

## REVIEW ARTICLE

## Assessing Cardiovascular Risk in Patients with Diabetes: An Update

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**Abstract:** The globalization of the Western lifestyle has resulted in increase of diabetes mellitus, a complex, multifactorial disease. Diabetes mellitus is a condition often related to the disorders of the cardiovascular system. It is well established that three quarters of diabetics, aged over 40, will die from cardiovascular disease and are more likely than non-diabetics to die from their first cardiovascular event. Therefore, it is of paramount importance to individualize treatment *via* risk stratification. Conditions that increase cardiovascular risk in people with diabetes include age more than 40 years, male gender, history of relative suffering from premature CHD, blood pressure and high LDL levels, presence of microalbuminuria, obstructive sleepapnea, erectile dysfunction and other conditions.

Several models have been developed in order to assess cardiovascular risk in people with and without diabetes. Some of them have been proven to be inadequate while others are widely used for years. An emerging way of risk assessment in patients with diabetes mellitus is the use of biomarkers but a lot of research needs to be done in this field in order to have solid conclusions.

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**ARTICLE HISTORY**

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Received: November 12, 2018  
Revised: August 14, 2019  
Accepted: August 26, 2019

DOI:  
[10.2174/1573403X15666191111123622](https://doi.org/10.2174/1573403X15666191111123622)

**Keywords:** Diabetes, cardiovascular risk, risk assessment, biomarkers, low density lipoprotein, coronary heart disease.

### 1. INTRODUCTION

Diabetes mellitus is a complex, multifactorial disease, which has increased dramatically in recent years due to the globalization of the Western lifestyle. Diabetes mellitus is a condition often related to disorders of the cardiovascular system. The cardiovascular system is widely affected from diabetes mellitus, from smaller (microangiopathy) to larger (macroangiopathy) arteries. Macrovascular cardiovascular disorders include peripheral and coronary artery disease and diabetic cardiomyopathy, and microvascular cardiovascular disorders include retinopathy, nephropathy and neuropathy.

Cardiovascular complications are now the primary causes of both morbidity and mortality related to diabetes. More than 75% of diabetics, aged over 40, will die from cardiovascular disease and are more prone compared to the

non-diabetics to die from their first cardiovascular event. The relative risk of coronary heart disease was increased by 66% in men and by 20% in females, according to the Framingham study after being screened for major cardiovascular risk factors and after 20 years of follow-up. Diabetic women seem more susceptible to cardiovascular risk than men. The impact of cardiovascular diseases in diabetic subjects in public health is already huge and is constantly increasing. Moreover, patients with diabetes experience silent, more advanced and associated with less favourable prognosis cases of CAD in than the non-diabetic population.

The prevalence of adult diabetes was globally increased from 4.7% in 1980 to 8.5% in 2014 escalating to the number of 422 million patients, as Global World Health Organization (WHO) Report of Diabetes announced. Furthermore, in many countries, the prevalence of diabetes in patients with CAD is up to 50%. Type 2 diabetes (T2DM) is associated with increased cardiovascular morbidity and mortality and is regarded as a “cardiovascular risk equivalent” [1]. T2DM, obesity, and cardiovascular disease (CVD) are pathogenetically similar [2]. The effects of tighter diabetes control on

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cardiovascular morbidity and mortality have been discussed with conflicting results that led to more focused current diabetes guidelines [3]. Even though developed countries have been experiencing great reductions in diabetes-related coronary mortality thanks to the outstanding advances in cardiovascular therapy, cardiovascular morbidity and mortality still remain high in the majority<sup>1</sup> of patients with diabetes [1]. Diabetes is commonly associated with other cardiovascular risk factors, interacting with these to accelerate atherogenesis. Therefore, there is a significant reduce in the risk of both fatal and non-fatal CVD from interventions, such as those targeting hyperglycaemia, hypertension and hypercholesterolaemia. The concept of screening an asymptomatic patient is really complex since diabetic cardiovascular autonomic neuropathy (CAN) which can damage the neural fibres that innervate the heart and cardiac vessels may lead to atypical clinical manifestations [4].

T2DM is an important risk factor for CAD, and specialists regard DM as an equivalent to established CAD risk. Diabetic patients show a high risk for the development of atherosclerotic CAD lesions for various causes such as hyperglycaemia, dyslipidemia and insulin resistance, which caused impaired platelet function, endothelial, vascular smooth muscle cell dysfunction and abnormal coagulation [3].

The first clinical manifestations of cardiovascular disease in type 2 diabetes are peripheral arterial disease and heart failure. The differences among relative risks of different cardiovascular diseases in patients with type 2 diabetes have uses for clinical risk assessment and trial design [5].

Moreover, the pathophysiology of CVD varies among the Type 1 DM and Type 2 DM. Hyperglycaemia affects more cardiovascular risk in Type 1 DM compared to Type 2 DM, whereas other factors seem to exert a more synergistic effect [6].

The ESC Guidelines on diabetes, pre-diabetes and cardiovascular diseases [7] report the following risk scores developed for people without diabetes: (1) Framingham Study risk equations based on age, sex, blood pressure, cholesterol (total and HDL) and smoking, with DM status as a categorical variable, (2) the European Systematic Coronary Risk Evaluation (SCORE) for fatal coronary heart disease and CVD, (3) the DECODE risk equation for cardiovascular death, incorporating glucose tolerance status and FPG, (4) the Prospective Cardiovascular Münster (PROCAM) scor-

ingscheme and (5) the Myocardial Infarction Population Registry of Girona (REGICOR). The risk engines developed for people with diabetes reported by the ESC Guidelines [7] are: (1) the United Kingdom Prospective Diabetes Study (UKPDS) risk score for CAD, (2) the Swedish National Diabetes Register (NDR) and (3) The Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified Release Controlled Evaluation (ADVANCE).

## 2. CARDIOVASCULAR RISK ASSESSMENT TOOLS

The Framingham trial was the first epidemiological study to prospectively investigate cardiovascular risk factors in a methodically structured population. It began in 1948, at a time when prominent cardiologists, such as Paul Dudley White, believed that one of the most important cardiovascular risk parameters, arterial hypertension, was "a mechanism to counter atherosclerosis and (consequently) should not interfere with "it" [8]. In the study, 5,209 men and women participated aging between 28-62, a random sample of 1/3 of the residents of Framingham, Massachusetts, who did not have cardiovascular disease. Twelve years later, with the initial analysis of the study results, it was realized that arterial hypertension and other risk factors were not enough. It took another six years before the first multifactorial analysis of risk factors for coronary artery disease was published [9]. In this analysis, seven risk factors: age, cholesterol, systolic blood pressure, body weight (gender and stature pre-screened), hemoglobin, smoking, and left ventricular hypertrophy found in electrocardiogram were used to calculate the risk for men and women aging between 28-62 years. In 1971, 5,124 more patients, adult children of the initially admitted and their women (second generation) joined the study. Glucose intolerance then replaced hemoglobin, and on the basis of the new equation, the American Heart Association issued in 1973 an aid to calculate the coronary heart disease risk in daily practice and the appropriate choice of methods addressing it [10].

In 1976, the American Journal of Cardiology published a study in which researchers confirmed the continuing nature of risk factors [11], namely, that there is no limit above which the risk and under which it is eliminated - Sir George Pickerin's [12] point of view on "over-the-counter" overdraft 16. In particular, the analysis of the results of the study demonstrated that:

(a) even subjects with systolic blood pressure below 140 mmHg were still in danger for cardiovascular events, (b) individuals with moderate levels of more than one risk factor may be at higher risk for cardiovascular events than those with a high level of single risk factor; and (c) risk factors have different effects on different cardiovascular endpoints (e.g. hypertension entails a higher risk for HCV and heart failure than for IKN and intermittent claudication) [11].

In 1982, American statistician Erica H. Brittain published in the West Journal of Medicine the first scoring boards for the possibility of coronary heart disease, separately for each gender, based on systolic blood pressure, tobacco use of left ventricular hypertrophy proved electrocardiographically, glucose intolerance and cholesterol in combination with age [13].

<sup>1</sup>Age is the strongest non-modifiable risk factor for CVD. The increase in cardiovascular risk is continuous and progressive either in men or women. The association of family history of myocardial infarction and incident coronary heart disease (CHD) in patients with diabetes is important, although the strength differs between studies. In general population, the incidence of a new myocardial infarction is higher in men than in women, with an age adjusted Hazard Ratio (95% CI) of 2.56 (2.53–2.60). In patients with diabetes, the men to women relation is much more narrow, however still higher in men: HR 1.22 (95% CI 1.18–1.25). Thus, the likelihood of a patient with diabetes to have an acute myocardial infarction solely due to gender is greatly attenuated when compared with individuals without diabetes. Active smoking is associated with the highest risk of total mortality and cardiovascular events among patients with diabetes, while smoking cessation is associated with a reduced risk in total mortality and cardiovascular events in patients with diabetes. [1].

At the beginning of the next decade, with the new epidemiological data that has emerged in the meantime (adding HDL cholesterol to risk assessments and extending ages to 74), a more detailed scoring system was designed for use by doctors in daily practice. In 1994, in order to ensure a broader representation of the Framingham city population and its surroundings, a new cohort of 507 people of diverse racial origin joined the study. A third generation of the study population (grandchildren who joined in 1948) followed in 2002, and the second year of the new 1994 cohort was added next year.

Meanwhile, the electrocardiographic evidence of left ventricular hypertrophy was subtracted from the prediction model for two main reasons: the correlation between blood pressure and left ventricular hypertrophy and the lack of consensus for its electrocardiographic diagnostic criteria [14]. Thus, the algorithm, published in 1998 following a 12-year follow-up of the Framingham Study, predicted the risk of developing coronary artery disease over a decade based on variables: age, sex, cholesterol levels, and possible hypertensive medication of the patient), diabetes and smoking [14].

In 2008, with the new findings of the Framingham Study, and in order to evaluate the 10-year risk not only for coronary artery disease, but also for peripheral vascular disease, heart failure, stroke and cardiovascular disease altogether, a new rating (2008 Framingham Risk Score) was proposed by a team of American biostatistics for use in primary health care [15]. The variables included in the altered version of this modified version are age-related sex, dyslipidemia, hypertension or antihypertensive therapy, smoking, diabetes, coronary heart disease and other atherosclerotic disease, which involve a high risk for coronary artery disease, and the family history of early coronary heart disease in close relatives. For the purpose of facilitating family doctors and cost savings, in addition to the model that includes all the above variables, the authors suggested as a reliable second model without laboratory determinations.

The Framingham Study followed a number of cohort studies, the results of which were used to design predictive cardiovascular risk models. Some of these models, with Framingham's first model, have been included in guidelines for therapeutic decisions [16]. In a recent systematic review, by 2013, 9,665 articles on the development of multifactorial models of cardiovascular risk stratification in the general population or the validity of their validity in different populations [17] were found in the digital databases of published Medline and Embase articles [17]. The number of relevant publications has increased steadily since 2000. Out of these thousands of articles, 212 describing the design of 363 forecasting models were selected for analysis. The risk parameters used for the creation of these 363 models are very variable: systolic single and / or diastolic blood pressure, lipidemic profile, smoking, BMI, but also alcohol, diabetes and other co-abnormalities such as atrial fibrillation and angina and, of course, age and gender, as well as the family history of cardiovascular disease and race, finally, younger or new risk factors including C-reactive protein, albumin and creatinine. The authors conclude that there are too many models of cardiovascular risk prediction, many of which are of dubious validity, and that rather than looking for new

models, research should focus on assessing and comparing existing ones [17].

Of the most analysts, five of the published studies are considered as providing the basis for the most reliable and validated predictive cardiovascular risk models [18-22] (Table 1): (1) Framingham (Table 1) [18], (2) SCORE (Systematic Coronary Risk Evaluation) (Table 1) [19], (3) PROCAM (Table 1) [20] (4) QRESEARCH, with QRISC1 and QRISC2 scoring tools, (Table 1) [21] and (5) SHHEC (Scottish Heart Health Extended Cohort) with a scoring tool ASSIGN (Table 1) [22]. However, according to Coleman *et al.* [23], the Framingham and SCORE models do not offer reliability concerning fatal CVD and CHD risk in type 2 diabetes. The underestimate seen with Framingham is not surprising since there were only 337 diabetic patients in this study. Additionally, the incorporation of diabetes as a categorical variable, implies that this disease increases the risk equally regardless of the glycemic control or of its duration. This limitation affects the SCORE equation, by quadrupling the risk for diabetic women and doubling for diabetic men.

Beside the models developed for cardiovascular risk assessment for patients with diabetes mellitus information on various biomarkers and imaging methods, along with traditional risk factors, offer evidence towards individualized cardiovascular risk assessment [24]. Contemporary strategy for risk stratification in subjects suffering from diabetes suggests the use of both single and serial levels of biomarkers. Research argues that these tests may ameliorate determining the possibility of clinical outcomes in pre-diabetic and diabetic subjects [25, 26]. In fact, glycosylated hemoglobin, as well as elevated glycated hemoglobin, creatinine or advanced glycation end products demonstrated correspondence and effectiveness in predicting CV risk and risk of asymptomatic atherosclerosis and CKD [27, 28].

However, it has not yet been well established that the use of cardiac biomarkers to clarify CV risk for subjects with type 2 diabetes with asymptomatic CV diseases is the optimal choice. There is no sufficient evidence proving the predictive ability of these biomarkers concerning complications in diabetics without known CV disease [29]. Additionally, some researchers doubt that conventional cardiac biomarkers including cardiac troponins, natriuretic peptides, soluble ST2 or galectin-3, can precisely predict CV risk in diabetics with known CV disease [29].

Some cardiovascular risk models are demonstrated in Table 1. In Figs. (1 and 2), scores of risk stratification for cardiovascular disease, concerning low and high risk subjects, are shown.

### 3. STUDIES UPON CARDIOVASCULAR RISK

A large population-based retrospective cohort study [30] (Table 2), in which 379,003 diabetic individuals and 9,018,082 non-diabetic individuals participated, tried to define the age of transition to high-risk cardiovascular condition in subjects with diabetes. A risk estimated more than 20% in 10 years of myocardial infarction, stroke and death from any other cause, led to the conclusion that high risk age is 48 years in men and 54 years in women. When

**Table 1. The most reliable and validated predictive cardiovascular risk models.**

Model	Measurements	Scoring system	
Framingham	Age total cholesterol smoking status HDL cholesterol systolic blood pressure.	<p>WOMEN Points total: Under 9 points: &lt;1%. 9-12 points: 1%. 13-14 points: 2%. 15 points: 3%. 16 points: 4%. 17 points: 5%. 18 points: 6%. 19 points: 8%. 20 points: 11%. 21=14%, 22=17%, 23=22%, 24=27%, &gt;25= Over 30%.</p> <p>MEN Points total: 0 point: &lt;1%. 1-4 points: 1%. 5-6 points: 2%. 7 points: 3%. 8 points: 4%. 9 points: 5%. 10 points: 6%. 11 points: 8%. 12 points: 10%. 13 points: 12%. 14 points: 16%. 15 points: 20%. 16 points: 25%. 17 points or more: Over 30%.</p>	
SCORE	Gender Age Smoking status Lipids Total cholesterol level or the ratio of total cholesterol to HDL cholesterol.	Charts for high and low risk countries (see Appendix).	
PROCAM	Age, LDL cholesterol, HDL cholesterol, triglycerides, smoking, diagnosis of diabetes, family history of MI, and systolic blood pressure.	<p>PROCAM score</p> <p>≤20</p> <p>21 - 28</p> <p>29 - 37</p> <p>38 - 44</p> <p>45 - 53</p> <p>54 - 61</p> <p>≥62</p>	<p>Cardiovascular risk</p> <p>&lt;1%</p> <p>1 - 2%</p> <p>2 - 5%</p> <p>5 - 10%</p> <p>10 - 20%</p> <p>20 - 40%</p> <p>&gt;40%</p>
QRESEARCH, with QRISK1 and QRISK2 scoring tools	Age gender systolic blood pressure ratio of total cholesterol to HDL cholesterol diabetes smoking status family history of MI treated hypertension BMI indicator of social lag in the residential area (for QRISK2 score only: nationality, chronic disease history).	Those with a score of 20% or more are considered to be at high risk of developing CVD.	
SHHEC with a scoring tool ASSIGN	Age gender residence family history diabetes smoking status blood pressure total cholesterol HDL cholesterol.	'High risk' (score 20 or more) indicates a need for further advice or treatment to reduce risk.	

**Table 2. Studies upon cardiovascular risk.**

Study	Participants	Method	Findings
Booth <i>et al.</i> , 2006 [27]	379,003 patients with diabetes and 9,018,082 adults without diabetes	Population-based retrospective cohort study.	The transition to a high-risk category occurred at a younger age for men and women with diabetes than for those without diabetes (mean difference 14.6 years). For the outcome of acute myocardial infarction (AMI), stroke, or death from any cause, diabetic men and women entered the high-risk category at ages 47.9 and 54.3 years respectively.
Huxley <i>et al.</i> , 2006 [28]	447 064	Meta-analysis of 37 prospective cohort studies.	The rate of fatal coronary heart disease was higher in patients with diabetes than in those without (5.4 v 1.6%). The overall summary relative risk for fatal coronary heart disease in patients with diabetes compared with no diabetes was significantly greater among women than it was among men: 3.50, 95% confidence interval 2.70 to 4.53 v 2.06, 1.81 to 2.34.
Polonsky <i>et al.</i> , 2010 (MESA) [29]	6,814 participants from the Multi-Ethnic Study of Atherosclerosis (MESA)	Model 1 used age, gender, tobacco use, systolic blood pressure, antihypertensive medication use, total and high-density lipoprotein cholesterol, and race/ethnicity. Model 2 used these risk factors plus CACS.	Over 5.8 years median follow-up, 209 CHD events occurred, of which 122 were myocardial infarction, death from CHD, or resuscitated cardiac arrest. Model 2 resulted in significant improvements in risk prediction compared to Model 1 (NRI=0.25, 95% confidence interval 0.16-0.34, p<0.001). With Model 1, 69% of the cohort was classified in the highest or lowest risk categories, compared to 77% with Model 2. An additional 23% of those who experienced events were reclassified to high risk, and an additional 13% without events were reclassified to low risk using Model 2.

(Table 2) Contd...

Study	Participants	Method	Findings
Qin <i>et al.</i> , 2013 [31]	130,000 diabetic patients	Meta-analysis of observational prospective studies	The relative risk (RR) comparing smokers with nonsmokers was 1.48[95% confidential interval (CI): 1.34-1.64] for total mortality (27 studies), 1.36(1.22-1.52) for cardiovascular mortality (9 studies), 1.54(1.31-1.82) for CHD (13 studies), 1.44(1.28-1.61) for stroke (9 studies) and 1.52(1.25-1.83) for MI (7 studies). Furthermore, the excess risk was observed among former and current smokers with a greater risk in current smokers.
Pan <i>et al.</i> , 2015 [32]	89 cohort studies	Meta-Analysis and Systematic Review	A total of 89 cohort studies were included. The pooled adjusted relative risk (95% confidence interval) associated with smoking was 1.55 (1.46–1.64) for total mortality (48 studies with 1,132,700 participants and 109,966 deaths), and 1.49 (1.29-1.71) for cardiovascular mortality (13 studies with 37,550 participants and 3163 deaths). The pooled relative risk (95% confidence interval) was 1.44 (1.34-1.54) for total cardiovascular disease (16 studies), 1.51 (1.41–1.62) for coronary heart disease (21 studies), 1.54 (1.41-1.69) for stroke (15 studies), 2.15 (1.62–2.85) for peripheral arterial disease (3 studies), and 1.43 (1.19-1.72) for heart failure (4 studies). In comparison with never smokers, former smokers were at a moderately elevated risk of total mortality (1.19; 1.11–1.28), cardiovascular mortality (1.15; 1.00–1.32), cardiovascular disease (1.09; 1.05–1.13), and coronary heart disease (1.14; 1.00–1.30), but not for stroke (1.04; 0.87–1.23).
Emdin <i>et al.</i> , 2015 [33]	100.354	Meta-analysis	Each 10–mm Hg lower systolic BP was associated with a significantly lower risk of mortality (relative risk [RR], 0.87; 95% CI, 0.78-0.96); absolute risk reduction (ARR) in events per 1000 patient-years (3.16; 95% CI, 0.90-5.22), cardiovascular events (RR, 0.89 [95% CI, 0.83-0.95]; ARR, 3.90 [95% CI, 1.57-6.06]), coronary heart disease (RR, 0.88 [95% CI, 0.80-0.98]; ARR, 1.81 [95% CI, 0.35-3.11]), stroke (RR, 0.73 [95% CI, 0.64-0.83]; ARR, 4.06 [95% CI, 2.53-5.40]), albuminuria (RR, 0.83 [95% CI, 0.79-0.87]; ARR, 9.33 [95% CI, 7.13-11.37]), and retinopathy (RR, 0.87 [95% CI, 0.76-0.99]; ARR, 2.23 [95% CI, 0.15-4.04]).
MRFIT study [35]	342,815 middle aged men in USA	16 year follow up	The 16-year follow-up in MRFIT, showing that the attack rates among Special Intervention participants were substantially reduced over those of controls on Usual Care, suggested to the cognoscenti that the trial had probably worked.
Wackers <i>et al.</i> , 2004 (DIAD) [36]	1,123 patients with type 2 diabetes, aged 50-75 years, with no known or suspected coronary artery disease	Patients randomly assigned to either stress testing and 5-year clinical follow-up or to follow-up only	A total of 113 patients (22%) had silent ischemia, including 83 with regional myocardial perfusion abnormalities and 30 with normal perfusion but other abnormalities ( <i>i.e.</i> , adenosine-induced ST-segment depression, ventricular dilation, or rest ventricular dysfunction). Moderate or large perfusion defects were present in 33 patients.
Maffei <i>et al.</i> , 2011 [37]	147 diabetic (mean age: 65±10 years; male: 89) and 979 nondiabetic patients (mean age: 61±13 years; male: 567) without a history of coronary artery disease (CAD)	CT Coronary Angiography (CTCA)	Diabetics showed a higher number of diseased segments (4.1±4.2 vs. 2.1±3.0; p<0.0001); a higher rate of CCS>400 (p<0.001), obstructive CAD (37% vs. 18% of patients; p<0.0001), and fewer normal coronary arteries (20% vs. 42%; p<0.0001), as compared to nondiabetics. The percentage of patients with obstructive CAD paralleled increasing CCS in both groups. Diabetics with CCS≤10 had a higher prevalence of coronary plaque (39.6% vs. 24.5%, p=0.003) and obstructive CAD (12.5% vs. 3.8%, p=0.01). Among patients with CCS≤10 all diabetics with obstructive CAD had a zero CCS and one patient was asymptomatic.

revascularization was included in the cardiovascular disease, the above age was reduced to 41 and 48 years for men and women, respectively. Furthermore, the transition from low to moderate risk category took place at the age of 35 and 45 years for men and women respectively.

As a result, low risk diabetic patients are regarded as men and women aged less than 35 and 45 years old respectively,

as long as they do not have any other risk factor. Thus, subjects above these ages are more prone to develop cardiovascular events.

A meta-analysis of 37 studies [31] (Table 2), (including 447,064 T2DM patients), showed that the relative risk (RR 95% CI) for fatal CHD among diabetic and non-diabetic subjects was greater in female gender 3.50 (2.0-4.53), than in

male 2.06 (1.81-2.34). Thus, diabetic women are presented with a relative risk for a fatal coronary event 50% higher than men. Hypertension and dyslipidemia are probably the causes of these risk profile. Another important element is that women less often receive the standard therapy against acute coronary syndrome.

In the MESA study [32] (Table 2), another independent factor for fatal or non-fatal CHD was family history. In addition, it seemed more effective than other parameters such as the Ankle Brachial Index, C-reactive protein and Flow Mediated Dilatation. A systematic review demonstrated that the family history of premature CHD could predict CHD, even though conventional risk factors were well controlled. However, traditional risk factor models did not show any predictive improvement with the addition of family history [33] (Table 2).

A meta-analysis of 46 studies, in which 130,000 diabetic patients participated, examined the relative risk (95% CI) of smokers and non-smokers. It was 1.48 (1.34-1.64) for total mortality, 1.36 (1.22-1.52) for CV mortality, 1.54 (1.31-1.82) for CHD events, 1.44 (1.28-1.61) for stroke and 1.52 (1.25-1.83) for AMI [34] (Table 2).

Active use of tobacco is related to greater risk of total mortality and cardiovascular events among diabetic individuals. Smoking cessation is correlated to a reduced risk in both mortality and cardiovascular events in diabetic subjects. A large meta-analysis [35] (Table 2), of 89 cohort studies of patients with diabetes, assessed the impact of active smoking on mortality. Active use of tobacco was related to a 50% increase in mortality and CV events in compared to non-smokers. Furthermore, former smokers had a worse risk profile than “never-smokers”. Thus, the cessation of smoking habit is very beneficial and time-dependent, since its early cessation seems reduce the cardiovascular risks more.

Another meta-analysis [36] (Table 2) including 40 trials, and 100,354 adults with T2DM, examined systolic blood pressure (SBP) lowering levels. They proved that for each 10-mmHg lowering in SBP, the risk for various cardiovascular outcomes lowered significantly: mortality (RR: 0.87; 95% CI 0.78-0.96); cardiovascular events (RR: 0.89 [95% CI 0.83-0.95], coronary heart disease (RR: 0.88 [95% CI 0.80-0.98]) and stroke (RR, 0.73 [95% CI 0.64-0.83]). According to ADA 2016, the goal of a systolic blood pressure of 140 mmHg and a diastolic blood pressure goal is 140 mmHg and 90 mmHg respectively in diabetic patients [37] (Table 2).

Cardiovascular (CVD) mortality information, from the ancillary observational MRFIT study [38] (Table 2), in the pre statin period, demonstrated that between 342,815 middle aged men in USA, (in which only 5163 had diabetes) who were followed up for 16 years, the adjusted risk of CVD death, stratified by cholesterol level, was significantly higher in diabetic patients than in non-diabetic ones. The CVD mortality was greater in patients with diabetes. The excess risk, as a cause of diabetes, varied from 47.9/10,000 persons-years with total cholesterol <180 mg/dl to 103.8/10,000 persons-years for diabetic men in the 260-279 mg/dL total cholesterol range.

The relative risk of CVD mortality for diabetic subjects varied from 2.83 to 4.46 according to the level of chole-

sterol. Thus, cholesterol is an independent risk factor for CVD mortality, which is strengthened by the presence of diabetes.

Wackers *et al.* [39] (Table 2) evaluated diabetics without cardiovascular symptoms, using adenosine Single Photon Emission Computed Tomography (SPECT) imaging and found positive test results for CAD in 22%. 41% of these individuals did not meet usual criteria for further investigation of coronary disease according. A study by Maffei *et al.* [40] (Table 2) demonstrated that both coronary calcium scores and coronary plaque burden were higher in diabetic compared to non diabetic individuals. Furthermore, it was shown that asymptomatic diabetics with high coronary artery calcium scores are more prone to develop ischaemia on stress imaging [40].

#### 4. DISCUSSION

It has been clear that the cardiovascular risk is positively affected from the presence of Type 2 diabetes. The stratification of cardiovascular risk is very important in order to individualize treatment. The lifetime risk is estimated to be higher for the diabetics compared to non diabetics, even though the five year risk seems equal. Factors such as age more than 40 years old, males, clinical and biochemical parameters, such as high blood pressure and high LDL, and renal dysfunction can exert an additive effect to the cardiovascular diseases. Last but not least, other important parameters including, fatty liver disease, obstructive sleep apnea and metabolic syndrome influence the cardiovascular status of the patients negatively and deteriorate their prognosis.

#### CONCLUSION

In conclusion, type 2 diabetes is a complex disease, which affects many people all over the world. It negatively influences the cardiovascular status of the patients, since it causes both macro and micro-vascular complications. Future research should be conducted in order to improve risk stratification tools and achieve a better clinical outcome of diabetic patients. Thus, the individualized treatment, after consideration of risk factors, would reduce the micro and macrovascular complications and ameliorate the prognosis of diabetes mellitus type 2.

#### LIST OF ABBREVIATIONS

CHD	=	Coronary Heart Disease
CAD	=	Coronary Arterial Disease
LDL	=	Low Density Lipoprotein
CVD	=	Cardiovascular Disease
CV	=	Cardiovascular
DM	=	Diabetes Mellitus

#### CONSENT FOR PUBLICATION

Not applicable

#### FUNDING

None.

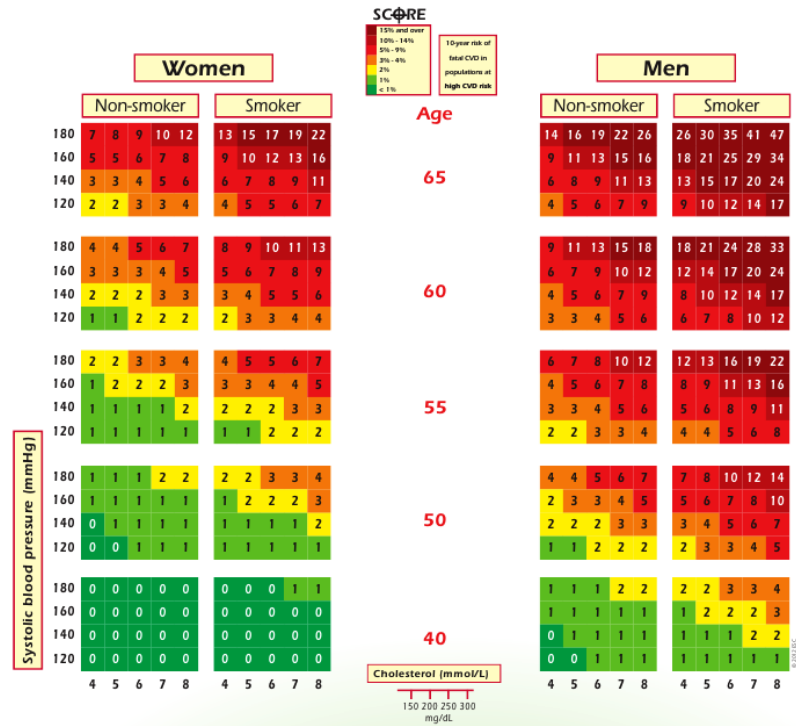
**CONFLICTS OF INTEREST**

The authors declare no conflict of interest, financial or otherwise.

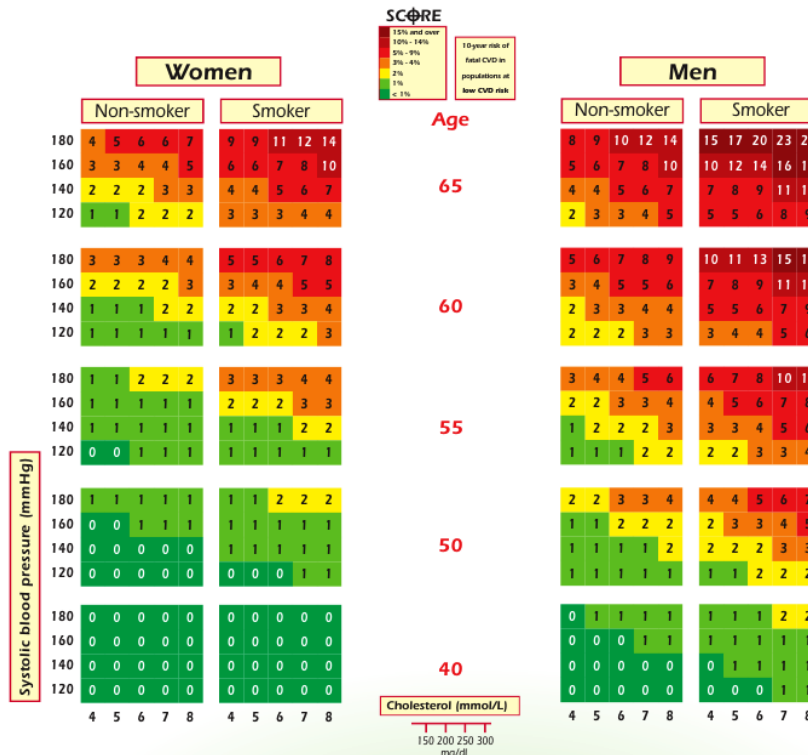
**ACKNOWLEDGEMENTS**

Declared none.

**Appendix**



**Fig. (1).** SCORE European High Risk Chart. (A higher resolution / colour version of this figure is available in the electronic copy of the article).



**Fig. (2).** SCORE European Low Risk Chart. (A higher resolution / colour version of this figure is available in the electronic copy of the article).

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