Silent coronary artery disease in type 2 diabetes: a narrative review on epidemiology, risk factors, and clinical studies

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Abstract

Silent coronary artery disease (CAD) is one of the manifestations of heart disease that particularly affects subjects with type 2 diabetes mellitus (T2DM). From a clinical point of view, silent CAD represents a constant challenge for the diabetologist, who has to decide whether a patient could or could not be screened for this disease. In the present narrative review, several aspects of silent CAD are considered: the epidemiology of the disease, the associated risk factors, and main studies conducted, in the last 20 years, especially aimed to demonstrate the usefulness of the screening of silent CAD, to improve cardiovascular outcomes in type 2 diabetes.

Keywords

Silent coronary artery disease, epidemiology, risk factors, screening

Introduction

Cardiovascular disease, and particularly coronary artery disease (CAD) remains the leading cause of death and morbidity in patients with diabetes mellitus [1]. This represents a primary public health problem, despite the important progressive improvement of clinical management of CAD, including new medical and surgical therapies, and the control of risk factors. Indeed, a dramatic reduction of CAD prevalence and incidence has been observed among the diabetic population, in the last 20 years [2], but in this promising scenario, a peculiar manifestation of CAD stands out, a potential life-threatening disease for the patients, that is "asymptomatic ischemic heart disease."

Silent coronary artery disease is the condition in which oxygen and nutritional support to the myocardium is lessened, usually due to the presence of an atherosclerotic narrowing of the coronary arteries, causing no pain, distress or discomfort. However, limitations of coronary artery flow reserve, and functional changes, such as endothelial dysfunction, and abnormal microcirculation could also be responsible for some myocardial hypoperfusion [3, 4]. Usually, the presence of diabetic neuropathy, causing abnormalities of pain perception, is believed to be the main reason for asymptomatic CAD in diabetic subjects, but true mechanisms leading

to this condition are not yet totally understood. Among proposed pathophysiologic mechanisms, attenuated sensory inputs from ischemic myocardium, and altered central processing of cardiac pain sympathetic afferent fibers [5], along with sympathetic denervation [6] have been suggested, but also abnormalities of cytokine production seem to contribute to impaired nociception [7]. A significant and strong correlation between cardiac autonomic neuropathy and silent myocardial ischemia has since long been demonstrated [8-11]. In the Detection of Silent Myocardial Ischemia in Asymptomatic Diabetic Subjects study (DIAD), an impaired cardiac autonomic function was in fact the strongest predictor of abnormal stress myocardial perfusion imaging, in diabetic patients without any history of CAD, and without clinical or instrumental manifestations of the disease [11].

Silent myocardial ischemia (SMI), and silent myocardial infarction (MI) are the two manifestations of silent CAD. Initially, the definition of SMI included three subgroups: totally silent ischemia (type I); silent ischemia after a myocardial infarction (type II); and mixed silent ischemia (type III), in which patients could present both painless and symptomatic periods of myocardial ischemia [12]. More recently, SMI was simply defined as an "objective documentation of myocardial ischemia in the absence of angina or anginal equivalents" [13] while the diagnosis of prior silent/unrecognized myocardial infarction has been recently revised in the 2018 ESC/ACC/AHA/WHF Expert Consensus Document Fourth Universal Definition of Myocardial Infarction [14]. The presence of at least one of the following criteria is considered sufficient for the diagnosis of silent MI (a) abnormal Q waves with or without symptoms in the absence of non-ischemic causes; (b) imaging evidence of loss of viable myocardium in a pattern consistent with ischemic etiology; or (c) pathoanatomical findings of a prior MI.

Then, if ischemic heart disease is manifested, it will often appear in an advanced stage, and is burdened by a very serious prognosis [15, 16]. It is well established that diabetes mellitus represents per se a condition favoring CAD, independent of the presence of the other risk factors typically associated with CAD, such as arterial hypertension, dyslipidemia, and obesity, and it is also well-known that silent CAD is more prevalent in diabetic patients, than in non-diabetic subjects [17, 18]. Given these premises, an early screening for silent CAD could appear an appealing tool for reducing cardiovascular complications and mortality among diabetic patients.

Silent CAD obviously remains unrecognised, if not ruled out by the application of diagnostic tool, but if it is advantageous or not to screen diabetic patients for silent CAD remains up to now a serious and unanswered question. This issue has since long been debated, but it is far from being resolved. Whether the screening is effective in reducing the cardiovascular outcomes, in patients with diabetes mellitus remains uncertain, and totally convincing evidence is lacking, despite several studies have been carried on trying to answer this primary argument. Currently available guidelines do not recommend the screening for silent CAD in asymptomatic diabetic patients, even if with a high cardiovascular risk, since the cost-effective benefits have not been clearly demonstrated by the most recent dedicated trials, and given the optimal medical treatment of all cardiovascular disease (CVD) risk factors is guaranteed [19-21].

However, there are still many uncertainties remaining on the interpretation of available results, especially linked to the selection of patient enrolled in these studies, to the various definitions of the disease, and to different methodologies employed.

The clinical relevance of silent coronary artery disease in type 2 diabetes

The importance of CAD as a relevant cause of morbidity and mortality in diabetes emerged in the second half of 1900 [22-24], and since then the interest for silent CAD as an important clinical condition for poor cardiovascular outcomes in diabetes has emerged and progressively increased [25-29]. Early data from the Framingham Heart study showed that about 50% of myocardial infarctions were totally silent, especially in diabetic individuals [30, 31]. Later, this figure appeared to be reduced, in the follow-up study of Framingham population, but again, more than 25% of total myocardial infarctions were asymptomatic, and casually discovered during the routine biennial electrocardiographic examinations [32]. In the United Kingdom Prospective Diabetes Study (UKPDS) the prevalence of silent myocardial infarction, based on the presence

of pathological Q waves, was of 17.5% in a population of 5,102 newly diagnosed type 2 diabetic patients (T2DM), enrolled from 1977 to 1991 [33].

Following these pieces of evidence, showing a significant proportion of previous silent myocardial infarction in diabetes, silent CAD was investigated by functional and atomic testing revealing a highly variable prevalence, ranging from around 10% to more than 50% [8, 26, 27, 34-40].

Observed differences in the prevalence of the disease in diabetic subjects can be ascribed to several factors: (1) to a different definition of "silent CAD"; (2) to different baseline level of ischemic cardiac risk of the studied populations; (3) to the presence of micro- and macro-vascular complications of diabetes; (4) to the presence of comorbidities; (5) to diabetes duration; (6) to the methodological approaches utilized for the diagnosis of silent CAD (i.e. the sensibility and specificity of the test); and, maybe (7) to the progressive improvement in the management of diabetes itself and its associated cardiovascular (CV) risk factors.

Functional tests for the screening of silent CAD include an electrocardiogram (ECG) exercise tolerance test, exercise/pharmacological stress echocardiography, and exercise/pharmacological myocardial perfusion imaging, while anatomic tests include a coronary artery calcium scoring by electron-beam computed tomography, CT angiography, cardiac magnetic resonance imaging and positron emission tomography [41, 42] (Table 1). The choice of the screening test can increase the possibility to predict the disease. Stress myocardial perfusion imaging (MPI) and stress echocardiography are more effective than ECG stress test in detecting silent CAD [42]. Furthermore, when two tests are concordant, the positive predictive value for detection of CAD improves [43].

Table 1. Main non-invasive tests for the screening of silent CAD

Test	Type	Advantages	Disadvantages
Exercise stress test	Functional	Low cost	Low sensitivity
		Physiologic stress	
Stress echocardiography	Functional	Low cost	Difficult in some patients
		Pharmacological/physiological stress	False negative if single vessel disease
		High specificity	
Radionuclide imaging	Functional	High sensitivity	Radiation
			False positive
Coronary artery calcium	Anatomic	Non-invasive	Radiation
			No stenosis evaluation
Coronary computed tomography angiography	Anatomic	High negative predictive value	No function evaluation
Magnetic resonance imaging	Anatomic/functional	Expensive	Preliminary studies

It is also clinically relevant to underline that myocardial ischemia can resolve, as demonstrated in the DIAD study, after patients underwent intensive CV risk factor control; in follow-up of the DIAD study, resolution of ischemia was found in 79% of 71 T2DM patients who initially had abnormal studies, after 3 years of optimal medical treatment [44]. Moreover, the prevalence of silent CAD seems to reduce over time: a French cohort of 770 T2DM, prospectively followed-up for a 10-year period, showed a progressive and steady reduction of SMI from 22.6% in 1999-2002, to 13.7% in 2003-2005 and to 5.9% in 2006-2009 ($P < 0.0001$) [45].

In the next paragraph, the main studies that evaluated the prevalence of silent CAD, performed after year 2000, will be considered. In these studies, it is not always specified whether patients are diagnosed as having T2DM or type 1 diabetes mellitus (T1DM), but eventually the ratio between type 2 and type 1 diabetes is so relevant, that we can assume results are compatible with T2DM.

Epidemiology of SMI

In the early 2000s, Miller et al. [36] conducting studies at the Mayo Clinic found that 58.6% out of 1,738 asymptomatic diabetic patients without known CAD, but with CVD risk factors had an abnormal stress single photon emission computed tomography (SPECT) imaging scan; in 18% of these patients a high-risk diagnostic test was observed [39]. In the Italian study by Faglia et al. [40], a positive exercise electrocardiogram or dipyridamole stress echocardiography was observed in 21.4% out of 141 T2DM without known CAD, but at high CV risk. A similar figure was obtained in the DIAD study, in which the prevalence of an abnormal myocardial perfusion imaging, among 522 T2DM patients aged 50-75 years, but not necessarily with CV risk factors, was of 22% [11]. In the study conducted by Zellweger et al. [46], published in the same period, aimed to assess the prevalence of CAD in asymptomatic diabetic patients at relatively low risk of CAD, using a dual-isotope myocardial perfusion test (MPS), the disease was much more common, being diagnosed in 39% out of 826 asymptomatic diabetic individuals. In a contemporary study by Anand et al. [47], the screening of SMI, combining coronary artery calcium (CAC) imaging and selective myocardial perfusion scintigraphy (performed when CAC > 100 Agatston units), showed an abnormal test (CAC > 10 Agatston units) in 46.3% out of 510 asymptomatic diabetic patients, thus demonstrating the presence of a significant coronary atherosclerosis in slightly less than the half of them. De Luca et al. [48] described a prevalence of SMI of about 1/3 in 189 patients with diabetes and no history of angina, having a treadmill exercise sestamibi stress test. In this study, SMI was diagnosed in 33% T2DM patients, compared to 15% of 191 non-diabetic patients. Nine studies carried out from 1999 to 2010 were considered in a metanalysis by Zhang et al. [49]; in this analysis, the prevalence of SMI detected by SPECT in the pooled sample was 26.1%.

The Basel Asymptomatic high-Risk Diabetics' Outcome Trial (BARDOT) was published in 2011; in this trial the prevalence of abnormal MPS was found still elevated, being of 22% among 400 diabetic patients without prior CAD, but at high CV risk [50]. In the contemporary Do You Need to Assess Myocardial Ischemia in Type-2 diabetes (DYNAMIT) study, SMI detected by a bicycle exercise test or dipyridamole single photon emission computed tomography (SPECT) was present or uncertain in 21.5% out of 316 screened T2DM patients without known CAD, but with at least two additional cardiovascular risk factors [51]. In the FACTOR-64 trial [52], a coronary computed tomography angiography (CCTA) was performed in 395 diabetic subjects, who were at high risk, but with an excellent medical management of CV risk factors; the degree of coronary involvement was categorized into 4 prespecified subgroups: from none/minimal (< 10% stenosis and minimal or no evidence of plaque and CAC score ≤ 10), to mild (10-49% stenosis in any coronary artery or CAC score > 10-100), to moderate (50-69% stenosis or CAC score > 100), and severe stenosis (≥ 70% stenosis in at least 1 major proximal or large coronary artery). Eleven percent out of the subjects showed severe stenosis at CCTA, 12% moderate, and 46% mild, while only 31% had a normal exam. Surprisingly, in the monocentric Italian DADDY-D (Does coronary Atherosclerosis Deserve to be Diagnosed earlY in Diabetic patients?) [37], silent CAD, investigated by exercise tolerance testing, was found in only 7.6% out of 520 T2DM patients, with no clinical CAD, but with a CV risk score ≥ 10% according to the Italian risk chart [53]. This figure is very close to results of another Italian study, the milan study on atherosclerosis and diabetes (MiSAD) group, published 18 years before [8]. The MiSAD evaluated by exercise electrocardiogram, and if abnormal, by an exercise thallium scintigraphy, 925 T2DM; 12.1% out of the patients presented SMI at exercise ECG, but this prevalence was reduced to 6.4% if positive response to both tests was applied. It is reasonable to suppose that these results could be due to the low cardiovascular risk presented by some populations, such as those of Southern Europe.

Data from the Guedalupe Afro-Caribbean diabetic population, reported a SMI prevalence of 23.1% in a group of 147 T1DM and T2DM (93.2% of all the patients), with CV risk factors [54]. In a Chinese study published in 2019, including 821 T2DM subjects screened by SPECT, the prevalence of SMI was 21.3% [55]. In another small pilot Chinese study, published in 2020, the CATCH (Cardiac Magnetic Resonance for Asymptomatic Patients with Type 2 Diabetes and Cardiovascular High Risk) study, that enrolled 63 asymptomatic DM patients with a Framingham risk score ≥ 20%, a silent obstructive CAD was evidenced by stress cardiovascular magnetic resonance in 20.6% of the studied patients [56].

A contemporary study performed in India found a treadmill test positive for SMI in 23.1% out of 338 asymptomatic T2DM subjects [57], while another Indian study that enrolled 97 T2DM observed that only 10% out of the asymptomatic patients showed evidence of SMI or silent MI at SPECT [58]. Finally, a small Saudi Arabian study evaluating 59 T2DM patients without history of CAD, but with multiple CV risk factors detected an abnormal scan in 37% of the patients who had undergone myocardial perfusion SPECT imaging [59].

Therefore, we can conclude that, apart from a few studies, the prevalence of silent CAD is similar, in different diabetic populations in the world.

The clinical burden of asymptomatic ischemic heart disease seems at least comparable to that of symptomatic CAD, if not worse. Total and cardiovascular mortality were found not significantly different in diabetic patients surviving a silent MI, with respect to survivors a symptomatic MI, in the majority of the studies [34, 60-62]. However, in a study by Zellweger et al. [46], in which the rate of annual critical ischemic events was comparable in asymptomatic diabetic patients and in diabetic patients with angina, the outcome rate was 3 times worse in patients with atypical manifestation of angina, such as the shortness of breath. Other authors found that diabetic patients with silent CAD show a higher cardiac mortality risk with respect to those with symptomatic CAD, suggesting that the reason for this poorer survival could be attributed to the lack of revascularization therapy in the former group [63]. On the other hand, in the Fremantle study, an Australian community-based observational study, the risk of cardiac death was reported lower in T2DM individuals with silent MI, than in patients with overt coronary heart disease [64]. In screening studies, unrecognized myocardial ischemia is associated with a relatively poor prognosis [65, 66]. It is interesting to note that silent ischemia accounts for 31% of all elective coronary revascularization indications, as demonstrated in the CORONOR study (Suivi d'une cohorte de patients CORonariens stables en région NORd-Pas-de-Calais) [67], collecting data from a prospective multicenter French registry, including 31% of diabetic patients.

Epidemiology of silent MI

The prevalence of silent MI in diabetic subjects is higher than in non-diabetic, and is generally reported of 2-7% [17, 68], but increases significantly with the cardiovascular risk of the patient, and depends on the diagnostic accuracy of methodology utilized, reaching 20-30% in high risk patients evaluated by myocardial single-photon emission computed tomography or magnetic resonance [18]. The prevalence of silent CAD among diabetic subjects, observed in main studies is summarized in Table 2.

Table 2. Prevalence of silent CAD among diabetic subjects, observed in major studies

Author (ref.), publication year	Number of subjects	Type of diabetes	Prevalence of silent CAD (%)	Method
Wackers et al. [11], 2004	522	T2DM	22	Abnormal SPECT
Anand et al. [47], 2006	510	T2DM	46.3	Significant CAC
Lièvre et al. [51], 2011	316	T2DM	21.5	Exercise test or dipyridamole SPECT positive or uncertain
Davis et al. [33], 2013	1,967	T2DM	16.6	ECG evidence of SMI
Zellweger et al. [50], 2014	400	T2DM	22	Abnormal MPS
Muhlestein et al. [52], 2014	395	T1DM	10.7 severe stenosis	Abnormal coronary computed tomography angiography
		T2DM	11.9 moderate stenosis	
			46.1 mild stenosis	
Turrini et al. [37], 2015	262	T2DM	7.6	Silent CAD at exercise test
Zhu et al. [55], 2019	614	T2DM	21.3	Abnormal SPECT

In the UKPDS, the prevalence of silent MI in T2DM patients was 17.5% and progressively increased over time [33]. This high rate, however, could be explained by the lack of specific ECG criteria used in this study [17]. In the cohort of the Fremantle Study, a diagnostic or probable Q-wave was detected in 3.9%

out of 1,269 T2DM subjects investigated, representing 43.9% of the total observed myocardial infarctions (symptomatic and silent) [64].

In an American study, silent MI diagnosed by treadmill exercise sestamibi stress test was observed in 18% of a total of 217 patients with diabetes *vs.* 7% of 224 patients without diabetes [48]. In this study, the prevalence of silent MI was 40% among diabetic subjects with 2-3 coronary risk factors, while 27% in patients with 0-1 coronary risk factors [48].

Kwong et al. [69] found a prevalence of myocardial scars, detected by cardiac magnetic resonance, in 28% out of 109 diabetic patients, without clinical evidence of the disease. In the Chinese CATCH study, silent myocardial infarction was detected by magnetic resonance in 7.9% of the subjects [56].

The incidence of silent MI was also investigated in several pharmacological and intervention randomized controlled trials (RCT) [18, 60, 70-75] enrolling patients in primary or secondary prevention, most often diagnosed using the 12-lead ECG and applying Minnesota-code criteria. In primary prevention studies, the incidence of silent MI is about 1/1,000 patients-year [70, 71, 76, 77], but it increases to 4-6/1,000 patients-year in subjects in secondary prevention or in high risk subjects, such as those in the PROactive pioglitazone clinical trial. In macrovascular events [72, 73], in the IDNT (Irbesartan Diabetic Nephropathy Trial) [78], and in the FIELD (Fenofibrate Intervention and Event Lowering in Diabetes) studies [60].

Data obtained from the JPAD (Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes) trial [76], a randomized controlled trial designed to examine the efficacy of low-dose aspirin therapy in primary prevention in T2DM patients, started in 2002 and concluded in 2008, but with a post-study follow-up until 2015, 25% of all myocardial infarctions were silent, with an incidence rate for silent MI of 1.44/1,000 patients-year, and of 4.26 for symptomatic MI [79].

The FIELD study specifically aimed to determine the incidence of silent MI, and its predictors, along with the effects of fenofibrate on this outcome in a large cohort of T2DM patients [60]. Silent MI was found in 265 patients (2.7% of all participants), with a cumulative incidence rate of 5.5/1,000 patients-year, during the 5 years of follow-up period, representing the 36.8% of all the recorded MI. The incidence of silent MI in the PROactive study [72, 73], that included patients with evidence of macrovascular disease, was similar, ranging from 2.9 to 5.5/1,000 patients-year [18]. In the IDNT study, that enrolled T2DM patients with hypertension, and nephropathy, the incidence of clinically unrecognized MI was 4/1,000 patient-years, in a follow-up period of 2.5 years [78].

Among more recent CVOTs (CardioVascular Outcome Trials), designed to evaluate the cardiovascular safety of sodium-glucose co-transporter-2 (SGLT2)-inhibitors and of glucagon-like receptor-1 agonists (GLP1-RA) in high cardiovascular risk T2DM individuals, silent MI was often considered, and its prevalence did not show any significant difference between treatment and placebo arms. In the EMPA-REG (Empagliflozin Reducing Excess Glucose) trial, the presence of a silent MI was analyzed in about 50% of at high risk patients enrolled: in 2,378 patients in the empagliflozin group and in 1,211 in the placebo group [80]. In this population, the incidence rate of silent MI was 6.2/1,000 patients-year (5.4/1,000 patients-year in the placebo group and of 7.0/1,000 patients-year in the empagliflozin group, P = 0.42). Silent MI was also assessed in all the participants in the LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results) trial [81] and in SUSTAIN-6 (Semaglutide in Subjects with Type 2 Diabetes) trial [82], both enrolling at high risk patients. The incidence rate of silent MI was 0.35/100 patients-year in the LEADER (0.4/100 patients-year in the placebo group and 0.3/100 patients-year in the liraglutide group, P = 0.37) [81], and 0.17/100 patients-year in the SUSATIN-6 (0.21/100 patients-year in the placebo group and 0.12/100 patients-year in the semaglutide group; P = 0.37) [82]. Therefore, data from recent CVOTs in T2DM on silent MI show an incidence very similar to that obtained in previous studies.

Interestingly, silent MI in T2DM was also investigated as a possible marker for CV risk prediction in 2 main studies, the UKPDS [33], and the ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial [83]. Results obtained from the UKPDS led to the conclusion that silent MI was an independent predictor of future fatal MI and all-cause mortality, but failed to demonstrate a more accurate prediction of risk when added to the UKPDS risk engine [33]. On the other hand, results obtained from the ACCORD trial, where

the prevalence of silent MI at baseline was 5.3% among the 5,539 eligible participants (mean age 62.8 ± 5.8 years), allowed to conclude that not only the presence of silent MI was associated with increased risks of all-cause mortality, cardiovascular mortality, congestive heart failure, and major coronary heart disease events, but also improved the discrimination capacity, when added in risk models [83].

Factors associated with silent coronary artery disease in type 2 diabetes

Many studies tried to identify independent predictors of silent CAD in T2DM, that could help in the selection of patients to be screened, answering one out of the pivotal questions still open, on the opportunity of screening silent CAD in diabetes. Results obtained from the different studies on predictors of SMI or silent MI are not always concordant, due to the specific characteristics of the studied populations, to their baseline CV risk, to the presence of diabetic micro- and macrovascular complications, to the choice of the variables to be investigated, and also, maybe to unknown genetic factors, and understudied markers.

The impact of sex differences in the diabetic population is often, but not always considered in the studies, and sometimes the results could be nullified by the small sample sizes of enrolled patients. In the general population of the Framingham [34] and the Cardiovascular Health Study [84], a higher risk of silent MI was observed in women, while recent results from the Atherosclerosis Risk in Communities (ARIC) study showed an incident rate of silent MI significantly higher in men than in women [85]. In the diabetic population, a greater prevalence of silent MI has been observed in women in the Fremantle [64], and in the UKPDS [33] studies. In the ACCORD cohort no evidence was found that silent MI, as detected by the Minnesota code, was more common in women than in men; rather, women showed a higher heart disease mortality rate compared to men [86]. Usually women complain less of chest pain and of typical symptoms of acute coronary syndrome, especially diabetic women [87, 88], but often asymptomatic women have a worse prognosis than asymptomatic males [86, 89].

Cardiac perfusion abnormalities seem to be more frequent among men than women [36, 39, 46, 50], and male sex is an independent predictor of SMI in the majority of the studies [11, 26, 36, 38, 39, 46, 70, 90]. In the DIAD study, the frequency of abnormal screening did not differ between men (24%) and women (19%), however women tended to show smaller MPI defects, and lower subsequent cardiac event rates with respect to men, so that the authors conclude that "symptomatic women with T2DM represent a subgroup for which screening for coronary artery disease does not appear warranted" [91]. Similarly, no difference was observed between men and women in the incidence of SMI in a Japanese study published in 2020, where women, nonetheless, experienced a worse prognosis, and only in female, but not in male, SMI was independently associated with major adverse cardiac events (MACE) [89].

ECG abnormalities are potent predictors of silent CAD. In the Milan study [8], ST-T abnormalities showed the highest odds ratio for SMI [9.27, confidence interval (CI) 4.44 to 19.38], and were the only independent predictors in women. In the DIAD study, only females showed a significant association with ischemic ST-segment depression, induced by adenosine infusion, in the presence of a normal myocardial perfusion (OR 3.4) [11]. Pathological Q waves were independently associated with a high-risk scan in the American study by Rajagopalan et al. [39]. In a more recent, small, Italian study, an abnormal ECG was the strongest, independent predictor of silent CAD in 102 asymptomatic T2DM individuals (OR 8.9, CI 1.27-62.5; P = 0.028) [92].

The presence of diabetes target organ damage has been investigated in several studies, and a higher prevalence of silent CAD was demonstrated for retinopathy [20, 26, 55, 93, 94], neuropathy [11, 95-100], and nephropathy [59, 101-104], as well as for peripheral vascular disease [105-112].

Diabetic retinopathy, and male gender increased the prediction of silent MI, in a French cohort of T2DM [93]. In a Chinese study of 821 T2DM, the prevalence of SMI was significantly different depending on the presence of diabetic retinopathy [55]. The percentages of SMI were 18.5% (75/405) among patients without diabetic retinopathy, 25.2% (37/147) among patients with non-proliferative diabetic retinopathy, and 30.6% (19/62) among patients with proliferative retinopathy [55]. Another recent study has found that presence and degree of DR are independently associated with silent CAD, in T2DM [94].

Silent CAD is a specific manifestation of diabetic autonomic neuropathy [95-98], and an abnormal cardiac autonomic function, measured by heart rate variability (HRV) is significantly associated with an increased risk of mortality [98]. T2DM subjects with cardiac autonomic neuropathy (CAN) are therefore susceptible for experiencing silent CAD. When both SMI and CAN are present, the risk of major cardiac events is significantly increased [99]. Vinik et al. [95] reported a consistent association between CAN and the presence of silent myocardial ischemia. Diabetic neuropathy and cardiac autonomic function were evaluated in all the patients of the DIAD study, and an abnormal heart rate response to Valsalva manoeuvre (odds ratio 5.6), was the strongest predictor for an altered cardiac test in this cohort [11, 100].

Another powerful predictor of silent CAD morbidity and mortality is erectile dysfunction, that is an early manifestation of ischemic heart disease [105-107]. Pathophysiological mechanisms common to CAD and erectile dysfunction involve abnormalities found in both vessels and nerves, and are ascribable to endothelial dysfunction, a decrease of nitric oxide-induced vasodilation and smooth muscle relaxation, and to diabetic autonomic neuropathy [96, 113]. T2DM with erectile dysfunction show a higher prevalence of silent CAD [106, 108], and the evaluation of erectile dysfunction in T2DM individuals has been suggested to be a powerful tool in improving the sensitivity of screening guidelines for SMI detection [109].

Diabetic nephropathy, is a well-known, strong predictor of CVD, and its association with silent CAD has been highlighted in several studies, even in the early stages of chronic renal disease [59, 101-104]. Microalbuminuria, a marker of incipient nephropathy, has been shown to be significantly associated with silent CAD, and is a powerful predictor of the disease [60, 100-103]. Al-Humaidi et al. [59] demonstrated that myocardial abnormalities detected by SPECT in T2DM, correlates with nephropathy. On the other hand, the majority of patients in dialytic therapy, with angiographically documented CAD, are asymptomatic [104].

Peripheral vascular disease has been shown to be independently associated with silent CAD in several studies [11, 39, 45, 108, 110, 111]. Rajagopalan et al. [39] concluded that ECG Q waves, and peripheral artery disease (OR 2.134, CI 1.150-3.961; P = 0.016) were the 2 most important variables associated with high risk findings on stress SPECT, in their analysis. In the population of BARDOT trial, peripheral artery disease independently predicted an abnormal MPS (OR 2.134, CI 1.150-3.961; P = 0.016) [110]. A recent prospective, multicenter study has demonstrated that the presence of carotid plaque is a predictor of silent CAD prevalence, severity, and extent in asymptomatic T2DM [111]. Therefore, the screening for carotid atherosclerosis has been recommended in identifying diabetic patients at higher risk for silent CAD [112].

Several studies have underlined the important role of a positive family history of CAD as a strong predictor of silent CAD and silent MI [26, 59, 114]. In a study by Kawano et al. [114], including 128 patients, the family history of CVD and/or long disease duration (> 11 years) were the best independent risk factors of SMI showing an OR of 1.060 and 4.000, respectively, by a multivariate analysis.

Finally, classical risk factors for ischemic heart disease, such as smoking, hypertension, hypercholesterolemia, diabetes duration have often (but not always) been demonstrated to be independently associated or predictors of silent CAD, in T2DM [90, 100, 110, 112]. The recent analysis of data of the BARDOT trial recognized, as independent predictors of an abnormal MPI, apart from male sex, and peripheral artery disease, the duration of diabetes (OR 1.049, CI 1.015-1.085; P = 0.005), smoking (OR 2.064, CI 1.109-3.839; P = 0.022), systolic blood pressure (OR 1.014, CI 1.00-1.03; P = 0.056), and also brain natriuretic peptide (OR 1.002, CI 1.001-1.004; P = 0.005) [110]. An exploratory analysis of the DIAD study, performed instead of multivariate assessment, precluded by the low number of events occurred in this study, suggested that other independent predictors of a future primary cardiac event, in addition to male sex and cardiac autonomic dysfunction, were: creatinine, peripheral vascular disease, and low-density lipoprotein levels [100]. Anand et. al. [47] demonstrated, in 510 asymptomatic T2DM subjects, that age, systolic blood pressure, diabetes duration, UKPDS risk score, CAC score, and extent of myocardial perfusion abnormalities were significant predictors of time to cardiovascular events. In the study by Scholte et al. [90], current smoking, duration of diabetes and the total cholesterol/HDL-cholesterol ratio were identified as independent predictors of an abnormal SPECT, in 120 asymptomatic T2DM individuals.

Therefore, to summarise, males seem to be more susceptible to manifest silent CAD, but women seem to have a worse prognosis. Classical risk factors for CVD i.e. positive family history, age, smoke, arterial hypertension, dyslipidaemia, and the duration and control of diabetes itself can significantly contribute to the development of silent CAD in diabetes. Diabetic chronic complications either macro- or microangiopathy are also important predictors of silent CAD. In particular, the evidence of ischemic ECG abnormalities strongly suggests silent CAD in asymptomatic diabetic subjects.

In the proposed algorithm for the screening of silent CAD, the presence of organ damage in diabetes, either micro- or macroangiopathic invariably is suggested as a suitable condition to consider a patient for the screening [19, 21, 115].

Studies aimed to demonstrate the benefit of screening silent CAD in type 2 diabetes-criticisms and unmet answers

Two important meta-analysis were published by Bauters and Lemeslein 2016 [116], and by Clerc et al. [117] in 2018, analyzing main studies aimed at demonstrating the usefulness of screening silent CAD in diabetic subjects. Five randomized trials for a total of 3,314 [116], and 3,299 [117] asymptomatic diabetic individuals were considered in these meta-analyses: the study by Faglia et al. [40] published in 2005, the DIAD study of 2009 [100], the DYNAMIT study of 2011 [51], the FACTOR-64 study of 2014 [52] and the DADDY-D study of 2015 [37]. All the studies enrolled patients with T2DM, apart from FACTOR-64, in which 12% of the subjects were T1DM.

In the analysis by Bauters and Lemesle [116], it emerged that the screening of silent CAD was unable to improve cardiovascular outcomes, with an odd ratio for all-cause death of 1.00 (95% CI 0.67-1.50), for cardiovascular death, of 0.72 (95% CI 0.33-1.57), for non-fatal myocardial infarction, of 0.71 (95% CI 0.40-1.27) and for the composite cardiovascular death or non-fatal myocardial infarction, of 0.60 (95% CI 0.23-1.52). Therefore, the conclusions of this meta-analysis were against the screening for silent CAD in diabetes.

On the other hand, the analysis by Clerc et al. [117], after considering several criticisms of the studies included in the analysis, also acknowledging that any mortality benefit can be demonstrated, concluded that "The present systematic review and meta-analysis suggests a reduction of cardiac events with the use of a CAD screening strategy in asymptomatic diabetic patients." These authors demonstrated that non-invasive imaging for CAD significantly reduced the primary composite endpoint of any cardiac event by 27%, with a number needed to treat (NNT) of 56 asymptomatic T2DM, to prevent 1 cardiac event over a 4-year period, comparing this benefit to that of statin use for primary prevention of ischemic heart disease events (-27%, NNT 78) [118]. This effect was mainly driven by lower rates of non-fatal MI (-35%) and of hospitalizations for heart failure (-39%); however, when assessed separately, the event rates of non-fatal MI (relative risk 0.65, P = 0.062), and hospitalization for HF (relative risk 0.61, P = 0.1) were not significant.

It must be acknowledged that several criticisms linked to each study design allows to raise some doubts on the generalizability of their conclusions. In the DIAD study, conducted in USA and Canada, 1,123 T2DM participants asymptomatic for CAD were randomly assigned to screening by adenosine (99) Tc (m)-sestamibi myocardial perfusion imaging, and followed-up for 5 years [11, 100]. The number of cardiac events, that included non-fatal MI and cardiac death, was non-significant between screened (events n = 15) and non-screened (events n = 17) subjects (HR 0.88, 95% CI 0.44-1.8, log-rank 0.12; P = 0.73). The entity of cardiac event rate observed in the DIAD study was very low (0.6% per year), as also underlined by the authors, who quote, as a comparison, the rate observed in the subgroup of T2DM patients without previous cardiac events enrolled in the ACCORD, equal to 1.4% event per year [119]. In the more recent CVD-REAL (The Comparative Effectiveness of Cardiovascular Outcomes) Nordic Study, referring to data obtained from national registries of Denmark, Sweden and Norway, for example, major adverse cardiovascular event rate (cardiovascular mortality, myocardial infarction, or stroke) was 2.12 per 100 patients-year, in T2DM subjects, new users of non-SGLT2 inhibitors glucose lowering drugs [120]. Therefore, patient selection in the DIAD study could not reflect the real-world population of T2DM patients. Moreover, the low rate of

events observed in the DIAD limits the statistical power of this study, and its capacity in excluding a true difference in the outcomes. In addition, in the subgroup of subjects with moderate or large MPI defects, the number of cardiac events was significantly higher with respect to subjects with normal MPI or with fewer or minor MPI defects (HR 6.3, 95% CI 1.9-20.1; P = 0.001), suggesting a significant benefit of the screening, in patients with a more advanced disease.

The DYNAMIT study [51], a French multicenter RCT that included T2DM patients with other risk factors was prematurely discontinued because of difficulties in recruitment of patients; moreover, as in DIAD study, the event rate was lower than expected, and the insufficient statistical power of this trial invalidates its results.

Again, in FACTOR-64 a low number of cardiac events was observed (2.9% in 4.8 years), probably due to the optimal medical management received by all the patients, as underlined by the authors; however, the evidence of CAD in the screened group was able to predict higher event rates [52].

The DADDY-D study is a single center Italian study aimed not only to screen silent myocardial ischemia by exercise tolerance testing (ETT) in at high risk T2DM, but also to treat patients by revascularization, when indicated [37]. This study failed to demonstrate that screening for asymptomatic CAD and revascularization favorably affects the occurrence of a first cardiac event. Anyway, as for other mentioned studies, these conclusions are biased by several limitations; first, the sample size was insufficient, with a female participant number lower than anticipated; secondly, the diagnostic test employed has a quite low sensitivity in detecting ischemia; and lastly, a reduced statistical power was implicit, due to an unexpectedly lower prevalence of positive tests.

Among all, only the study by Faglia et al. [40] was able to conclude that screening silent CAD in T2DM at high cardiovascular risk is effective in reducing future major cardiac events. These authors studied 71 subjects using exercise electrocardiogram test and dipyridamole stress echocardiography; if one of these tests was positive, the patient underwent a coronary angiography, and then surgical or percutaneous revascularization, if stenoses ≥ 50% of vessel diameter were present. The control group consisted in 70 non-screened T2DM subjects. During the mean follow-up period of 53.5 months, 1 major (myocardial infarction) and 3 minor events (angina) occurred in the screening arm, while 11 major and 4 minor events occurred in the control arm (P of all events = 0.018).The conclusions of this paper are that: "The NNT of the study does indicate the feasibility of screening for unknown CAD in subjects with type 2 diabetes mellitus with high cardiovascular risk," also adding "economic cost does seem to be acceptable if the screening test consists in the sole use of dipyridamole stress echocardiography [40]."

These results are strengthen by a recent review and meta-analysis, by Beller et al. [121] who considered only studies performed with coronary CT angiography, in 5,012 asymptomatic diabetic individuals; these authors conclude that the presence of obstructive CAD (*vs.* nonobstructiveor no CAD) is a strong and independent predictor of cardiovascular events (HR 4.07, 95% CI 2.30-7.21), with an increased HR also for non-obstructive plaque (*vs.* no CAD) of 2.17 (95% CI 1.11-4.25).

To summarize, the interpretation of results from the studies aimed to demonstrate the usefulness of screening silent CAD in T2DM subjects cannot be univocal, and definitive, primarily depending on the level of risk of studied populations, and secondarily on the therapeutic management applied to patients.

Final remarks and conclusions

In the last 20 years, research has actively tried to answer the question whether it is useful or not to screen T2DM patients for silent CAD in terms of cost/benefit ratio, but a definitive indication is still lacking. The American Diabetes Association (ADA) guidelines recommend not screening asymptomatic diabetic patients for silent CAD [21]. The "2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the European Association for the Study of Diabetes" equally do not recommend routine screening of CAD in asymptomatic diabetic subjects [19]; however, these guidelines suggest to apply a risk stratification approach, concluding that stress testing or computed tomography coronary angiography (CTCA) may be indicated in very high-risk asymptomatic individuals. Thus, coronary risk stratification represents a critical step in deciding whether or not to address a patient to screening.

Criteria suggested by ESC Guidelines [19] and ADA Position statement [21] for considering the screening of CAD in type 2 asymptomatic diabetic patients are summarized (Table 3).

Table 3. Criteria suggested by ESC 2019 [19] and ADA 2020 [21] for considering the screening of CAD in type 2 asymptomatic diabetic patients

ESC 2019: patients at very high risk, i.e. with any of the following:	ADA 2020: presence of any of the following:
- Peripheral arterial disease - High CAC score (> 400 Agatston) - Proteinuria - Renal failure [eGFR < 30 mL/(min·1.73 m²)] - Left ventricular hypertrophy - Retinopathy - Three of more major risk factors (age, hypertension, dyslipidemia, smoking, obesity)	- Atypical cardiac symptoms (unexplained dyspnea, chest discomnfort) - Signs or symptoms of associated vascular disease [including carotid bruits, transient ischemic attacks, stroke, claudication, peripheral artery disease, electrocardiogram abnormalities (e.g. Q waves)]

eGFR: estimated glomerular filtration rate

The treatment at target of all CV risk factors is currently universally considered the best approach for silent CAD in T2DM. Moreover, the benefits of revascularization in diabetic patients with silent CAD seem to be restricted to patients with severe CAD, who usually show also important comorbidities, such as chronic renal failure, left ventricular dysfunction and peripheral or carotid occlusive arterial disease. Available randomized trials have limitations and do not confirm the value of invasive treatment of ischemic heart disease [122, 123].

Therefore, the screening for silent CAD in asymptomatic T2DM patients still remains a possible approach to improve cardiovascular outcomes in this population, but until more large-scale, randomized trials are accomplished, no definitive conclusions can be drawn.

Abbreviations

ACCORD: the Action to Control Cardiovascular Risk in Diabetes

ADA: American Diabetes Association

BARDOT: the Basel Asymptomatic High-Risk Diabetics' Outcome Trial

CAC: coronary artery calcium

CAD: coronary artery disease

CAN: cardiac autonomic neuropathy

CV: cardiovascular

CVD: cardiovascular disease

DADDY-D: the Does coronary Atherosclerosis Deserve to be Diagnosed earlY in Diabetic patients?

DIAD: the Detection of Silent Myocardial Ischemia in Asymptomatic Diabetic Subjects

DYNAMIT: the Do You Need to Assess Myocardial Ischemia in Type-2 Diabetes

ECG: electrocardiogram

ESC: European Society of Cardiology

FACTOR-64: the Screening for Asymptomatic Obstructive Coronary Artery Disease Among High-Risk Diabetic Patients Using CT Angiography, Following Core 64 – FACTOR-64

MI: myocardial infarction

MiSAD: Milan Study on Atherosclerosis and Diabetes

MPI: myocardial perfusion imaging

MPS: myocardial perfusion test

SMI: silent myocardial ischemia

SPECT: single photon emission computed tomography

T1DM: type 1 diabetes mellitus

T2DM: type 2 diabetes mellitus

UKPDS: the United Kingdom Prospective Diabetes Study

Declarations

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The author contributed solely to the paper.

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The author declares that she has no conflicts of interest.

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