]. Decreased LV ejection fraction, aortic stenosis or more subtle cardiac modifications–such as changes in LV geometry and systolic or diastolic function alterations–may be detected. Concentric remodelling and LV hypertrophy are also frequent [105], and are known risk factors for heart failure and CV events [106,107]. LV hypertrophy may be linked to hypertension and obesity, but is also independently associated with diabetes [108,109]. LV dilation, decreased LV ejection fraction or rest wall motion abnormalities, such as hypo- or akinesia, may also be observed in asymptomatic diabetes patients. These abnormalities may be related to myocardial ischaemia and/or silent MI, and are associated with a greater likelihood of significant coronary stenosis [110]. When segmental hypokinesia is observed, severe coronary stenosis is highly suspected and coronary angiography is indicated. It can be preceded by a stress test to evaluate the extent of myocardial ischaemia. When segmental hypokinesia is moderate or doubtful, stress test imaging or CCTA is indicated. When akinesia is observed, a prior silent/unrecognized MI should be suspected [109] and coronary angiography is indicated, preceded by stress test imaging in order to assess myocardial viability and associated myocardial ischaemia.

However, most often, asymptomatic diabetes patients present with a normal LV ejection fraction. A decrease in LV global longitudinal strain can be observed in 25% or more of patients without known cardiomyopathy [111,112], and has been associated with a higher risk of CV events and death [113,114]. In apparently healthy diabetes patients, diastolic dysfunction is also common [115], but may be linked to age or associated comorbidities, such as hypertension or obesity [116]. Diastolic dysfunction has also been associated with more adverse outcomes [114,117].

Rest cardiac magnetic resonance imaging

CMR with late gadolinium enhancement (LGE) is now considered as a reference method to detect and estimate the size of MI. This method is more sensitive than ECG [118] or SPECT [119]. Using the LGE technique, the presence of unknown MI was reported to be relatively common in T2D patients as LV LGE was found in 25% of symptomatic patients [118,120] and 17% of asymptomatic patients [121]. LV LGE was also the strongest predictor of outcome during follow-up, even after adjusting for diabetes-specific risk models [46]. It has been also shown that presence of LV LGE is an independent predictor of cardiac death and MI in patients with diabetes mellitus (hazard ratio 4.5, 95% confidence interval 1.5–13.1) [122].

Many studies have shown that CMR can provide several markers to assess myocardial structure and function in patients with diabetes. The detection of cardiomyopathy by CMR is still based on the high accuracy of measurements of the end-diastolic and end-systolic volumes and of each ventricle ejection fraction. More sensitive parameters, such as the automated and reproducible longitudinal strain analysis by feature tracking of the left ventricle or left atrium, can be used to detect abnormalities of longitudinal contraction suggesting CAD before the appearance of symptomatic heart failure or decreased ejection fraction [123].

Functional markers of coronary artery disease

Each screening method for CAD offers advantages, but has limitations (Table 1).

Exercise testing

Exercise testing is attractive due to its low cost, simplicity, and wide availability. For diagnostic purposes, exercise testing must be interpreted using scores in line with the recent French Society of Cardiology guidelines [124], and may lead to a conclusion of high, intermediate or low CAD probability. It is important to note that the positive and negative predictive values of ST-segment depression is low and European guidelines recommend exercise ECG for the assessment of exercise tolerance, symptoms, arrhythmias, BP response, and event risk in selected patients [125]. Exercise ECG may be considered as an alternative test to rule in or rule out CAD when other non-invasive or invasive imaging methods are not available [125]. Apart from ST-segment changes, several additional factors must be considered, including abnormal changes in heart rate and BP during exercise and immediate recovery. Scores derived from multivariable statistical analyses, including clinical and exercise data, have demonstrated superior discriminatory power compared to the single ST response [126].

The exercise testing protocol is individualized (Supplementary data, Text S2). The criteria in favour of myocardial ischaemia during exercise testing are also summarized in Supplementary data, Text S2.

Table 1
How to assess coronary artery disease in very high-risk patients.

	Technical modality	Main information[a]	Limitations	Warnings
SPECT	Stress test (see exercise test) Often combined with pharmacological vasodilation	Location of ischaemia Extent of ischaemia	Cost	False positive in case of LBBB False positive in permanent LV pacing False negative in balanced 3-vessel disease
Stress echocardiography	Exercise (cycloergometer) in supine position Pharmacological agent (usually dobutamine ± atropine)	Location of ischaemia Extent of ischaemia	Good echogenicity needed Expertise needed Only moderate stress test performed	Avoid in case of arrhythmia Avoid if history of ventricular arrhythmia Stop beta-blocker beforehand
Stress CMR imaging	Pharmacological agent (adenosine) No exercise stress test	Location of ischaemia Extent of ischaemia High sensitivity Multimodality	Availability Expertise needed No stress test performed	Claustrophobia Pacemaker generates artefact
CCTA	Iodine injection No stress test	Coronary artery stenosis Extent of plaques through the whole coronary tree Very high sensitivity	Irradiation Expertise needed Does not evaluate ischaemia	Avoid in case of arrhythmia Iodine injection Low specificity, especially in case of calcifications (avoid if CAC score > 1000 and even > 400)
Exercise testing	Stress test (cycloergometer or treadmill)	ECG changes Heart rate response Assesses physical capacity Guides retraining	Extent of ischaemia difficult to evaluate Low sensitivity Low specificity	Enough physical capacity needed Requires normal basal ECG

CAC: coronary artery calcium; CAD: coronary artery disease; CCTA: coronary computed tomography angiography; CMR: cardiac magnetic resonance; ECG: electrocardiogram; LBBB: left bundle branch block; LV: left ventricular; MI: myocardial infarction; SPECT: single-photon emission computed tomography.
[a] Excluding the evidence of previous MI.

Multiple studies have reported an inverse relationship between exercise capacity and mortality in individuals with diabetes (see Supplementary data, Text S2). Therefore, exercise testing must be considered to evaluate functional capacity and prescribe exercise training (or an adapted physical activity programme in sedentary patients who wish to start vigorous physical activity [> 6 METs]).

Single-photon emission computed tomography

A large body of evidence supports the diagnostic value of myocardial perfusion imaging by SPECT in patients with diabetes [127], which allowed SPECT to gain a central role in SMI screening. SPECT relies on the assessment of myocardial uptake of a radiolabelled perfusion imaging agent as a surrogate of myocardial blood flow. The imaging agent (thallium-201- or technetium-99m-labelled agents such as Sestamibi or Tetrofosmin) is administered at peak stress obtained by exercise combined, when necessary, with pharmacological vasodilation. There are some warnings with SPECT, and the conditions of acquisition of stress SPECT must be rigorous (see Supplementary data, Text S3). A summed stress score > 3 is generally used as a cut-off to define abnormal scans in multicentre surveys.

The risk of cardiac events has been shown to be related to the extent of perfusion abnormalities [128], and the information provided by SPECT is additional to clinical risk factors [129]. The type of stress should also be considered, as patients with a normal SPECT who undergo a pharmacological stress with adenosine or dipyridamole alone–or those unable to perform adequate exercise–are at higher risk of cardiac events [130] (see Supplementary data, Text S3). The role of SPECT as a guide to revascularization in asymptomatic T2D patients at high coronary risk is interesting.

Stress echocardiography

Stress echocardiography is an easy to perform, safe (very rarely causing severe complications), commonly available, non-ionizing and inexpensive method for detecting stress-induced ischaemia compared to stress SPECT or CMR [131]. In case of significant stenosis, during exercise or pharmacologically induced stress, ischaemia induces a very rapid wall motion abnormality (hypokinesia, akinesia or dyskinesia) in the region supplied by the diseased artery. Stress echocardiography is based on the comparison of wall thickening between rest and stress using a 16- or 17-LV segment model. The test is considered positive when a degradation of wall thickening is observed in at least one segment. Exercise echocardiography should be preferred to pharmacological testing (see Supplementary data, Text S4). In patients with poor acoustic windows, the use of a contrast agent for LV cavity opacification improves image quality, the percentage of LV segments visualized and diagnostic accuracy. The worse prognosis associated with SMI assessed by stress echocardiography has been shown in patients with and without diabetes [132].

Stress cardiac magnetic resonance imaging

To detect obstructive CAD, adenosine stress CMR has been shown to be very competitive compared to SPECT [133,134] or stress echo in the general population and in patients with diabetes (sensitivity 88%; specificity 82%; positive predictive value 90%; and negative predictive value 79%) [135]. However, the validation stress CMR studies have only enrolled small numbers of patients with diabetes [136]. A recent dedicated study in 173 consecutive T2D patients with suspected myocardial ischaemia has shown that patients with no inducible ischaemia ($n = 94$) experienced an annualized event rate of 1.4% compared to 8.2% ($P = 0.0003$) in those with inducible ischaemia ($n = 79$) [137]. The presence of inducible ischaemia was the strongest unadjusted predictor, better than detection of LGE, for cardiac death and non-fatal MI during a mean 2.9-year follow-up [137].

Coronary flow reserve and perfusion positron emission tomography

Myocardial blood flow is mainly determined by vascular resistances at the level of the small arteries and microcirculation. The presence of epicardial coronary stenosis or diffuse atherosclerosis is likely to limit myocardial blood flow increase after infusion of a vasodilator such as adenosine or dipyridamole, a functional test for coronary flow reserve evaluation. In case of balanced ischaemia due to three-vessel disease, qualitative perfusion analysis by SPECT may be falsely negative due to homogeneously reduced tracer uptake, while global and regional myocardial blood flow quantification will demonstrate a balanced coronary flow reserve reduction. Together with improved image quality derived from technical advances (such as spatial resolution and attenua-

tion correction), myocardial blood flow quantification by PET could improve the diagnostic value (see Supplementary data, Text S5).

Anatomical evaluation of coronary artery disease

Coronary artery calcium score

CAC score is a quick, safe and inexpensive method to detect coronary atherosclerosis that has been developed over the two last decades. CAC scanning is associated with low radiation (1–2 mSV), equivalent to the dose for a mammogram. CAC score assesses the volume of coronary calcifications and assumes that each calcification corresponds to an atherosclerotic plaque. Patients are stratified according to the Agatston score: CAC score < 10 (very low risk), < 100 (low risk), 100–400 (moderate risk) and > 400 (high risk) AU [138]. However, CAC score should be evaluated relative to subjects of the same age, sex and race/ethnicity [139]. The new Multi-Ethnic Study of Atherosclerosis (MESA) risk score [140] estimates 10-year coronary risk using CAC score plus traditional risk factors (risk enrichment). The prevalence of high CAC score is > 20% among asymptomatic patients with diabetes, greater in the elderly and greater than in those without diabetes [141–143].

Many studies have shown that CAC score is independently associated with coronary and CV events, including death [144,145]. Patients with a CAC score > 300 AU have a 10-fold increased risk of coronary events compared with patients with a CAC score of 0, hence CAC scoring offers improved discrimination and allows reclassification [67,146]. In patients with diabetes, the prognostic significance of elevated CAC in predicting adverse events is greater than in non-diabetic individuals (Supplementary data, Text S6). However, no prospective studies have confirmed whether the detection of subclinical CAD by CAC score leads to an improvement in clinical outcomes.

Interestingly, a meta-analysis has shown a relationship between CAC score magnitude and the likelihood of inducible myocardial ischaemia using SPECT [146]. CAC severity identifies patients most likely to benefit from statins in primary CV prevention [147]. CAC score may also help clinicians and patients in decision making, changing their behaviour, and encouraging initiation and continuation of preventive therapies, as supported by a randomized study that showed that patients randomized to CAC scanning had better risk factor control than those who did not undergo CAC scanning [147].

In conclusion, CAC score improves CV risk stratification in the heterogeneous population of patients with diabetes. The absence of coronary calcifications indicates a low annual mortality rate, similar to that of individuals without diabetes. On the contrary, a high CAC score allows identification of patients at the greatest risk, who could benefit from SMI screening and more aggressive clinical treatment. However, the CAC score threshold used for the decision of treatment intensification can change depending on ethnicity and age [139]. ADA and ESC/EASD guidelines have included CAC score as a risk modifier (class IIb ["may be considered"] recommendation for ESC/EASD) [6,56].

Coronary computed tomography angiography

Because of its good diagnostic performance and easy access, CCTA–which includes acquisitions without and with a contrast medium injection contrast–is increasingly being proposed as a first-line investigation in symptomatic patients with suspected CAD [148]. In symptomatic subjects [149] or asymptomatic subjects [150], diabetes has been shown to be associated with a greater diffusion of atheroma detected by CCTA all along coronary arteries. In asymptomatic patients with diabetes, anatomical analysis of plaques can help to detect future vulnerable plaques at risk of acute future events [151]. In the Scottish Computed Tomography of the Heart (SCOT-HEART) trial, 4146 patients evaluated for thoracic pain were randomized to the usual care pathway or additional CCTA [66]. In the CCTA group, 2.3% of patients had an MI or died of coronary heart disease, compared to 3.9% in the usual care group, with an even greater difference in the subgroup of patients with diabetes. This decrease in mortality and MI was attributed to the decision of starting a medical treatment due to the detection of obstructive or non-obstructive coronary lesions by CCTA. Conversely, the FACTOR-64 study, which randomly assigned asymptomatic patients with diabetes to CAD screening by CCTA or standard optimal diabetes care failed to show a significant decrease in events in the CCTA group [152]. However, this population was not at very high risk (CAC score > 100 in 40.7%), proximal severe stenosis was only detected in 6% of the patients in the CCTA group, and the effect of revascularization–which was only performed in a few patients (6% of patients with CCTA; 1.8% of patients without CCTA)–was not discriminative in reducing overall mortality. Altogether, these results suggest that CCTA may be considered in symptomatic patients, but needs further evaluation in asymptomatic patients with diabetes. In addition, when the CAC score is high, CCTA analysis become difficult due to the blooming effect linked to the presence of calcifications.

Coronary angiography

Coronary angiography is not used to screen for coronary stenosis. Rather, it is used to assess coronary artery stenosis in patients with evidence of ischaemia or significant stenosis on CCTA when revascularization is considered. Diabetes is associated with more severe, complex and diffuse lesions on angiography [18,153]. Occlusion of a coronary artery branch has been observed in one third of diabetes patients without MI [153], twice as high as in non-diabetic patients. In addition, when such occlusion was observed, patients with diabetes were less likely to develop collateral circulation [154].

Fractional flow reserve

Fractional flow reserve (FFR) is a dynamic assessment of coronary flow during coronary angiography. FFR is based on the supposed linear relationship between pressure and flow in hyperaemia, with minimal and stable vascular resistance. Its value depends on the degree and length of the stenosis, myocardial mass concerned and microcirculation integrity with maximum vasodilation capacity (Supplementary data, Text S7). Some studies have specifically investigated the prognostic value of FFR in patients with diabetes. Recently, this question was addressed in an outcome study of 1983 patients with stable CAD (701 with diabetes) enrolled in 40 centres in two European countries [155]. The 1-year major adverse cardiovascular events (MACE) rates were similar in reclassified and non-reclassified diabetes patients with FFR (9.7% and 12.0%, respectively; $P = 0.37$), and FFR-based deferral was associated with lower MACE rates than in those undergoing revascularization (8.4% vs 13.1%, $P = 0.04$). Patients for whom the information derived from FFR was disregarded (6%) had the highest MACE rates, regardless of diabetes status. Thus, routine integration of FFR for CAD management in patients with diabetes is associated with a high rate of treatment reclassification and management strategies guided by FFR, including revascularization deferral, and seems to be safe in patients with diabetes.

Algorithm for the stratification and management of coronary risk in asymptomatic patients with diabetes

It is now accepted that the evaluation of the risk of CAD should not be based solely on classical risk factors; and risk scales have not

been adapted to patients with diabetes [6]. Therefore, we propose an algorithm (Fig. 2) for patients with T2D or T1D aged 35 to 75 years. The first step is to identify patients with an obvious very high risk on the basis of the presence of organ damage. The second step is to identify patients suspected to be at high risk, based on duration of diabetes, the presence of microangiopathic complications and risk factors that are not well controlled. It is noteworthy that HbA1c, BP and LDL-C levels above the targets despite therapeutic management increase the a-priori risk of patients [63]. Patients not at high risk are classified as being at moderate risk. For all high-risk patients, we propose to stratify risk according to CAC score, considering age because the score is highly related to age [139]. Indeed, the CAC score seems to be very interesting because it is focused on coronary arteries and is easy to perform.

In very high-risk patients, screening for CAD may be proposed. When screening for CAD is decided upon, the local facility and organization must guide the choice of screening method (functional tests or CCTA). If CAD screening is positive, cardiological advice is recommended and coronary angiography can be proposed. If CAD screening is negative, the patient remains at very high risk (Fig. 2). The therapeutic targets are defined according to risk category and are presented in Table 2. Coronary risk should be reassessed annually in moderate-risk patients. In very high-risk patients with negative CAD screening, CAD screening should be repeated every 3–5 years if they remain strictly asymptomatic.

Coronary artery disease screening in specific populations

Severe obesity

Severely obese patients (with body mass index $\geq$ 35 kg/m^2) and candidates for bariatric surgery are more likely to suffer from CVD and are at increased risk of CV mortality [156]. Therefore, preoperative non-invasive risk stratification is important to minimize the perioperative risk [157], especially in patients with CV comorbidities. In a small study of asymptomatic morbidly obese patients, 44% of those with subclinical coronary lesions on CCTA had diabetes [158].

The accuracy of exercise SPECT often seems to be compromised in severely obese patients [159], leading physicians to favour attenuation-corrected images or opt for perfusion PET [160]. CCTA might be an alternative method in obese patients at very high risk. The diagnostic value of coronary dual-source computed tomography has been investigated in a small group of patients undergoing bariatric surgery [161]. This method appeared to be a robust alternative imaging tool for the preoperative assessment of patients undergoing bariatric surgery. The long-term predictive value of CCTA in severely obese patients has also been suggested [162].

This highlights the need for specific studies on larger samples to validate a consensus for cardiac screening in severely obese patients with diabetes. Indeed, neither French national (Haute Autorité de Santé [HAS; French National Authority for Health]) nor international guidelines recommend any specific cardiac screening before bariatric surgery.

Older adults

Diabetes is of great concern in older adults, as around one third of patients with diabetes are aged $\geq$ 70 years. In the GERODIAB study–a multicentre, prospective, observational study in French patients aged $\geq$ 70 years with T2D–CAD prevalence increased from 30% at inclusion to 41% after 5 years of follow-up, and patients with CAD had a lower survival rate [163]. This may encourage physicians to assess the coronary risk in older adults with diabetes, particularly for those who have good health, are active and have longer life expectancy.

Patients with end-stage renal disease or on dialysis

In diabetes patients with end-stage renal disease, data from the Liraglutide Effect and Action in Diabetes: Evaluation of CV Outcome Results (LEADER) study have shown that nearly 20% of patients with eGFR 30–59 mL/min/1.73m^2 and 24% of patients with eGFR $<$ 30 mL/min/1.73m^2 experienced a major CV event during the 3.8 years of follow-up in the placebo group [164]. The same trend was observed in the EMPA-REG OUTCOME trial, with a rate of CV events of around 40% in patients with eGFR 60–90 mL/min/1.73m^2 and 60% in those with eGFR $<$ 60 mL/min/1.73m^2, compared to 32% in patients with eGFR $>$ 90 mL/min/1.73m^2 [165].

Patients with CKD have a higher prevalence of CAD at angiographic evaluation with multi-vessel disease and ECG evidence of previous ischaemia [166]. Interestingly, Ramphul et al. assessed CV risk in patients with CKD prior to kidney transplantation, including 35% with diabetes, and among the subset of patients with CVD, highlighted the interest of dobutamine stress echocardiography in identifying those with CAD [167]. However, coronary interventions did not improve survival.

Pregnancy

Diabetes complications can worsen during pregnancy and should be assessed before conception to allow for early management. The standard assessment includes screening for retinopathy, nephropathy and CAD. However, who and how to assess for CAD is not specified in French recommendations for patients with T1D [168]. The Endocrine Society clinical practice guidelines relating to diabetes and pregnancy recommend that if a woman with diabetes has a sufficient numbers of CV risk factors (particularly diabetes duration and age), screening for CAD should be undertaken in advance of withdrawing contraceptive measures or otherwise trying to conceive [169]. If a woman with diabetes and CAD is seeking to become pregnant, due to the potential risks of pregnancy for her and the foetus, CAD severity should be evaluated, treatment initiated, and counselling provided before the woman withdraws contraception or otherwise tries to conceive [169]. Indeed, MI during pregnancy is associated with adverse maternal and foetal outcomes including foetal and maternal demise [170,171].

Before anaesthesia

As perioperative risk may be increased by the presence of heart disease in patients with diabetes, the joint French diabetology and anaesthesiology position statement recommends evaluating the presence of heart disease before surgery [172]. Briefly, patients scheduled for major surgery should be referred to a cardiologist if they have a Lee index score $\geq$ 2 and a functional capacity $<$ 4 METs (able to cycle on a flat road). In patients with no coronary history, no symptoms and no specific ECG anomaly, the algorithm proposed in the current position paper (Fig. 2) may be applied.

Potential benefit of coronary artery disease assessment in asymptomatic patients with diabetes

Risk factor modification

Detection of high or very high risk of CAD implies the need for strict CV risk factor control. The pioneer Steno-2 study demon-

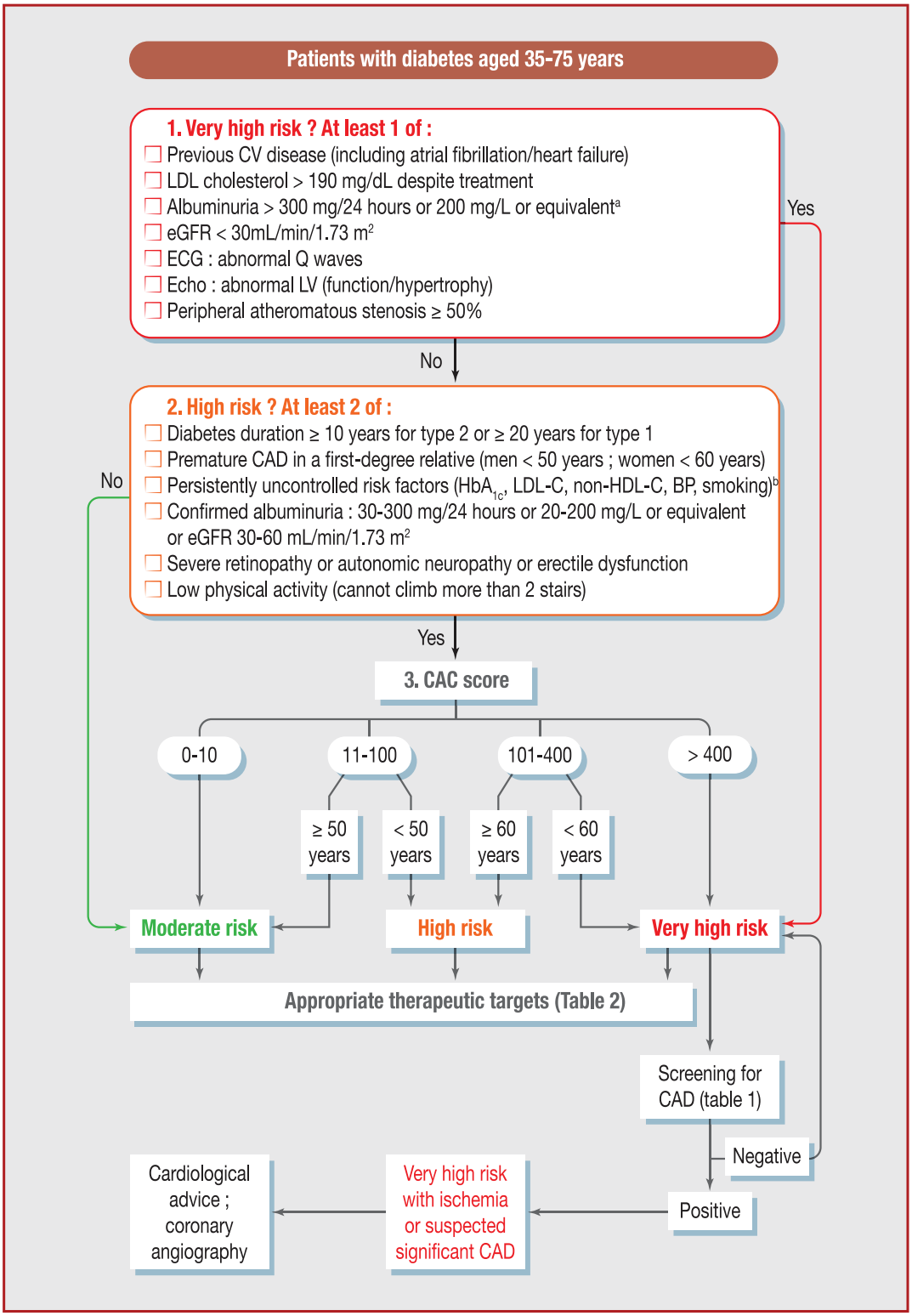

Figure 2. Algorithm for the stratification and management of the risk of coronary artery disease in asymptomatic patients with diabetes in 3 steps. Firstly, medical history, clinical examination, ECG and usual biological parameters are considered. Cardiac echography or any exploration of peripheral arteries can be used if available. Step 1. The red box selects patients at very high risk because of target organ damage. The patient is considered at very high risk if at least one item in the red box is ticked. If no item is ticked, the orange box (Step 2. High risk?) has to be checked. This step is particularly important for patients with T2D for ≥ 10 years who represent the majority of the diabetes population. If no or only one item is ticked in the orange box, the patient can be considered at moderate risk. If the patient has two or more items ticked in this box, CAC score may be proposed for stratification (Step 3). The risk will be considered according to Agatston score: 0–10 AU: moderate risk; 11–100 AU: moderate risk if age is ≥ 50 years and high risk if age is < 50 years; 101–400 AU: high risk if age is ≥ 60 years and very high risk if < 60 years; > 400 AU: very high risk. In very high, risk patients screening for CAD can be performed according to local protocols. According to HAS recommendations [209], CKD-EPI is the best formula to estimate GFR. AU: Agatston units; BP: blood pressure; CAC: coronary artery calcium; CAD: coronary artery disease; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; CV: cardiovascular; HbA1c: glycated haemoglobin; HAS: Haute Autorité de Santé (French National Authority for Health); HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; ECG: electrocardiogram; Echo: echocardiogram; eGFR: estimated glomerular filtration rate. [a]Albumin/creatinine ratio on spot urine: ≥ 300 mg/g. [b]Despite the currently recommended therapeutic management.

Table 2
Therapeutic targets according to risk category.

	Moderate risk	High risk	Very high risk	Very high risk with suspected significant CAD	Comments
Target HbA1c	< 7%	< 7%	7%	7%	Consider the patient profile–less stringent goal in frail patients
Avoid hypoglycaemia	+	+	+++	+++	Mainly with insulin/sulfonylureas/glinide treatments
Use of GLP-1 RAs		++	+++	+++	Consider different drug profiles
Use of SGLT2 inhibitors		++	+++	+++	Particular benefit for the prevention of heart and renal failure
LDL-C target (mg/dL)	< 100	< 70	< 55	< 55	Statin ± ezetimibe–PCSK9 inhibitors may be considered
Secondary lipid goal: non-HDL-C (mg/dL)	< 130	< 100	< 85	< 85	Fenofibrate could be proposed in specific patients
Smoking cessation	+++	+++	+++	+++	Use a structured smoking cessation programme with pharmacological agents if necessary
Blood pressure target (mmHg)	130/80	130/80	130/80	130/80	Target 130/80 mmHg or lower if well tolerated Not < 120/70 mmHg
Use of RAAS blockers		++	+++	+++	Cardiac and kidney protection
Aspirin 75–100 mg/day	No	No	+	++	If low risk of bleeding–PPI can be added
Physical activity	+++	+++	+++ Rehabilitation	+++ Rehabilitation	Adapted to each patient–initial exercise test can help 150 minutes/week divided into 3 sessions Target heart rate: < 80% predicted maximum heart rate (220–age)
Diet	++	++	+++	+++	Weight loss support in overweight patients Favour a Mediterranean diet
Algorithm reassessment	Each year	Each year	NA	NA	For cardiac echo and duplex examination, reassessment should be according to local practice
CAC score reassessment	No	3–5 years	No	No	CAC is a risk modifier
CAD screening reassessment	No	No	3–5 years[a]	3–5 years[a]	If initial screening is negative If symptoms (chest pain or dyspnoea) occur, immediate reassessment

CAC: coronary artery calcium; CAD: coronary artery disease; GLP1-RA: glucagon-like peptide 1 receptor agonist; HbA1c: glycated haemoglobin; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; NA: not applicable; PCSK9: proprotein convertase subtilisin/kexin type 9; PPI: proton pump inhibitor; RAAS: renin-angiotensin-aldosterone system; SGLT2: sodium-glucose co-transporter-2.

strated that an intensive multifactorial approach in addition to lifestyle changes allowed a 53% CV event rate decrease after a 7.8-year intervention period and a 51% mortality decrease after a follow-up of 21 years, which corresponds to a median life gain of 7.9 years [173]. The targets to achieve for blood glucose, LDL-C and BP–and the choice of treatments–depend on the risk level and some patient characteristics. In addition, important information has recently come from CV outcomes trials [6], which have shown that some classes of glucose-lowering treatments improve CV prognosis and should be preferred for patients with CAD or other evidence of very high CV risk. Table 2 summarizes the recommendations.

Lifestyle changes

The Société Francophone du Diabète (SFD; Francophone Society of Diabetes), EASD and ADA recommend lifestyle management as the first step for the prevention/treatment of CVD, even though it is difficult to measure its efficacy. In the Action for Health in Diabetes (Look AHEAD) study, patients with T2D who were randomized to the intensive lifestyle intervention arm lost more weight and achieved better metabolic and risk factor control, which were sustained for 4 years, but without a reduction in CV outcomes [174]. Weight control represents the cornerstone of treatment in overweight patients, and a diet with reduced lipids, energy intake, salt and alcohol, but rich in fibre, vegetables, fruits and low-fat dairy products, favouring a Mediterranean diet should be recommended. Smoking cessation is also critically important. A high CAC score appears to be a marker that can encourage dietary modifications and statin therapy [175]. A physical activity programme should be offered, as aerobic and resistance training improves CV risk factors, particularly glucose and BP levels [176]. Three to five physical activity sessions of moderate intensity per week should be recommended, for a total of 150 minutes per week.

Glucose control

Glucose control for macrovascular disease prevention/treatment remains a matter of debate. While dysglycaemia is clearly associated with CV risk increase, the effect of improving blood glucose on CV risk remains controversial. In the United Kingdom Prospective Diabetes Study (UKPDS), intensive glucose control was associated with a reduced risk of MI in patients with newly diagnosed T2D, but did not reach statistical significance [177]. More recent randomized controlled studies–such as ACCORD [178], Action in Diabetes and Vascular Disease: Preterax and Diamicron - Modified Release Controlled Evaluation (ADVANCE) [179] and Veterans Administration Diabetes Trial (VADT) [180]–did not show any benefit of intensive glycaemic control on CV mortality. However, a meta-analysis has suggested that a 1% HbA1c reduction is associated with a 15% risk reduction in non-fatal MI [181] and UKPDS in patients with T2D showed a benefit on MACE after a long follow-up, supporting the importance of early glucose control [182]. However, these studies also highlighted the potential deleterious role of hypoglycaemic events, which were more frequent in the intensive glycaemic control arms. Consequently, the glycaemic target should be individualized according to several factors including age, CV risk, the presence of CVD, comorbidities and hypoglycaemia risk. HbA1c < 7% should be

recommended, but in some high-risk young patients with no evidence of CVD, a more stringent target might be considered. In high or very high CV risk patients–including those with evidence of cardiac disease–glucose-lowering drugs with a risk of causing hypoglycaemia (sulfonylureas, glinides, insulin) should be avoided if possible. Drugs that reduce post-prandial glucose excursions, including glucagon-like peptide 1 receptor agonists (GLP-1 RAs), dipeptidyl peptidase 4 inhibitors and sodium-glucose co-transporter-2 (SGLT2) inhibitors, seem attractive to reduce glucose variability [183].

It is now important to consider the use of glucose-lowering drugs that have clearly shown benefits in CV prevention. These include GLP-1 RAs (liraglutide, semaglutide and dulaglutide), which reduce mostly atherosclerotic outcomes; and SGLT2 inhibitors, which reduce mostly heart failure incidence [6], as stated in recent French guidelines [184] and the 2019 EASD/ADA [185] and ESC/EASD 2019 guidelines [6]. Such drugs are recommended in the patients with CVD or at very high risk, particularly those with end-organ damage [6]. One additional advantage of GLP-1 RAs and SGLT2 inhibitors for patients with CVD is that they do not induce hypoglycaemia when not associated with insulin-secreting agents (sulfonylureas, glinides) or insulin.

Blood pressure control

Hypertension affects up to 67% of patients with T1D aged over 30 years [186] and > 60% of patients with T2D. Several studies have demonstrated the benefit of BP control (systolic < 140 mmHg; diastolic < 85 mmHg) on CV outcomes. However, the optimal BP target is still being debated. According to a recent meta-analysis, reducing systolic BP to < 130 mmHg was associated with significant reductions in CV events and all-cause mortality [187]. In patients with CAD, BP < 120/70 mmHg was associated with adverse CV outcomes including mortality [188]. The ESC/EASD 2019 guidelines [6] recommend that, in patients with diabetes, office BP should be targeted to a systolic BP of 130 mmHg (< 130 mmHg if tolerated, but not < 120 mmHg), with a diastolic BP targeted to < 80 mmHg (but not < 70 mmHg). In older adults (> 65 years), systolic BP should be 130–139 mmHg [6].

Management options for hypertension include lifestyle changes. Evidence supports first-line pharmacological therapy with a renin-angiotensin-aldosterone system (RAAS) blocker–either an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker–particularly in diabetes patients with albuminuria or LV hypertrophy [6]. Achieving a BP goal often requires combination therapies. It is therefore recommended to initiate treatment with a combination of a RAAS blocker and a calcium channel blocker or a thiazide/thiazide-like diuretic. A single-pill fixed-dose combination of two drugs should be considered to improve adherence [6]. Beta-blockers must be reserved for: (1) patients with resistant hypertension despite a combination of three antihypertensive drugs and (2) patients with heart failure, ventricular arrhythmia or CAD.

Lipid control

In UKPDS, LDL-C was shown to be the first/main risk factor associated with CAD [189]. A meta-analysis of statin therapies, which included 18,886 people with diabetes from 14 randomized control trials, reported a 21% MACE reduction per mmol/L of LDL-C lowering, as in non-diabetic individuals [190]. Thus, in patients with diabetes, in addition to lifestyle interventions, statin therapy is recommended, with the specific LDL-C target depending on CV risk [191]. A combination of simvastatin with ezetimibe must be considered, as suggested by the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) study, which showed a significant reduction in CV events among patients with diabetes treated with this combination after an acute coronary event [192]. In very high-risk patients, the LDL-C level should be < 1.4 mmol/L (< 55 mg/dL) [6]. When LDL-C is not at target despite treatment combining a maximum-tolerated statin dose with ezetimibe, the use of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, which have been shown to significantly reduce CV events, must be discussed [193,194].

Evidence [195] supports considering diabetes patients' residual risk and atherogenic dyslipidaemia–defined as the presence of high fasting triglycerides levels (> 2.3 mmol/L [> 200 mg/dL]) and low high-density lipoprotein cholesterol (HDL-C) levels (< 1.0 mmol/L [< 40 mg/dL] in men; < 1.3 mmol/L [< 50 mg/dL] in women) in high-/very high-risk patients on maximally tolerated statin therapy. Non-HDL-C (total cholesterol–HDL-C) should be a secondary goal for the treatment of atherogenic dyslipidaemia, targeting levels of 0.8 mmol/L (30 mg/dL) above the LDL-C goal [195]. A meta-analysis has shown that fenofibrate induces a significant MACE reduction in diabetes patients with atherogenic dyslipidaemia [196]. Thus, as suggested in French Society of Endocrinology guidelines, fenofibrate may be considered in high-/very high-risk patients with diabetes whose LDL-C is at target but with triglyceride levels still > 2.26 mmol/L (> 200 mg/dL) and low HDL-C levels [191]. If triglycerides remain high despite statins or fibrates, a high dose of omega-3 fatty acids (4 g/day) or icosapent ethyl may be used [197].

Antiplatelet therapy

Even though several trials (e.g. Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes [JPAD] [198], Prevention Of Progression of Arterial Disease And Diabetes [POPADAD] [199]) did not demonstrate a significant benefit of aspirin in primary prevention, a recent meta-analysis has suggested that low-dose aspirin decreases the rates of stroke in women and MI in men with diabetes [200]. The ASCEND trial [201] has shown that, in patients aged > 40 years with diabetes, aspirin for primary prevention decreased the CV event rate, but was associated with an increase in major bleeding, mostly gastrointestinal. The group of patients with higher CV risk also demonstrated a higher risk of bleeding. Therefore, the systematic use of aspirin cannot be recommended in all patients with diabetes for primary prevention. In those with high or very high CAD risk, low-dose aspirin may be proposed if the bleeding risk is low [6]. Patients with high bleeding risk include older adults (especially women), patients with cognitive dysfunction and those with a history of bleeding or peptic ulcer [202]. Unfortunately, no study has investigated the potential impact of aspirin in diabetes patients with evidence of subclinical coronary atherosclerosis. Interestingly, body weight could affect aspirin pharmacodynamics–in high-weight patients, aspirin appears less effective with less bleeding [203]. Finally, clopidogrel does not appear to be better than aspirin in patients with diabetes [204].

The addition of an oral anticoagulant has not been investigated in patients with diabetes in primary prevention, and is associated with high bleeding risk. In case of atrial fibrillation needing anticoagulant treatment, antiplatelet therapy must be stopped.

Revascularization

In patients with significant CAD, anti-ischaemic treatment and revascularization using angioplasty or bypass surgery can be proposed, although treatment strategies are outside the scope of this consensus paper. According to the last ESC/EASD guidelines [6], the presence of significant CAD–whether symptomatic or not–

Table 3
Gaps in knowledge.

Knowledge gaps
The value of a multiparametric approach (combination of 2 or 3 non-invasive methods) for CAD screening requires further study
There is an urgent need to know more about coronary risk in young patients with T1D
Coronary risk, and more generally CV risk, in patients with monogenic diabetes requires specific studies
Whether or not patients with diabetes who are older than 75 years may benefit from coronary risk stratification and screening for CAD needs to be clarified
The benefit of the new glucose-lowering treatments in patients with silent CAD needs to be evaluated in specific trials
Aspirin use in high- or very high-risk patients as defined in the algorithm needs to be evaluated

CAD: coronary artery disease; CV: cardiovascular; T1D: type 1 diabetes.

switches the patient to secondary prevention. Recommendations concerning the management of these patients have been published by the ESC [148].

Interventional studies that have addressed the question of coronary artery disease screening in asymptomatic patients with diabetes

Identifying patients with silent CAD should encourage increasing medical therapy, including optimal control of risk factors, and may lead to consideration of coronary revascularization when appropriate. However, such a screening does not clearly translate into a reduction of CV events and remains debated.

Some randomized controlled trials that have studied screening for and/or treatment of SMI have been performed (Supplementary data, Table S3 and Text S8). A meta-analysis of these trials, including a total of 3299 patients, 189 of whom experienced cardiac events during follow-up, showed that non-invasive CAD screening significantly reduced cardiac events by 27% (number needed to screen: 56). This result was driven by important, albeit non-significant, decreases in non-fatal MI and hospitalization for heart failure [205].

In the Basel Asymptomatic high-Risk Diabetics' Outcome Trial (BARDOT), a combined invasive and medical strategy for silent CAD versus medical therapy alone reduced SPECT progression, but with a non-significant MACE reduction [71]. Similarly, among patients with stable CAD, the recent Objective Randomised Blinded Investigation With Optimal Medical Therapy of Angioplasty in Stable Angina (ORBITA) study showed no long-term benefit of revascularization on clinical symptoms or angina [206]. The Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) study, which included 2368 T2D patients with stable CAD also showed no benefit from revascularization compared to optimal medical treatment [207]. Recently, the comparison of initial invasive versus conservative strategies in patients with stable CAD has been compared in the International Study of Comparative Health Effectiveness With Medical and Invasive Approaches (ISCHEMIA) and ISCHEMIA-CKD, in which 41% and 55% of patients, respectively, had diabetes [208]. In both studies, there was no demonstration of a benefit of an initial invasive strategy on ischaemic CV events or deaths [208].

Thus, assessing diabetic patients for CAD and invasive procedures (revascularization) have not demonstrated clear benefit on cardiac morbidity and mortality. Routine screening of CAD is not recommended but screening may be indicated in very high risk patients [6].

Conclusions

Coronary risk stratification should be considered as a critical step to decide whether or not to perform CAD screening, and to define therapeutic goals and optimal treatments. However, further studies are needed to improve our knowledge regarding the coronary risk estimate and management among people with diabetes (Table 3), and the cost-effectiveness ratio of our algorithm (Fig. 2) needs to be evaluated.

Disclosure of interest

The authors declare that they have no competing interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.diabet.2020.08.002.

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