Risk Stratification for Asymptomatic Coronary Artery Disease in patients with Type II Diabetes Mellitus

Lekha Adik Pathak¹, Ronak V Ruparelia², Krishna K Bhadiadra³

Abstract

There is strong correlation between coronary artery disease (CAD) and Type II Diabetes Mellitus (T2DM). This can be attributed to early atherosclerosis in diabetic subset as compared to non-diabetic population. However, owing to neuropathy and other metabolic milieu, which exists in patients with diabetes mellitus, many patients present late to the health care for atherosclerosis and its complications. CAD being one of the commonest complication of atherosclerosis process, it comprises a huge number of patients suffering from T2DM. And many such patients are asymptomatic for longer period of time. Here in this review we will discuss about importance of various risk factors and their roles in detecting subclinical atherosclerosis and silent ischemia in asymptomatic patients with diabetes. We will also discuss about various imaging modalities and their role in asymptomatic CAD patients with T2DM.

Introduction

Diabetes mellitus (DM) is a chronic metabolic disorder defined by presence of hyperglycemia and/or insulin resistance. DM can be classified as type 1 diabetes mellitus or type 2 diabetes mellitus based on baseline pathology. The 2016 Global World Health Organization (WHO) report of Diabetes estimated a worldwide adult diabetes prevalence in 422 millions of individuals in 2014, rising from 4.7% in 1980 to 8.5% in 2014.¹ As per International Diabetes Federation, rates of diabetes are increasing worldwide. And the estimated number of people living with diabetes will reach the number of 642 million by 2040.²

Diabetes Mellitus and Coronary Artery Disease

Multiple risk factors are found to be associated with DM that leads to development of coronary artery disease (CAD). These risk factors are dyslipidemia, hyperglycemia, hypertension, kidney failure and overweight. Owing to these risk factors, diabetics are prone to have various vascular complications ranging from microvascular (renal, retinal and neuropathic) to macrovascular (coronary artery and cerebral arteries).³ Apart from classical risk factors for CAD, several other factors like increased oxidative stress, increased coagulability, low grade inflammation, endothelial dysfunction and autonomic neuropathy are often present in patients with DM and contribute directly to development of CAD.

The risk of CAD increases two to four fold in diabetics as compared to non-diabetics.⁴ Diabetics have accelerated atherothrombosis as well as early onset of atherosclerosis.⁵,⁶ The atherosclerosis related to DM is more diffuse, more extensive, more complex and rapidly progressive as compared to non-diabetics. As a result, coronary angiogram in a diabetic is more often complex multivessel CAD.

Pathophysiology

Long standing hyperglycemia induces inflammation in the vessel wall, promoting atherosclerosis and abnormal vascular findings (e.g. earlier onset, higher degree, and more disseminated and aggressive) are much more common in diabetics compared with individuals without diabetes.⁷ Impaired fibrinolytic system balance and abnormalities of platelet structure and function results in a persistent prothrombotic milieu.⁸ Various adverse effects induced by hyperglycemia are as follows:

A. Metabolic factors: Endothelial dysfunction, vascular effects of advanced glycation end products, adverse effects of circulating free fatty acids and increased systemic inflammation.

B. Vascular anatomic characters: More frequent diffuse disease, higher prevalence of extensive CAD, left main disease and multivessel disease. The narrow calibre vessels are associated with impaired collateral development.

C. Adverse prothrombotic milieu and high atherosclerotic burden: Diabetics have a higher atherosclerotic burden and plaques, which are high risk and vulnerable to rupture.⁹ Proteofibrinolytic system and platelet biology are also unfavourably altered in diabetes.

The degree of pathophysiological changes varies from person to person amongst diabetics. Hence the clinical presentation varies from asymptomatic to stable angina and acute coronary syndrome (ACS) which includes unstable angina, STEMI and non-STEMI.¹⁰

Diabetes Mellitus: A CAD Risk Equivalent ???

Diabetics have 2 to 4 times increased risk of cardiovascular morbidity and mortality¹¹ than non-diabetics. The NCEP (National Cholesterol Education Program) as well as guidelines from Europe considered T2DM as CAD equivalent, and considered it as the highest risk category.¹²,¹³ This recommendation was based upon

¹Director of Dept. of Cardiology, Nanavati Hospital, Mumbai, Maharashtra; ²Interventional Cardiologist, Bankers Heart Institute, Vadodara, Gujarat; ³DY Patil Medical College, Navi Mumbai, Maharashtra; ²Corresponding Author

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43% lower than individuals without T2DM patients without prior CAD was much lower among T2DM without CAD than in non-diabetic patients with prior CAD (HR 1.70 vs. 2.80). In another meta-analysis, cardiovascular risk was evaluated through coronary artery calcium score (CAC) at baseline. The study revealed a 28.5% prevalence of diabetic patients with zero CAC scores, indicating a similar 5-year survival rate as in patients without diabetes.

So a significant part of patients amongst diabetics exists in lower CAD risk category, especially men less than 35 years of age, women less than 45 years of age and patients with diabetes duration of less than 10 years without other risk factors. While in the presence of traditional risk factors or evidence of subclinical coronary disease (e.g. high coronary calcium score), the coronary risk is much increased and patients may be classified at a higher risk category.

This is in contrast to older studies considering all diabetics as a “CAD risk equivalent”. Currently, 2013 ACC/AHA guidelines, 2016 ADA standard of diabetes care and the 2016 European Society of Cardiology (ESC) no longer consider diabetes a coronary risk equivalent. The ACC/AHA guidelines recommends stratification for patients with diabetes into 2 risk categories. Diabetics younger than 40 years with shorter duration of diabetes are defined as lower risk category. This categorization allows recognition of those who might benefit more from intensive cardiovascular interventions, intensive statin or aspirin preventive, while avoiding overtreatment in lower risk cases. It also allow the clinician to decide whether to intensify risk reduction actions through specific newer drugs for glucose control such as SGLT-2 inhibitors or GLP-1 agonists, which recently have shown additional cardiovascular protector effect.

### How to identify Asymptomatic Diabetic patients at high risk for CAD

Silent myocardial ischemia is defined as the presence of objective evidence of myocardial ischemia in the absence of chest discomfort or another anginal equivalent symptom. The goal of risk stratification is to protect the patient from subsequent serious coronary events. The available screening tests can be divided into invasive (coronary angiography) and non-invasive tests. Non-invasive tests are preferred over invasive tests owing to its simplicity and cost effectiveness. Various non-invasive tests are described in Table 1.

**Table 1: Screening methods for detecting asymptomatic coronary artery disease in patients with diabetes**

<table>
<thead>
<tr>
<th>Screening methods</th>
<th>Detection of prevalent CHD</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resting electrocardiogram (ECG)</td>
<td>Functional tests</td>
<td>Widely available, very low cost</td>
</tr>
<tr>
<td>Exercise ECG</td>
<td>Low sensitivity and specificity</td>
<td>Relatively low cost, widely available. Many patients unable to exercise. Some have uninterpretable baseline ECGs</td>
</tr>
<tr>
<td>Radionuclide single proton emission computed tomography (SPECT) myocardial perfusion imaging (MPI)</td>
<td>Good sensitivity (80-90%) and specificity (75-90%)</td>
<td>Moderate to high cost</td>
</tr>
<tr>
<td>Myocardial perfusion imaging (MPI) with positron emission tomography (PET)</td>
<td>High sensitivity for myocardial viability studies, Acute global and regional measurements of myocardial perfusion, blood flow, and function at stress and rest in a single study</td>
<td>Better image quality because of higher spatial resolution, less scattered, and fewer attenuation artifacts.</td>
</tr>
<tr>
<td>Stress echocardiography</td>
<td>The sensitivity and specificity are satisfactory (80-85%)</td>
<td>Costly, not universally available</td>
</tr>
<tr>
<td>1. Exercise stress echo</td>
<td>Able to assess LV function and valvular abnormalities</td>
<td>Low cost, widely available</td>
</tr>
<tr>
<td>2. Pharmacologic stress echo (dobutamine, adenosine, and dipyridamole)</td>
<td></td>
<td>Operator dependent</td>
</tr>
<tr>
<td>Coronary artery calcium score (CAC)</td>
<td>High sensitivity for myocardial calcium score, the coronary calcium score (CAC) at baseline. The study revealed a 28.5% prevalence of diabetic patients with zero CAC scores, indicating a similar 5-year survival rate as in patients without diabetes.</td>
<td></td>
</tr>
<tr>
<td>Multidetector-row computed tomography (MDCT) angiography</td>
<td>High sensitivity (85-90%) and specificity (93-98%)</td>
<td>Good sensitivity, specificity, and negative predictive value. High radiation doses</td>
</tr>
<tr>
<td>Magnetic resonance imaging (MRI)</td>
<td>High sensitivity (83-90%) and specificity (72-84%)</td>
<td>Able to assess myocardial structure and function and characterize ischemic, inflammatory and various types of cardiomyopathies</td>
</tr>
<tr>
<td>Not adequately investigated</td>
<td></td>
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</tr>
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</table>

The observation that patients with “T2DM without a prior MI (Myocardial Infarction)” were at the same risk for MI (20 and 19 percent, respectively) and coronary mortality (15 versus 16 percent) as compared to patients “without DM with prior MI”.14

Recent studies indicate that CAD risk in T2DM is not universally similar amongst various diabetic subsets. A meta-analysis of 13 epidemiological studies observed that, the CAD risk in T2DM patients without prior CAD was 43% lower than individuals without diabetes with a prior MI.15 In a large population-based cohort, the CAD risk was much lower among T2DM without CAD than in non-diabetic patients with...
no significant difference in the primary endpoint (cardiac death or nonfatal MI) between the screening and no-screening groups. Similarly, DYNAMIT (Do You Need to Assess Myocardial Ischemia in Type-2 diabetes), a smaller study of 631 asymptomatic patients with T2DM and at least two other CAD risk factors randomized patients to either screening with rMPI with symptom-limited bicycle exercise or dipyridamole SPECT) or no screening. The prevalence of silent myocardial ischaemia was found to be 21.5%, similar to the DIAD study. After a mean follow-up of 3.5 years, there was no significant difference in the composite primary endpoint (death from all causes, nonfatal MI, nonfatal stroke, or heart failure requiring emergency intervention) between the screening and the non-screening group.

Sensitivity and Specificity of a test are the core requirements while considering any test for risk stratification. In addition, whether the information gained from the study lead to additional testing and / or a meaningful change in the patient’s therapy is also of utmost importance.

**Various approaches for Risk stratification of CAD in Diabetics**

2013 ACC / AHA Approach: ACC / AHA proposed an approach based on the global risk estimation. The panel considered diabetics aged between 40 and 75 years, who have a baseline LDL between 70 and 189 mg/dL should be stratified into a higher or a lower risk category to receive either high or moderate intensity treatment with statin. The ACC/AHA calculator was developed to estimate the 10-year risk for the first atherosclerotic cardiovascular disease (ASCVD) event. For patients with diabetes, the guidelines indicate intensive statin treatment for patients with an ASCVD risk above 7.5% in 10 years. If the risk is below this cut-off, moderate-intensity statin treatment is indicated. In patients aged less than 40 years, or above 75 years, the evidence of benefit is less clear.

2016 ADA Approach: It recommends risk stratification including 3 variables: age, the existence of previous cardiovascular events and the presence or not of risk factors. ADA risk factors include: LDL-c above 100 mg/dL, high blood pressure, smoking, overweight/obesity and family history of premature ASCVD. All patients with definite ASCVD events should receive high-intensity statin therapy, independently of age. In patients between 40 and 75 years without ASCVD events, but in the presence of cardiovascular risk factors, it is recommended high-intensity statin therapy. In older or younger patients, if in the presence of risk factors, either moderate or high-intensity statin therapy can be indicated. In younger patients with- out ASCVD or risk factors, ADA considers that lifestyle therapy alone may be more appropriate.

Here we describe a systematic approach to asymptomatic coronary artery disease in patients with T2DM.

**A. Detailed clinical history / Risk Factor Assessment**

1. **Age:** It is the strongest non-modifiable risk factor for CAD. A large population based retrospective cohort study defined the relation between age and various risk categories for CAD in diabetics. Transition from low to moderate risk category occurred at 35 and 45 years while the transition to high risk category occurred at 48 and 54 years for men and women respectively.

2. **Gender:** In general population, the incidence of new MI is higher in men than in women. While in patients with diabetes, the men to women ratio is much narrow. And when considering the mortality rate from coronary diseases, women with diabetes are at a higher risk than men. A meta-analysis observed that the relative risk for fatal CAD was greater among women in patients with and without diabetes. This was probably due to a less favourable cardiovascular risk profile in women linked to hypertension and hyperlipidemia. The presumed reduced likelihood of women receiving the standard treatment for acute coronary syndrome and cardiovascular prevention is also important.

3. **Family History:** The Women’s health study studied postmenopausal women with diabetes without CAD. The study observed that the incidence of CAD in those with at least 1 first degree relative with CAD was 50% higher while it was 79% higher in those with 2 or more affected first degree relatives. In the MESA study positive family history considered an independent risk factor and performed better than ankle brachial index, c reactive protein and flow mediated dilation. The ACC/AHA 2013 guidelines recommend to consider family history of premature CAD as a major risk factor defined as male <55 years and female <65 years in any first degree relative.

4. **Smoking:** It is one of the most important reversible risk factor for CAD. Active smoking is associated with the highest risk of total mortality and cardiovascular events, while smoking cessation reduces both mortality and cardiovascular events in diabetics. The incidence of acute MI increases six-fold in women and three-fold in men who smoke at least 20 cigarettes per day. Active smoking was associated with more than 50% increase in mortality and CV events.

5. **Hypertension:** Hypertension is a major risk factor for atherosclerotic cardiovascular disease (ASCVD) and microvascular complications. A recent meta-analysis observed that for each 10-mmHg lowering in SBP there was a significant lowering in risk for mortality, cardiovascular events, coronary artery disease and stroke.

6. **Long duration and early onset of diabetes:** Patients with diabetes duration longer than 10 years are considered at increased risk. Diagnosis of diabetes at an early age is an additional risk independently of diabetes duration. In a large cross-sectional survey, using data from the China National HbA1c Surveillance System (CNHSS), observed higher risk in the group with earlier onset of T2DM.

7. **Obstructive sleep apnea (OSA):** OSA is associated with an increased incidence of fatal MI. Diabetics are at high risk of OSA and should be questioned for symptoms, which may warrant further investigation and treatment.

8. **History of other atherosclerotic vascular diseases:** Clinical history (transient ischemic attack, mesenteric ischemia, or claudication) and physical examination (for bruits and peripheral pulses) is important to determine the presence of vascular diseases. Atherosclerotic diseases involving lower extremity, cerebral, renal or mesenteric arteries identifies a patient with diabetes who is at increased risk for CAD. A diminished ankle-brachial index is a sensitive indicator.
of increased risk for future CVD events. In patients with claudication or asymptomatic peripheral arterial disease, 90% of deaths are attributable to CAD.

B. Laboratory work up

1. Blood lipids: Dyslipidemia is associated with cardiovascular morbidity and mortality. MERFIT study, in pre statin era showed that the absolute adjusted risk of CAD death, stratified by cholesterol level was several times higher in diabetics then in non-diabetics. The Cholesterol Treatment Trialists’ (CTT) Collaborators meta-analysis observed that reducing LDL-c by 1 mmol/l with a statin reduces the CAD relative risk, a linear phenomenon that is likely to occur similarly at any level of baseline LDL-c, at least through a limit down to LDL-c 50 mg/dL. Thus, cholesterol is strong and independent risk factor for CAD mortality, which is potentiated by diabetes.

2. Low glomerular filtration rate and microaluminuria: Both independently increase the cardiovascular risk in healthy as well as T2DM patients. The HOPE study observed that, after 4.5 years of follow up, the relative risk for the primary end point (MI, stroke or CV death) in T2DM was 1.97 as compared to 1.61 in non-DM. For every 0.4 mg/mmol of increase in albumin-to-creatinine ratio, the adjusted hazard ratio of major CV events increased by 5.9%.

3. Severe hypoglycaemia: Severe hypoglycaemia (defined as hypoglycemic episode requiring assistance) increases approximately twice the risk of cardiovascular disease in T2DM. In the Hong Kong Diabetes Registry study, patients with severe hypoglycaemia showed increased incidence of mortality compared with those without SH, respectively: (32.8 vs. 11.2%). A possible mechanism is the acute induction of pro-inflammatory and pro-atherosclerotic mediators. In an experiment hypoglycemia in healthy T1DM patients acutely increased circulating levels of PAI-1, VEGF, vascular adhesion molecules (VCAM, ICAM, E-selectin), IL-6, and markers of platelet activation (P-selectin).

4. High sensitivity CRP: Ridkar et al observed that hs-CRP was strongly related to the incidence of cardiovascular events, even after adjustments for age, smoking status, diabetes, categorical levels of blood pressure and the use of hormone therapy. Although the data regarding CRP in diabetic patients is controversial, a retrospective study, Diabetes Heart Study indicated that CRP may predict mortality in T2DM, but at a higher value than AHA CRP threshold of >3mg/l.

Based on above clinical parameters and laboratory work up, patient may be subjected to various imaging or non-invasive testing mentioned below.

C. Role of Imaging / non-invasive testing

1. Electrocardiogram: An abnormal ECG in diabetic patient usually trigger evaluation for underlying CAD. The abnormal ECG finding may ranges from abnormal Q-waves, deep T-wave inversions or bundle branch block to silent myocardial infarction. Testing in these patients should probably not be considered “screening,” but rather evaluation of an objective abnormality for clinical reasons. However, nonspecific ST-T wave changes also are a strong predictor of inducible ischemia in asymptomatic diabetic patients.

2. Echocardiography: The prevalence of asymptomatic LV dysfunction (LVEF < 50%) is 6% in men and 0.8% in women in general population and is twice as common in diabetics. Timely intervention to rule out ischemic etiology can reduce mortality to great extent.

Pharmacological stress echocardiography is another modality useful for risk stratification in asymptomatic diabetics with good diagnostic accuracy. Pharmacological agents being used for stress ECHO are either coronary vasodilators (dipyridamole or adenosine) or positive inotropic agents (dobutamine). The former increases differences in coronary flow reserve between normal and diseased vessel, whereas the latter mimics the effect of exercise on myocardial contraction. A positive dobutamine or dipyridamole stress echocardiography is predictive of mortality, in both diabetic and nondiabetic individuals. However, pharmacological stress ECHO loses 2 important sets of information, namely the exercise capacity of the patient and the precise workload threshold for the development of symptoms, such as angina. Bigi et al evaluated the prognostic value of pharmacological stress ECHO in diabetic patients suspected of CAD and demonstrated that the post stress wall motion score was the sole independent prognostic indicator.

More recently exercise ECHO is being used for the evaluation of asymptomatic CAD. During exercise ECHO patient undergoes ECHO evaluation pre and immediate post exercise.

3. Exercise Stress Testing: Stress testing provides physiological evidence of clinically significant coronary artery disease. It gives indirect evidence of reduced coronary flow reserve. The yield of stress testing in asymptomatic T2DM patients can be improved by proper patient selection based on pre-test clinical risk factors mentioned above.

There are many drawbacks of exercise stress testing like lack of exercise capacity secondary to underlying peripheral vascular disease (PVD), pulmonary, neurological, or orthopedic conditions. Other sets of patients are those who fail to achieve target heart rate on trade mill. Still others may have pre-existing abnormalities in the resting ECG, like bundle branch blocks, that obscure accurate reporting. Many of these concerns apply to the diabetic patient, who is inherently at whose exercise potential is often limited by obesity, deconditioning, PVD, or sensory or motor neuropathy.

4. Nuclear Imaging: Stress testing combined with radionuclide myocardial perfusion imaging is more sensitive and specific than exercise stress testing alone. In DIAD study the prevalence of perfusion defect or LV function abnormality was found to be 22% amongst diabetics. Stress nuclear test uses radionucleotides such as thallium and Tc-99m-sestamibi to perform myocardial perfusion imaging.

MPI SPECT has the ability to provide operator independent measurement of myocardial perfusion and function in 3 dimensions. The visualization of regions of under perfused myocardium not only increases diagnostic accuracy, it also provides more precise information regarding LV shape and function. It also allows more precise assessment of the amount and specific location of myocardium at risk as well as the area of scar. Patient’s symptoms and the
extent of ischaemia, scar and decrease of ejection fraction will guide the treatment strategy. If more than 10% of the myocardium is ischaemic, it is very likely that patients will benefit from revascularisation.

One study done by two investigators from well-known laboratories in nuclear cardiology suggested that the stress ECHO and stress nuclear imaging have equal sensitivity but the stress ECHO is slightly more specific. A recent meta-analysis almost confirmed this findings, but the reanalysis suggested no major differences.

5. Positron Emission tomography Scan: The non-invasive assessment of coronary flow reserve (CFR = stress divided by rest myocardial blood flow) using PET is a powerful tool that integrates the effects of focal stenosis, diffuse disease, and coronary microvascular function and has been shown that impaired CFR (below the median) was associated with an adjusted 3.2- and 4.9- fold increase in the rate of cardiac death for diabetic and nondiabetic persons, respectively (P = 0.0004).

6. Coronary artery calcium score (Figure 1): Calcium is a common component of atherosclerotic plaques and is not present in the normal, “healthy” vessel wall. Atherosclerotic plaque proceeds through progressive stages where instability and rupture can be followed by calcification, providing stability to an unstable lesion. Agatston score is the most widely used calcium score. Simplified calcium scores of 0, 1 to 100, 101 to 400, and greater than 400 represent no, mild, moderate, and severe coronary calcification, respectively. Calcium score provides superior discrimination and risk stratification compared with the aforementioned other risk markers.

In diabetics, higher extent of coronary artery calcium was found compared with non-diabetic patients, with a great heterogeneity. The MESA Study observed higher event rate with high CAC score in patients with T2DM. In one series, of 155 asymptomatic diabetics, 72% had positive CAC scores and 48% had a CAC score >102. In PREDICT STUDY, CAC was a highly significant independent predictor of events (p < 0.001). A doubling in CAC was associated with a 32% increase in risk of events. There was a progressive increase in hazard ratio according with the CAC score level, comparing to CAC <10. In a large study the increase in mortality was proportional to increases in CAC.

Negative results were observed in a subsequent large study examining the benefit of screening for CAD in diabetics without prior CAD (FACTOR-64 trial). FACTOR-64 trial observed that after a mean follow-up of 4 years, there was no significant difference in the primary endpoint (composite of all-cause mortality, nonfatal MI, or unstable angina) following screening with CCTA.

The long-term predictive value of CAC score for all-cause mortality in asymptomatic diabetics was recently addressed in a 15-year cohort study. The cumulative mortality rate over 15 years according to baseline CAC score was greater in T2DM than in non-diabetic individuals. Interestingly, a CAC zero conferred a similar mortality rate between T2DM and non-DM patients for the first 5 years. After 5 years, however, the risk of mortality increased significantly for diabetic patients even in the presence of a baseline CAC = 0.

Zero calcium is also consistent with the absence of noncalcified plaques and relevant coronary stenosis in more than 87% and 99% of patients, respectively. Absent coronary calcium therefore has an excellent negative predictive value for CAD and is a very important cornerstone of CAD risk stratification, either as a standalone result or in combination with functional testing.

7. CT Coronary Angiography: CT angiography is highly accurate for diagnosing CAD and predicting patient outcome based on the presence, extent and severity of CAD. In the SCOT HEART trial, CTA was significantly better than exercise treadmill testing. Also patients undergoing CTA had better outcomes than those assessed by ETT alone.

Although CTA has a potential advantage for detecting the entire spectrum of atherosclerotic plaque in asymptomatic diabetic patients, there are no data to suggest that it would perform better than a much simpler CAC. This is based on numerous studies in low-to-intermediate-risk patients with suspected CAD, wherein < 1.0% of patients had significant stenosis on CTA if the CACS was 0. At this juncture, routine CTA is not considered an appropriate test in asymptomatic patients.

8. Carotid intima-media thickness and carotid plaque: Carotid wall intima-media thickness (CIMT) is the distance from the lumen-intima interface to the media-adventitia interface of the artery wall, determined by a carotid artery ultrasound. It is a surrogate marker for new acute myocardial infarction and stroke in individuals above 65 years old, when maximal IMT is above 1.1 mm, both in common and in internal carotid arteries. Interestingly, CIMT seems to perform better in obese than in lean T2DM patients.

A carotid plaque, defined as the thickness of the intima, is a simple and highly reproducible method to quantify atherosclerosis. In asymptomatic patients with T2DM, the sum of the maximum plaque thickness above 1.1 mm from both sides of the carotid wall, increases the predictive value for detecting coronary stenosis greater than 50% (obstructive CAD).

Although promising, CIMT and carotid plaque detection are currently not recommended for routine use for risk assessment.

9. Non-alcoholic fatty liver disease: Non-alcoholic fatty liver disease is an independent predictor of CAD among patients with T2DM. The Valpolicella Heart Diabetes Study showed independent association of NAFLD with new CAD event after adjusting multiple confounding variables.

D. Assessment through risk score calculators:

Currently there are at least 45 risk calculators which are exclusive for patients with diabetes. Risk calculators enables the clinician to estimate an individual patient’s risk of developing CAD.

The UKPDS risk engine was originally designed by the Oxford University and may be the most popular global risk calculator for patients with diabetes. Components include age, duration of diabetes, gender, systolic blood pressure, total cholesterol, HDL cholesterol, smoking status, ethnicity and atrial fibrillation.

Conclusion

Asymptomatic CAD is common in
patients with T2DM. T2DM increases risk of CAD by 2 to 4 fold, but cannot be considered a risk equivalent due to the high heterogeneity. Risk stratification is necessary to individualize treatment. Almost 30% of diabetics have a 5-year CHD risk similar to general population, however, lifetime risk seems to be invariably high in almost all diabetics. Age above 40 years, diabetes diagnosis of more than 10 years, the presence of a first degree family history with premature CHD, male gender, high blood pressure, LDL above 100 mg/dl, low renal function, microalbuminuria, presence of non-alcoholic fatty liver disease, obstructive sleep apnea and specially chronic hyperglycemia and severe hypoglycemia are conditions that increase cardiovascular risk. Coronary artery calcium score, hs-CRP and CIMT can be useful tools.

For now, risk stratification in the patient with diabetes should include the traditional risk factors with or without risk calculators. Emerging risk factors are still awaiting confirmatory studies. For being useful in clinical practice a risk factor must be strongly associated with the outcome. They must have a favourable cost-effectiveness profile.

Although the yield of MPI in asymptomatic diabetics is excellent, it is unlikely to be cost-effective if used routinely to screen all asymptomatic diabetic patients. At present, evaluation of the calcium score may be beneficial in asymptomatic CAD patients with T2DM. Coronary CT angiography is also an excellent tool to exclude CAD, having a negative predictive value of 97 – 99%.

The current guidelines leave a lot of room as to which test to choose for non-invasive CAD risk stratification. The selection of the particular modality is, in part, led by the pre-test probability of CAD and local availability, expertise and preference. However, whenever possible, an imaging-based test should be possible.

A novel strategy provides excellent discrimination of a low-risk population (no CAC), a moderate-risk population with evidence of non-obstructive CAD (with CAC and normal MPI), which warrants aggressive risk factor management, and a high-risk population with obstructive CAD (with moderate-severe CAC and abnormal MPI), which may benefit from invasive angiography and revascularization. Initial studies utilizing this strategy have revealed promising results, but the clinical and cost-effectiveness of such approaches need to be evaluated in future prospective trials.

**Our Approach**

3 basic questions which we need to answer

1. Which patients with diabetes are at increased risk for adverse cardiovascular outcomes?
   - The primary aim of risk stratification is to identify patients with high cardiac risk whose outcome might be improved with aggressive risk factor modification, medical management or revascularization of coronaries (Figure 2).
   - In day to day practice, risk stratification starts with the assessment of the pre-test probability, means the possibility of that person having CAD. Calculation of pre-test probability in asymptomatic patient is generally based on patient’s age, gender, family history, history of habits, evidence of other atherosclerotic vascular disease, renal disease, abnormal resting ECG or ECHO. Based on this patient is classified into low, intermediate or high pre-test probability of CAD. The numerical value of risk can be derived by use of various risk calculators.
     - However, clinical factors that confer risk for adverse cardiac events does not always predict which patient will have abnormal screening test. And more so, negative screening test does not rule out possibility of cardiac events.
     - Patients with a low probability of disease (<15%) does not require to undergo any further testing. However, in specific cases patients may benefit from further risk factor modification. Patients with an intermediate probability (15–85%) of CAD should undergo further non-invasive testing (e.g. Exercise Stress Test, Pharmacological / Exercise Stress ECHO or CT Calcium Scoring). In patients with a high probability of disease (>85%), non-invasive testing does not add much with respect to CAD diagnosis but may help to provide a better idea of the individual patient’s risk. Patients with a high pre-test probability of CAD therefore may directly undergo invasive coronary angiography, also with the possibility of treatment in the same procedure.

2. What are the implications of an
early diagnosis of coronary ischemia or atherosclerosis?

- Diabetics are at high risk for CAD, and aggressive treatment of risk factors is recommended in T2DM with asymptomatic CAD. The role of coronary imaging / non-invasive testing like MPI here is not to document the presence of coronary atherosclerosis but to identify those with more extensive disease. Diabetics with more extensive disease gets benefited by further testing and aggressive management.

- The available data suggests that patients with ischemia involving 10% or more of the left ventricle have a better outcome after myocardial revascularization compared with the results of medical therapy alone. Retrospective studies have shown similar results in patients with diabetes.

3. What tests, or sequence of tests, should be considered? With what frequencies should testing be done?

- At this point of time, the best non-invasive test for diabetic patients being evaluated for CAD remains unclear. Until further information is available, the choice of test should be based on local availability and expertise, cost considerations, as well as certain clinical concerns, such as the precise purpose for the test and unique patient-specific characteristics.