Chapter (I)

Noninvasive assessment for stable coronary artery disease

Diagnosis and assessment of stable coronary artery disease:

The diagnosis and assessment of SCAD involves clinical evaluation and specific cardiac investigations such as stress testing or coronary imaging. These investigations may be used to confirm the diagnosis of ischemia in patients with suspected SCAD to identify or exclude associated conditions or precipitating factors, assist in stratifying risk associated with the disease and to evaluate the efficacy of treatment. In practice, diagnostic and prognostic assessments are conducted simultaneously and many of the investigations used for diagnosis also offer prognostic information (figure 1) (Montalescot et al., 2013).

Before any testing, we must assess the general health, comorbidities and quality of life of the patient. Ambulatory ECG monitoring if there is clinical suspicion that symptoms may be associated with a paroxysmal arrhythmia. The initial ECG is the most informative tool for early risk stratification as it provides important diagnostic and prognostic information and is pivotal in the triage process (Lee et al., 1985).

Furthermore, adverse prognosis has been related directly to the degree of ST-segment depression. Patients with minor, nonspecific changes and absence of high-risk clinical features are at low risk, but marked and symmetrical T-wave inversion (≥ 0.20 mV) is consistent with ACS (Ruddox et al., 2012).
Three major steps used for decision-making:

Figure (1): Non-invasive testing in patients with suspected SCAD and an intermediate pre-test probability (PTP) (after 2012 ACC/AHA Guidelines SIHD) Consider age of patient versus radiation exposure. In patients unable to exercise use echo or SPECT/PET with pharmacologic stress instead. CMR is only performed using pharmacologic stress. Patient characteristics should make a fully diagnostic coronary CTA scan highly probable, consider result to be unclear in patients with severe diffuse or focal calcification (fihn et al., 2012).
Step 1: Determination of Pretest Probability (PTP):

The process begins with a clinical assessment of the probability that SCAD is present in a particular patient. Although many non-invasive cardiac investigations can be used to support the diagnosis of SCAD, the optimal use of resources is only achieved if pre-test probabilities based on simple clinical findings are first taken into consideration (Huebner et al., 2010).

In patients presenting with chest pain suggestive of stable angina pectoris, numerous diagnostic strategies can be used. The reference standard for diagnosing coronary artery disease (CAD) is conventional coronary angiography (CCA). However, CCA is expensive and involves a small risk of complications and death. Therefore, non-invasive testing is recommended to select patients who will benefit from coronary angiography (Hendel et al., 2006).

The clinical value of non-invasive diagnostic tests depends on the test sensitivity, the specificity, the potential gain from making the correct diagnosis, the potential harm caused by false-positive test results, and the pre-test probability of the suspected disease (Genders et al., 2011).

In choosing the appropriate test for a particular patient with chest pain suggestive of CAD, the pre-test probability of CAD is crucial. Also Diamond and Forrester demonstrated the importance of the pre-test probability on interpreting test results in their classic paper in 1979, using estimates from autopsy and cross-sectional studies, they developed a simple but elegant model that considers age, sex, and type of chest pain to estimate the probability of obstructive CAD in patients between 30 and 70 years old (Diamond and Forrester, 1979). In spite of its limitations, the Diamond – Forrester model is still used in current guidelines (Hendel et al., 2006).
Although other cardiovascular risk factors such as diabetes, smoking and dyslipidemia have been included in, e.g. the Duke Clinical Score the predictive effects of other risk factors in diagnostic models are often small compared with the predictive effects of age, sex, and type of chest pain. Furthermore, complicated models are less likely to be used by physicians in clinical practice especially since non-invasive diagnostic tests are commonly ordered immediately at the first visit. The Diamond–Forrester model allows the immediate calculation of an estimate of the patients’ pre-test probability of CAD, without the need to wait for laboratory findings or exercise test results (Link and Tanner, 2001).

Interpretation of non-invasive cardiac tests requires a Bayesian approach to diagnosis. This approach uses clinicians’ pre-test estimates [termed pre-test probability (PTP)] of disease along with the results of diagnostic tests to generate individualized post-test disease probabilities for a given patient. The PTP is influenced by the prevalence of the disease in the population studied, as well as clinical features (including the presence of CV risk factors) of an individual. Major determinants of PTP are age, gender and the nature of symptoms (table 1) (Perk et al., 2012).

Table (1): Clinical pre-test probabilities in patients with stable chest pain symptoms

<table>
<thead>
<tr>
<th>Age</th>
<th>Typical angina</th>
<th>Atypical angina</th>
<th>Non-anginal pain</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men</td>
<td>Women</td>
<td>Men</td>
</tr>
<tr>
<td>30–39</td>
<td>59</td>
<td>28</td>
<td>29</td>
</tr>
<tr>
<td>40–49</td>
<td>69</td>
<td>37</td>
<td>38</td>
</tr>
<tr>
<td>50–59</td>
<td>77</td>
<td>47</td>
<td>49</td>
</tr>
<tr>
<td>60–69</td>
<td>84</td>
<td>58</td>
<td>59</td>
</tr>
<tr>
<td>70–79</td>
<td>89</td>
<td>68</td>
<td>69</td>
</tr>
<tr>
<td>≥80</td>
<td>93</td>
<td>76</td>
<td>78</td>
</tr>
</tbody>
</table>

† Groups in white boxes have a PTP, 15% and hence can be managed without further testing.
† Groups in blue boxes have a PTP of 15–65%. They could have an exercise ECG if feasible as the initial test. However, if local expertise and availability permit a non-invasive imaging based test for ischemia this would be preferable given the superior diagnostic capabilities of such tests. In young patients radiation issues should be considered.
† Groups in light red boxes have PTPs between 66–85% and hence should have a non-invasive imaging functional test for making a diagnosis of SCAD.
† In groups in dark red boxes the PTP is .85% and one can assume that SCAD is present. They need risk stratification only (Perk et al., 2012).
PTP testing may do harm if the number of false test results is higher than the number of correct test results. Non-invasive, imaging-based diagnostic methods for CAD have typical sensitivities and specificities of approximately 85%. Hence, 15% of all diagnostic results will be false and, as a consequence, performing no test at all will provide fewer incorrect diagnoses in patients with a PTP below 15% (assuming all patients to be healthy) or a PTP above 85% (assuming all patients to be diseased). In these situations, testing should only be done for compelling reasons. This is the reason why guidelines for SCAD recommend no testing in patients with a low PTP <15% and a high PTP >85%. In such patients, it is safe to assume that they have no obstructive CAD or obstructive CAD (Genders et al., 2012).

Sensitivity and specificity are often used to describe the accuracy of a given diagnostic method, but they incompletely describe how a test performs in the clinical setting. First, some diagnostic methods may perform better in some patients than in others such as coronary computed tomography angiography (CTA), which is sensitive to heart rate, bodyweight and the presence of calcification (Montalescot et al., 2013).

Second, although sensitivity and specificity are mathematically independent from the PTP, in clinical practice many tests perform better in low-risk populations; in the example used above, coronary CTA will have higher accuracy values when low-likelihood populations, which are younger and have less coronary calcium, are subjected to the examination. Because of the interdependence of PTP (the clinical likelihood that a given patient will have CAD) and the performance of the available diagnostic methods (the likelihood that this patient has disease if the test is positive, or does not have disease if the test is negative), recommendations for diagnostic testing need to take into account the PTP (Hendel et al., 2006).

The low sensitivity of the exercise ECG, only 50% (despite an excellent specificity of 90%) is the reason why the number of false test results will become higher than the number of correct test results in populations with a PTP > 65% (Fraker et al., 2007).
Therefore, 2013 ESC Guidelines for SCAD recommend not employing the exercise stress test in such higher-risk populations for diagnostic purposes. However, the test may nevertheless provide valuable prognostic information in such populations (Montalescot et al., 2013).

Knowledge of a patient's pre-test probability is recommended and required according to Bayes’ theorem, the probability, of a patient having the disease after a test has been carried out is the product of the disease probability before the test and the probability that the test was accurate. However additional factors may be included while determining the PTP; these include the characters of the chest pain and assessment for risk factors (Kontos et al., 2010).

Although risk factors predict the long-term probability of a coronary event, cardiac risk factors are usually not helpful in identification of coronary causes of chest pain; however, in patients <40 years of age, it was reported that a very high risk factor burden (4 to 5 risk factors) increased the likelihood of coronary artery disease by >20-fold compared with the absence of any risk factors. Physical examination for signs of peripheral arterial disease or cerebrovascular disease, LV dysfunction, may aid in diagnosis. Additionally lab testing for risk factors of atherosclerosis (lipid profile, fasting blood glucose, glycated hemoglobin, and creatinine) is required (Han et al., 2007).

**Step 2: Diagnosis** of SCAD or non-obstructive atherosclerosis by non-invasive testing in patients with an intermediate probability of disease.

**Step 3: Stratification for risk** of subsequent events.

Once the diagnosis of SCAD has been made, further management decisions depend largely on the severity of symptoms and the patient’s risk for adverse cardiac events. Stratification for risk is usually done on the basis of available non-invasive tests, in order to select patients who may benefit from invasive investigation and revascularization. Depending on the severity of symptoms, early invasive coronary
angiography may be performed with appropriate invasive confirmation of the significance of a stenosis (FFR) and subsequent revascularization, bypassing non-invasive testing in Steps 2 and 3 (Fihn et al., 2012).

The ability to predict, and potentially intervene to avert adverse future events is an extremely desirable goal to a range of interested patients, from the individual patient, to health care providers, to medical insurers, yet accurate risk prediction remains a challenge. The long-term prognosis of SCAD depends upon a number of factors, such as clinical and demographic variables, LV function, the result of stress testing and coronary anatomy as determined by angiographic techniques. When discussing risk stratification in patients with SCAD, event risk refers primarily to the risk of CV death and MI, and serves to identify patients at high event risk who will benefit from revascularization beyond the amelioration of symptoms (Hachamovitch et al., 2011).

Previously, identification of high event risk was solely based on the Duke Treadmill Score and a >2% annual risk of cardiac death was felt to be the threshold beyond which coronary angiography was recommended to identify the need for revascularization. This value was based on the CV mortality in the placebo arms of studies in ‘high-risk’ populations, such as in the diabetic Micro albuminuria, cardiovascular, and renal sub-study of the Heart Outcomes Prevention Evaluation study (MICRO-HOPE) and the Impact Of Nicorandil in Angina (IONA) studies, where the annualized CV mortality rates were >2%. In 2013 ESC Guidelines, Patients with an annual mortality >3% are defined as high event risk patients. Therefore, in the current guidelines, it is the goal of an event risk-driven diagnostic strategy to identify patients with an annual mortality >3% per year, low event risk patients are those with an annual mortality <1% per year and the intermediate event risk group has an annual mortality of ≥1% but ≤3% per year (table 2) (Montalescot et al., 2013).
Table (2) Definitions of risk for various test modalities.

<table>
<thead>
<tr>
<th>Test Modality</th>
<th>High risk</th>
<th>Intermediate risk</th>
<th>Low risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise stress ECG</td>
<td>CV mortality &gt;3%/year.</td>
<td>CV mortality between 1 and 3%/year.</td>
<td>CV mortality &lt;1%/year.</td>
</tr>
<tr>
<td>Ischaemia imaging</td>
<td>Area of ischaemia &gt;10% (&gt;10% for SPECT); limited quantitative data for CMR – probably ≥2/6 segments with new perfusion defects or ≥3 dobutamine-induced dysfunctional segments; ≥3 segments of LV by stress echo.</td>
<td>Area of ischaemia between 1 and 10% or any ischaemia less than high risk by CMR or stress echo.</td>
<td>No ischaemia.</td>
</tr>
<tr>
<td>Coronary CTA</td>
<td>Significant lesions of high risk category (three-vessel disease with proximal stenoses, LM, and proximal anterior descending CAD).</td>
<td>Significant lesion(s) in large and proximal coronary artery(ies) but not high risk category.</td>
<td>Normal coronary artery or plaques only.</td>
</tr>
</tbody>
</table>

(Montalescot et al., 2013).

The risk assessment sequence can be described as:

**Risk stratification using ventricular function:**

The strongest predictor of long-term survival is LV function. In patients with SCAD as LVEF declines, mortality increases. Hence, stress imaging should be employed instead of the exercise ECG. Although the likelihood of preserved ventricular systolic function is high in patients with a normal ECG and no history of prior MI, asymptomatic ventricular dysfunction is not uncommon. Therefore, a resting echocardiogram is recommended in all patients with suspected SCAD (Raymond et al., 2003).

**Risk stratification using stress testing:**

Symptomatic patients with suspected or known CAD should undergo stress testing to perform event risk stratification and use this as the basis for therapeutic decisions if they are candidates for coronary revascularization. However, no randomized trials have been published demonstrating a better outcome for patients randomized to event risk stratification by stress testing, as compared with those without, and the evidence base therefore consists of observational studies only (Von Bardeleben and Tiemann, 2013).
As most patients will have undergone some form of diagnostic testing anyway, these results can also be used for event risk stratification. Patients with a high PTP >85%, who do not need diagnostic testing, should undergo stress imaging for event risk stratification purposes and the indication for revascularization should be discussed, considering the patient’s risk of events, as appropriate. If patients with a PTP >85% have early ICA for symptomatic reasons, additional FFR may be required for event risk stratification as appropriate (Genders et al., 2012).
Non-invasive modalities for assessment of coronary artery stenosis

(1) Stress electrocardiogram:

Because of its simplicity and widespread availability, treadmill or bicycle exercise testing, using 12-leads ECG monitoring, remains a useful option in patients with suspected stable coronary artery disease (SCAD) and a pre-test probability (PTP) (15–65%) at which the test performs well (Fox et al., 2006).

Diagnostic accuracy:

The main diagnostic ECG abnormality during ECG exercise is horizontal or downsloping ST-segment depression ≥ 0.1 mV, persisting for at least 0.06–0.08s after the J-point, in one or more ECG leads but in about 15% of patients, ST-segment changes appear only during the recovery phase. To obtain maximal diagnostic information the test should be symptom/sign-limited and performed without the influence of anti-ischemic drugs. Using exercise ST-depression ≥ 0.1 mV or 1 mm to define a positive test, the reported sensitivities and specificities to detect significant CAD (usually diameter stenosis ≥ 50%) range between 23–100% (mean 68%) and 17–100% (mean 77%), respectively. Adding cardiopulmonary exercise testing may improve sensitivity significantly, but this combination of tests is not widely used. It is important to remember that these numbers are valid only in patients without significant ECG abnormalities at baseline (Gibbons et al., 2002).

Prognostic considerations:

The prognostic exercise testing markers include exercise capacity, BP response and exercise-induced ischemia (clinical and ECG). Maximum exercise capacity is a consistent prognostic marker. This measure is at least partly influenced by the extent of rest ventricular dysfunction and the amount of further LV dysfunction induced by exercise (Pradhan et al., 2012).
However, exercise capacity is also affected by age, general physical condition, comorbidities and psychological state. Exercise capacity may be measured by maximum exercise duration, maximum metabolic equivalent (MET) level achieved, maximum workload achieved, maximum heart rate and double (rate–pressure) product. The Duke Treadmill score is well validated, combining exercise time, ST-deviation and angina during exercise to calculate the patient’s event risk. High event risk patients with an annual mortality > 3% can also be identified using the Duke risk calculator (Pradhan et al., 2012).

**Limitations:**

Exercise ECG testing is not of diagnostic value in the presence of left bundle branch block (LBBB), paced rhythm and Wolff-Parkinson-White syndrome, in which ECG changes are not interpretable. Additionally, false positive results are more frequent in patients with abnormal resting ECG in the presence of LVH, electrolyte imbalance, intraventricular conduction abnormalities, atrial fibrillation and use of digitalis (Pradhan et al., 2012).

Also in patients with autonomic dysfunction and sensory neuropathy, the perception of angina may be diminished and abnormal rest and exercise-induced heart rate (e.g., chronotropic incompetence) and blood pressure responses are common. Exercise ECG testing is also less sensitive and specific in women. However, randomized trial, comparing an initial diagnostic strategy of exercise nuclear myocardial perfusion imaging (MPI) with standard exercise treadmill testing, in symptomatic women with suspected CAD and preserved functional capacity who were able to exercise, did not show an incremental benefit of the more expensive MPI strategy on clinical outcomes (Shaw et al., 2011).

Exercise ECG may be inconclusive; for example, when 85% of maximum heart rate is not achieved in the absence of symptoms or signs of ischaemia, exercise is limited by orthopedic or other non-cardiac problems, or ECG changes are equivocal. In this group of patients, an alternative non-invasive imaging test with pharmacologic stress should be selected (Pradhan et al., 2012).
(2) Single Photon Emission Computed Tomography (SPECT).

SPECT imaging has been available since the 1970s and has given us a large body of evidence confirming its diagnostic and prognostic value. The commonly used radioisotopes are thallium-201 and technetium-based agents such as 99Tcm sestamibi and 99Tcm tetrofosmin. Ischaemia is suspected when there is reduced tracer uptake on the stress acquisition which is reversible on the rest acquisition (figure 2). A fixed defect, i.e. a defect present on both stress and rest acquisitions, is suggestive of an infarct provided attenuation artifacts are ruled out.

![Figure 2: Reversible ischaemia on myocardial scintigraphy scan in the anterior wall (arrows) (Melikian et al., 2010).](image)

**Diagnostic accuracy:**

The sensitivity and specificity for the diagnosis of significant coronary stenosis (defined as >50% stenosis) were 86% and 74%, respectively (Underwood et al., 2004). A false negative study may be a feature of three-vessel and left main stem disease because SPECT assesses relative perfusion. Normal perfusion is seen in up to 13–15% of patients with left main stem disease on account of balanced ischemia in multivessel disease (Melikian et al., 2010).
False positive tests due to attenuation artifacts lower the specificity. For example, an elevated diaphragm results in an apparent fixed defect in the inferior wall in men, and breast artifact gives rise to an apparent defect in the anterior wall in women. Implementing gated studies, attenuation correction algorithm and prone imaging help improve the specificity by reducing the number of equivocal scans in such cases. Referral bias, introduced by the fact that only patients with a positive test will undergo an invasive angiogram, also falsely lowers the specificity (Berman et al., 2006).

**Prognostic considerations:**

A negative study confers an annualized risk of less than 1% of adverse cardiac events. An abnormal study is associated with an annual event rate of 6.7–7% (Underwood et al., 2004). The annual event rate increases with increasing severity of the perfusion defect. The warranty period refers to the frequency of follow up testing following a negative study. The warranty period is approximately 5 years in a clinically stable patient with no new symptoms or signs. The individual risk and the warranty period are dependent on the age and sex of the patient, stress-induced ECG changes and associated comorbidities such as diabetes and renal dysfunction (Dondi et al., 2004). The annual risk varies from 1.4% to 1.8%. The risk is highest for an 80-year-old female diabetic patient, in whom the warranty period is only 1–2 years (Hachamovitch et al., 2011).

**Myocardial perfusion scintigraphy using PET**

Although less well studied than SPECT, PET has better diagnostic accuracy for detection of CAD, including in women. Advantages of PET over SPECT include lower radiation exposure, higher resolution, and fewer attenuation artifacts that allow for better image quality even in obese patients. In addition, PET can uniquely quantify blood flow, thus allowing detection of micro vascular angina. The main limitations of PET are limited availability and increased cost (Span et al., 2006).
(3) Stress echocardiography:

Myocardial ischemia is caused by a transient imbalance between oxygen supply and demand. A typical cascade of events in a well-defined time sequence will occur after the onset of ischemia. The forerunner is abnormal myocardial perfusion and endothelial dysfunction, followed by regional wall motion dyssynergy and only at a later stage by electrocardiography (ECG) changes and pain. SE aims to detect regional wall motion abnormalities under ischemic conditions and thus allows diagnosis at an earlier stage of the cascade than would be achieved by symptoms or ECG changes (Picano et al., 2000).

Interpretation of stress echocardiography:

Interpretation is usually by visual assessment based on analysis of thickening and inward systolic motion before, during and after stress. The heart is typically divided into a 17 segment model and a score assigned to each segment at baseline and during stress based on the degree of thickening. The presence of a new or worsening regional wall motion abnormality in 1 or more segments identifies an ischemic response. The site of this response gives a clue as to the artery affected (Cerqueira et al., 2002).

The extent of ischemia is based on the number of affected segments, the occurrence of ischemia at an early stage of the test, the wall motion score index at rest and peak stress, and a slow recovery time. Global left ventricular (LV) ejection fraction and end systolic volumes may also be calculated at baseline and at peak stress. A fall in either of these parameters is an indicator of significant ischemia (figure 3) (Gunalp et al., 1993).
Figure (3) the left ventricle can be divided into 17 segments from two-dimensional standard imaging views: parasternal short-axis, apical four-chamber and apical two-chamber. This image depicts the name, location and anatomical landmarks for selection of the basal (tips of the mitral valve leaflets), mid-cavitary (papillary muscles) and apical (beyond papillary muscles but before cavity ends) short-axis slices for the recommended 17-segment nomenclature. LAD= Left anterior descending; LCX= Left circumflex; RCA= Right coronary artery (Gunalp et al., 1993).

Diagnostic accuracy:

The accuracy of this technique is consistently reported to be good with sensitivity and specificity averaging 82% and 81%, respectively in comparison to perfusion imaging and superior to exercise ECG. As with other forms of stress testing, the accuracy is lower in those with single vessel disease. Accuracy is also reduced in patients taking beta blockers but this can be overcome by administration of atropine to achieve the target heart rate. Advances in image acquisition, analysis, and interpretation have enhanced the accuracy and prognostic value of the test (Pellerin and Brecker, 2002).

Prognostic considerations:

A normal stress echo carries a very low risk (<1% per year) of major cardiac events in the subsequent 5 years. A positive stress test carries a 10%–30% risk of further cardiac events, with risk being greatest in those with the highest ischemic burden. The prognostic value of DSE is independent and additive to resting echo and exercise ECG (Picano et al., 2000).
(4) Stress Cardiac Magnetic Resonance (CMR):

Cardiac magnetic resonance (CMR) stress testing, in conjunction with a dobutamine infusion, can be used to detect wall motion abnormalities induced by ischemia. The technique has been shown to have a comparable safety profile to dobutamine stress echocardiography (DSE) (Weinreb and Abu-Alfa, 2009).

Dobutamine stress CMR may be useful in patients with sub-optimal acoustic windows, especially those in whom pharmacologic perfusion imaging using adenosine is contra-indicated. Perfusion CMR is more widely used than dobutamine stress CMR. Previous studies had confirmed the good diagnostic accuracy of CMR perfusion imaging at 1.5 Tesla (T), as compared with nuclear perfusion imaging. Analysis is either visual, to identify low signal areas of reduced perfusion (ischemic zones), or with computer assistance to determine the up-slope of myocardial signal increase during the first pass (Greenwood et al., 2012). Quantitative CMR perfusion measurements demonstrate good correlations with FFR measurements. Although not widely available, the use of high-strength magnets at 3.0T provides higher diagnostic accuracy as compared with 1.5 T machines (Bernhardt et al., 2012).

Prognostic considerations:

There is an independent association between adverse cardiac outcomes in multivariate analysis for patients with an abnormal dobutamine stress CMR and > 99% event-free survival in patients with no evidence of ischaemia over a 36-month follow-up (Korosoglou et al., 2010).

Similar data exist for perfusion CMR performed by adenosine. Assuming that the biological principles are the same for stress echocardiography and stress SPECT as they are for CMR, new wall motion abnormalities (≥ 3 segments in the 17 segment model) induced by stress or stress-induced reversible perfusion deficits >10% (≥ 2 segments) of the LV myocardium should be regarded as indicating a high event risk situation (Jahnke et al., 2007).
However, there are as yet no data providing proof that this distinction can be made by CMR in the same way as with SPECT. In fact CMR estimates of the extent of perfusion deficit as a percentage of the entire LV are imprecise, as compared with SPECT, as only three slices of the LV are currently examined by standard available CMR machines (Fordyce et al., 2016).

**Safety aspects of cardiovascular magnetic resonance:**

Electronic devices such as pacemakers, defibrillators, infusion pumps, and others are considered as absolute contraindications. There is up to now one pacemaker type which obtained approval from regulatory authorities to be CMR compatible, and other manufacturers will certainly follow soon with similar products (Roguin et al., 2008). However in general, implanted devices such as heart valves, occludes, and stents are compatible with MR, at least up to 1.5 T (Syed et al., 2006).

Coronary MR Angiography allows for non-invasive visualization of the coronary arteries without exposing the patient to ionizing radiation. A small, multicenter study showed sensitivity, specificity and positive and negative predictive values of 88, 72, 71 and 88%, respectively, in a patient-based analysis. However, long imaging times, lower spatial resolution and operator dependency remain major limitations. Advantages of the technique include evaluation of overall cardiac anatomy and function in the same examination. However, at present, MR coronary arteriography must still be regarded primarily as a research tool and is not recommended for routine clinical practice in the diagnostic evaluation of SCAD (Kato et al., 2010).

Claustrophobia is present in up to 5% of cases and the use of a tranquilizer is very effective (Tschirch et al., 2008). Concerning the administration of contrast medium, nephrogenic systemic fibrosis (NSF) was described where the skin and in severe cases internal organs develop a fibrosis which can lead to death. This NSF is documented in some cases worldwide for linear gadolinium chelates, whereas macrocyclic gadolinium chelates are considered of very low risk (Weinreb et al., 2009).
(5) Multidetector- Computed Tomography (MDCT):

CT imaging of the coronary arteries can be performed without contrast injection (coronary calcium scoring) or after intravenous injection of iodinated contrast (coronary CTA).

A) Calcium scoring.

Multi detector row CT permits the detection of coronary calcification in non-contrast enhanced data sets. Calcified lesions are usually quantified using the ‘Agatson score’ (Table 3). With the exception of patients with renal failure who may have medial calcification, coronary calcium is a consequence of coronary atherosclerosis. The amount of calcium correlates roughly to the total amount of atherosclerosis present in the coronary arteries but correlation with the degree of luminal narrowing is poor. Even with severe calcification, luminal stenosis is not necessarily present and a ‘zero’ calcium score cannot be used to rule out coronary artery disease in symptomatic individuals, especially when young and with acute symptoms (Fihn et al., 2012).

Table 3: Coronary calcium score (Agatson score).

<table>
<thead>
<tr>
<th>CCS (Agaston)</th>
<th>Risk</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Non-Identified</td>
<td>Negative test. Findings are consistent with a low risk of having a cardiovascular event in the next 5 years.</td>
</tr>
<tr>
<td>1-10</td>
<td>Minimal</td>
<td>Minimal atherosclerosis is present. Findings are consistent with a low risk of having a cardiovascular event in the next 5 years.</td>
</tr>
<tr>
<td>11-100</td>
<td>Mild</td>
<td>Mild coronary atherosclerosis is present. There is likely mild or minimal coronary stenosis. A mild risk of having CAD exists.</td>
</tr>
<tr>
<td>101-400</td>
<td>Moderate</td>
<td>Moderate calcium is detected in the coronary arteries and confirms the presence of atherosclerotic plaque. A moderate risk of having a cardiovascular event exists.</td>
</tr>
<tr>
<td>&gt;400</td>
<td>High</td>
<td>A high calcium score may be consistent with significant risk of having a cardiovascular event within the next 5 years.</td>
</tr>
</tbody>
</table>

(Weustink and De Feyter, 2011).
B. Coronary computed tomography angiography:

After intravenous injection of contrast agent, CT can visualize the coronary artery lumen. Adequate technology (at least 64-slice CT) and patient selection, as well as careful patient preparation, are mandated. According to expert consensus, only patients with adequate breath holding capabilities, without severe obesity, with a favorable calcium score (e.g. Agatson score <400) and distribution, in sinus rhythm and with a heart rate of 65 beats per minute or less, should be considered for coronary CTA if necessary, the use of short-acting B-blockers or other heart rate-lowering medication is recommended (Abbara et al., 2010).

Since the specificity of coronary CTA decreases with increasing amounts of coronary calcium and the prevalence of coronary artery stenosis was found to be high in symptomatic individuals with an Agatson score >400 it is reasonable not to proceed with coronary CTA if the calcium score exceeds 400. The influence of calcium on the accuracy of coronary CTA is less pronounced in low heart rates and for modern CT systems (Villines et al., 2011).

In the event that a calcium score is not obtained and calcifications are only seen on the completed coronary CTA scan, it may be prudent to refrain from stenosis quantification in areas of extensive calcifications and call the test ‘unclear’ (Paech et al., 2011). In patients with suspected CAD, multicenter studies using 64-slice CT have demonstrated sensitivities of 95–99% and specificities of 82 as well as negative predictive values of 97–99% and positive predictive value (91–93%) for the identification of individuals with at least one coronary artery stenosis by ICA (Budoff et al., 2008).

Also, coronary CTA remains less reliable in patients with coronary stents, due to artifacts caused by metal and the limited spatial resolution of CT. The assessment of
CABG is highly accurate while the evaluation of native coronary vessels in post-bypass patients is difficult and prone to false positive findings (Ropers et al., 2006).

Prospective trials which have randomized patients to the use or non-use of coronary CTA looking at hard clinical endpoints in stable chest pain patients, are currently not available (just as for the other imaging techniques), registry data confirm an excellent prognosis if coronary CTA demonstrates the absence of coronary artery disease (Meijboom et al., 2007).

The diagnostic performance of coronary CTA is best for individuals at the lower range of intermediate PTP for the disease. Thus, coronary CTA may be useful in ruling out coronary disease in such patients. Under the same prerequisites, coronary CTA should also be considered in patients with a stress test result that contradicts clinical judgment (especially a positive stress test result when clinical judgment speaks against the presence of severe stenosis) if ICA would otherwise be chosen to rule out CAD (Meijboom et al., 2007).

Given the false-positive result of stress tests in some populations, such as patients with LVH, coronary CTA may be warranted as a first-line test in selected individuals. However, coronary CTA cannot rule out functional CAD in these patients. No data are available to support ‘screening’ coronary CTA in asymptomatic individuals and CTA should not be used for this purpose. New developments in coronary CTA, such as CT-FFR need further validation (Min et al., 2012).

Unlike invasive coronary angiography, CT coronary angiography (CTA) not only assesses disease within the coronary lumen but can also provide direct qualitative and quantitative information about non-obstructive atherosclerotic plaque burden within the vessel wall. Thus, it is possible that CTA-based patient evaluation may provide more clinically relevant information on which to base risk assessments compared with conventional “lumenography” (Di Carli and Hachamovitch, 2007).
The opportunity to non-invasively visualize coronary anatomy is the major reason for the current interest in cardiac MDCT. With the introduction of 16- and 64-slice MDCT systems, improved temporal and spatial resolution as well as substantially shorter scan times led to improved image quality throughout the entire coronary tree and thus significant improvement in the accuracy for the detection of coronary artery stenoses when compared with previous generations (Hamon et al., 2006).

Pooling the data of more than 800 patients yields a sensitivity of 89% (95% CI 87–90) with a specificity of 96% (95% CI 96–97) and a positive and negative predictive value of 78% (95% CI 76–80) and 98% (95% CI 98–99). Importantly, the negative predictive value was high in all studies, indicating that the technique may be most suitable as a non-invasive tool to rule out significant CAD and avoid further imaging or invasive angiography. However, it is important to realize that patient selection may still heavily influence results, with substantially impaired image quality in patients with higher heart rates or arrhythmias (Leschka et al., 2006).

Image quality may also be degraded in patients with severe CAD due to the presence of extensive calcifications which potentially limit precise assessment of the stenosis severity (Ong et al., 2006).

Preliminary studies using this technique showed that up to 98% of all coronary segments could be visualized without motion artifacts, even without lowering the heart rate by administration of beta blockers. Moreover, even in patients without stable sinus rhythm, a high accuracy could be obtained, and an initial, small study reported a high accuracy for stenosis detection in patients with advanced CAD (Scheffel et al., 2006).

In addition, 256-slice MDCT systems, whose large coverage along the patient’s longitudinal axis may allow imaging of the entire heart in a single cardiac cycle and will make coronary CT angiography less susceptible to arrhythmias or heart rate variability (Kido et al., 2007).
Lesion severity and functional relevance:

The limited temporal and spatial resolution of CT may create difficulties in accurately assessing the severity of coronary artery stenosis. There is a tendency to overestimate the degree of luminal narrowing by CT when compared with invasive angiography and pronounced calcification of a vessel segment can make lesion assessment particularly difficult. Usually, calcification will lead to overestimation, rather than underestimation of lesion severity (Hoffmann et al., 2008).

Furthermore, coronary CT angiography is limited to the anatomic visualization of stenosis and does not provide information as to the functional relevance of a lesion. In head-to-head comparison of MDCT and nuclear myocardial perfusion imaging with SPECT in 114 patients with intermediate likelihood of CAD, only 45% of patients with an abnormal MDCT had abnormal perfusion on SPECT (Schuijf et al., 2006).

Even in patients with obstructive lesions on MDCT, 50% still had a normal SPECT and only fraction of patients with obstructive coronary lesions demonstrate ischaemia on SPECT and positron emission tomography (PET) perfusion imaging. For this reason, although 64-slice MDCT is a reliable tool to rule out functionally relevant CAD in a non-selected population with an intermediate pre-test likelihood of disease, an abnormal coronary CT angiogram does not necessarily predict ischaemia (Namdar et al., 2005).

In a study, hybrid PET/CT was evaluated in patients with suspected CAD, which yielded a sensitivity and specificity of 90 and 98%, respectively, for the detection of haemodynamically relevant coronary lesions. Rispler et al., 2007 who compared an experimental SPECT/MDCT hybrid imaging device for the assessment of coronary anatomy and myocardial perfusion in 56 patients with angina pectoris. They found that the sensitivity, specificity, positive predictive and negative predictive values for MDCT were 96, 63, 31, and 99%, respectively, compared with 96, 95, 77, and 99%, respectively, for the combined SPECT/MDCT examination. The authors concluded that hybrid imaging led to an improvement of diagnostic accuracy (table 4) (Rispler et al., 2007).
Table (4): The use of coronary computed tomography angiography for the diagnosis of stable coronary artery disease.

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
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<tbody>
<tr>
<td>Coronary CTA should be considered as an alternative to stress imaging techniques for ruling out SCAD in patients within the lower range of intermediate PTP for SCAD in whom good image quality can be expected.</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>Coronary CTA should be considered in patients within the lower range of intermediate PTP for SCAD after a non conclusive exercise ECG or stress imaging test or who have contraindications to stress testing in order to avoid otherwise necessary invasive coronary angiography if fully diagnostic image quality of coronary CTA can be expected.</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>Coronary calcium detection by CT is not recommended to identify individuals with coronary artery stenosis.</td>
<td>III</td>
<td>C</td>
</tr>
<tr>
<td>Coronary CTA is not recommended in patients with prior coronary revascularization.</td>
<td>III</td>
<td>C</td>
</tr>
<tr>
<td>Coronary CTA is not recommended as a 'screening' test in asymptomatic individuals without clinical suspicion of coronary artery disease.</td>
<td>III</td>
<td>C</td>
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*(Fihn et al., 2012)*

(6) Computed Tomography Fractional Flow Reserve:

Recent advancements of CT technologies have enabled several novel methods to assess the functional significance of coronary stenosis in addition to anatomical information. One of these is the application of computational fluid dynamics to coronary CT angiography (CCTA) images. With this technology, FFR can be computed using images from conventional CCTA (CT-derived computed FFR; $FFR_{CT}$) without any invasive procedure and without hyperemia *(Kim et al., 2010)*.

A prospective, multicenter clinical trial, *Diagnosis of Ischemia-Causing Stenosis Obtained via Non-invasive Fractional Flow Reserve (DISCOVER-FLOW)* study, was performed to assess the diagnostic performance of $FFR_{CT}$ in the prediction of the functional significance of stenosis. In this study, 103 patients (159 vessels) with stenosis in a major epicardial coronary artery who had diagnostic quality CT images from 64 or
more detector row CT scanners were consecutively enrolled and the diagnostic accuracy of CCTA (≥50% stenosis) and FFR\textsubscript{CT} were compared. On a per-vessel basis, accuracy, sensitivity, specificity, positive predictive value, and negative predictive value for FFR\textsubscript{CT} and CCTA were 84.3%, 87.9%, 82.2%, 73.9%, 92.2%, respectively, and 58.5%, 91.4%, 39.6%, 46.5%, 88.9%, respectively (Koo et al., 2011).

This study showed that noninvasive FFR derived from CCTA (FFR\textsubscript{CT}) had a high diagnostic performance for the detection and exclusion of significant coronary lesions. This novel technology may potentially reduce unnecessary invasive procedures. Moreover, combination of virtual intervention and this technology can help to determine the treatment strategy in complex lesions prior to the invasive procedure (figure 4) (Min et al., 2011).

Figure(4): Anatomically obstructive stenosis with a lesion causing ischaemia (a) Multiplanar reformat of coronary computed tomography angiography demonstrating obstructive (> 50 %) stenosis white arrow) in the proximal portion of LAD. (b) Invasive coronary angiography confirms the LAD stenosis (red arrow) with corresponding haemodynamically significant reductions in coronary pressure in the first diagonal branch (0.78) (and distal LAD (0.58) by FFR. (c) Noninvasive computation of FFR from FFR\textsubscript{CT} of the first diagonal branch (0.79) and distal LAD (0.57), demonstrating lesion-specific ischaemia of the proximal LAD stenosis (Min et al., 2011).
Invasive coronary angiography:

Non-invasive testing can establish the likelihood of the presence of obstructive coronary disease with an acceptable degree of certainty. Thus, ICA will only rarely be necessary in stable patients with suspected CAD, for the sole purpose of establishing or excluding the diagnosis. Such situations may arise in patients who cannot undergo stress imaging techniques, in patients with reduced LVEF <50% and typical angina. ICA may, however, be indicated following non-invasive risk stratification for determination of options for revascularization. In patients who have a high PTP and severe symptoms, or a clinical constellation suggesting high event risk, early invasive coronary angiography without previous non-invasive risk stratification may be a good strategy to identify lesions potentially amenable to revascularization. FFR testing is advised if appropriate (Morgan et al., 2005).

Methods used to perform invasive coronary angiography have improved substantially, resulting in the reduction of complication rates with rapid ambulation. This is especially true for ICA performed via the radial artery. The composite rate of major complications associated with routine femoral diagnostic catheterization, mainly bleeding requiring blood transfusions is still between 0.5–2%. The composite rate of death, MI, or stroke is of the order of 0.1–0.2%. Invasive coronary angiography should not be performed in patients with angina who refuse invasive procedures, prefer to avoid revascularization, who are not candidates for PCI or CABG, or in whom revascularization is not expected to improve functional status or quality (Agostoni et al., 2004).

Invasive assessment of functional severity of coronary lesions:

Coronary angiography is of limited value in defining the functional significance of stenosis. Yet the most important factor related to outcome is the presence and extent of inducible ischemia. This and alleviation of angina symptoms caused by significant stenosis is the rationale for revascularizing such lesions. If, on the other hand, a stenosis
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is not flow-limiting, it will not cause angina and the prognosis without coronary intervention is excellent, with a hard event rate of, 1% per year (Pijls et al., 2007).

Although non-invasive ischemia testing is very precise in determining the functional implications of single-vessel disease, this is more difficult and complex in multi-vessel disease. Therefore, interventional guidance by non-invasive ischemia testing through imaging techniques may be sub-optimal under such circumstances (Hachamovitch et al., 2011).

The functional severity of coronary lesions visualized angiographically may be assessed invasively, either by measuring coronary flow velocity (CFR), or intracoronary artery pressure (FFR). The CFR is the ratio of hyperemic to basal flow velocity and reflects flow resistance through the epicardial artery and the corresponding myocardial bed. Measurements depend on the status of the microcirculation, as well as on the severity of the lesion in the epicardial vessel. FFR is considered nowadays as the gold standard for invasive assessment of physiological stenosis significance and an indispensable tool for decision making in coronary revascularization (Pijls et al., 2012).

FFR provides guidance to the clinician in situations when it is not clear whether a lesion of intermediate angiographic severity causes ischemia. Such situations are encountered in practice when noninvasive ischemia testing was not performed before catheterization or multi-vessel disease is found at coronary angiography. Use of FFR in the catheterization laboratory accurately identifies which lesions should be revascularized and improves the outcome in most elective clinical and angiographic conditions. The use of FFR has been upgraded to a Class IA classification in multi-vessel PCI in the ESC Guidelines on coronary revascularization (Wijns et al., 2010). Fractional flow reserve is calculated as the ratio of distal coronary pressure to aortic pressure measured during maximal hyperemia. A normal value for FFR is 1.0, regardless of the status of the microcirculation, and stenosis with FFR.0.80 are hardly ever associated with exercise-induced ischemia (Pijls et al., 2007).