CLINICAL PRACTICE GUIDELINES

MANAGEMENT OF

STABLE ANGINA PECTORIS

July 2010
STATEMENT OF INTENT
This clinical practice guidelines (CPG) is meant to be a guide for clinical practice, based on the best available evidence at the time of development. Adherence to these guidelines may not necessarily guarantee the best outcome in every case. Every health care provider is responsible for the management of his/her patient based on the clinical picture presented by the patient and the management options available locally.

PERIOD OF VALIDITY
This CPG was issued in 2012 and will be reviewed in 5 years or sooner if new evidence becomes available.

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http://www.moh.gov.my
http://www.acadmed.org.my
http://www.malaysianheart.org
MESSAGE FROM DIRECTOR GENERAL OF HEALTH, MALAYSIA

Malaysia is now being confronted with the rising epidemic of cardiovascular risk factors. Data from the Third National Health and Morbidity Survey (NHMS III) in 2006 showed that 63% of Malaysians had at least one cardiovascular risk factor, 33% had two risk factors and 14% had three or more risk factors. Hypertension remains the number one risk factor with a prevalence rate of 38%, followed by central obesity (37%), hypercholesterolaemia (24%) and hyperglycaemia (15%). The cardiovascular risk-factor clustering provides a clear impression of the true cardiovascular disease burden in the population.

Coronary artery disease is one of the most rampant NCD in the world. It is the major cause of morbidity and mortality in our hospitals. Data from MOH hospitals in 2010 has shown that diseases of the circulatory systems (which also include cerebrovascular diseases) accounted for 25.4% of total deaths. This makes cardiovascular diseases as the main cause of death in MOH hospitals.

Currently there are much pharmacological and technological advancement in the management of cardiovascular diseases. However I firmly believe that the appropriate management of patients with heart diseases is beyond prescribing the latest drugs or stents. These are important and necessary of course, nevertheless, we must not lose sight of the central role of therapeutic lifestyle changes such as a healthy balanced diet, regular aerobic exercise and reduction and cessation of unhealthy habits such as tobacco use and alcohol consumption. The key word here is patient empowerment.

I greatly welcome this guideline into the growing family of CPGs in the management of non-communicable diseases. Guidelines such as this are important decision support tools, not only for doctors, but for all health professionals involved in the management of patients with cardiovascular diseases. I would like to thank all of those involved for their time and energy in developing this guideline. However, the publication of this guideline is only the first step. I strongly urge concrete steps be taken to disseminate the information contained in this guideline and to monitor the effectiveness of its implementation in Malaysia.

Thank you.

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Director General of Health, Malaysia
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RATIONALE AND PROCESS OF GUIDELINE DEVELOPMENT

Rationale
Coronary artery disease (CAD) comprises a broad spectrum of manifestation ranging from asymptomatic atherosclerosis to stable angina pectoris (SAP), acute coronary syndrome (ACS), myocardial infarction (MI) and congestive heart failure (CHF). The management of SAP has not been extensively studied in large randomised clinical trials.

In Malaysia, these patients may be managed by cardiologists, physicians and primary care doctors. The CPG on Management of SAP was developed to help guide clinicians in the management of this group of patients. No previous guideline was available in Malaysia prior to this.

Process
This CPG was initiated by the National Heart Association of Malaysia (NHAM) in collaboration with the Academy of Medicine Malaysia (AM) and Ministry of Health Malaysia (MOH). The guideline committee consisted of cardiologists, physicians and primary care physicians from the government hospitals, universities and private hospitals.

This CPG was adapted from the European Society of Cardiology (ESC) Guidelines on the Management of Stable Angina, 2006. The CPG was evaluated using the Appraisal of Guidelines for Research and Evaluation (AGREE) prior to adaptation. Further evidence was evaluated from relevant publications from January 2006 through December 2009.

Literature search was carried out at the electronic databases of PUBMED/MEDLINE, Cochrane Databases of Systemic Reviews (CDSR), journal full text via OVID search engine. Refer to Appendix 3 for the terms used to retrieve articles.

Reference was also made to other guidelines on the management of stable angina pectoris including The American College of Cardiology (ACC)/American Heart Association (AHA) 2007 chronic angina focused update of the ACC/AHA 2002 Guidelines for the Management of Patients With Chronic Stable Angina; European Society of Cardiology (ESC) Guidelines on the Management of Stable Angina, 2006; ACC/AHA guidelines for the clinical application of echocardiography, 1997; European guidelines on cardiovascular disease prevention in clinical practice (constituted by representatives of nine societies and by invited experts), 2007; American Diabetes Association, Standards of Medical Care in Diabetes, 2008; Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines, 2004; ACC/AHA guidelines of percutaneous coronary interventions, 2001. Malaysia CPG on management of Type 2 Diabetes Mellitus, 2009; Malaysia CPG on Prevention of Cardiovascular Disease in Woman, 2008; Malaysia Consensus statement from on the utilization of cardiac CT, 2008; Malaysia CPG on Management of Acute ST Segment Elevation Myocardial Infarction (STEMI), 2007; Malaysia Medical Nutritional Therapy Guidelines for Hyperlipidaemia and Hypertension, 2005; Malaysia CPG on Management of
Obesity, 2004; Malaysia CPG on Treatment of Tobacco Use and Dependence, 2003; Malaysia Clinical Practice Guidelines on Dyslipidaemia, 2003; Malaysia CPG of UA/NSTEMI, 2002; Malaysia CPG on Erectile Dysfunction, 2000; Malaysia Guidelines for Medical Practitioners performing medical examinations for vocational licence (PSV and GDL).

In addition, the reference lists of all relevant retrieved articles as well as the reference list of the other guidelines reviewed were used to identify further studies.

All relevant information was discussed thoroughly over several meetings before a draft guideline was prepared. The draft was submitted to the Technical Advisory Committee for Clinical Practice Guidelines, as well as the Health Technology Assessment (HTA) and Clinical Practice Guidelines Council, MOH Malaysia for review and approval. This was then submitted to a group of external reviewers selected from MOH hospitals, academic institutions as well as the private sector.

Objectives
These guidelines are intended to provide education and awareness on ways to:
1. Identify patients with stable angina
2. Assess, risk stratify and manage these patients appropriately

Clinical Questions
The clinical questions addressed in these guidelines include:
1. How does one diagnose a patient with SAP and exclude patient with unstable angina?
2. Having identified patients with SAP, what appropriate tests should be done for diagnosis and prognostication?
3. Which patients should be referred for invasive procedures?
4. What appropriate treatment modalities, either non-pharmacological and/or pharmacological to be utilised?

Target Group
This guideline is directed at all healthcare providers treating SAP – general practitioners, medical officers, general and family physicians and cardiologists.

Target Population
This guideline is for the management of patients with Stable Angina Pectoris. It excludes patients with new-onset angina, crescendo angina and rest angina.

Applicability
The recommendations outlined are very much dependant on local expertise and availability of resources and does not apply universally to all healthcare providers. Factors which need to be taken into consideration at the local level in applying these recommendations include:
1. Organizational barriers
2. Cost implications
Expected Benefits
It is hoped that with appropriate usage of these guidelines, only those patients in whom there is general agreement will benefit from invasive management strategies will be referred to tertiary cardiac centres for further care whereas those patients who can be safely and adequately managed conservatively utilising management options outlined within these guidelines will continue in the care of their appropriate healthcare providers.

Criteria for Monitoring/Audit Purposes
The algorithm in Figure 1 is suggested to be used as a clinical pathway for evaluation of patients with SAP.

Patients identified as SAP patients may be audited against this pathway to see whether the processes in diagnosing and managing these patients are adhered to. The detailed appropriate processes will need to be determined within the local setting e.g. with respect to appropriate stress testing modality.

Therapeutic options also make excellent criteria for audit purposes e.g. proportion of patients given adequate advice and monitored for non-pharmacological (lifestyle) intervention and use of appropriate pharmacological agents within local setting.

Dr. Azani Mohd Daud
Chairperson
## Grades of Recommendation

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Conditions for which there is evidence and/or general agreement that a given procedure/therapy is beneficial, useful and/or effective</td>
</tr>
<tr>
<td>II</td>
<td>Conditions for which there is conflicting evidence and/or divergence of opinion about the usefulness/efficacy of a procedure/therapy</td>
</tr>
<tr>
<td>IIa</td>
<td>Weight of evidence/opinion is in favor of its usefulness/efficacy</td>
</tr>
<tr>
<td>IIb</td>
<td>Usefulness/efficacy is less well established by evidence/opinion</td>
</tr>
<tr>
<td>III</td>
<td>Conditions for which there is evidence and/or general agreement that a procedure/therapy is not useful/effective and in some cases may be harmful</td>
</tr>
</tbody>
</table>

## Levels of Evidence

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Data derived from multiple randomised clinical trials or meta analyses</td>
</tr>
<tr>
<td>B</td>
<td>Data derived from a single randomised clinical trial or large non randomised studies</td>
</tr>
<tr>
<td>C</td>
<td>Only consensus of opinions of experts, case studies or standard of care</td>
</tr>
</tbody>
</table>

### Levels of Evidence
Adapted from the American Heart Association (AHA) and the European Society of Cardiology (ESC)
Clinical Evaluation of patients with chest pain

In general, processes within this red box can most likely be undertaken by primary care physicians if required.

Chest pain

CLINICAL EVALUATION
1. History
2. ECG
3. Basic investigations

Non anginal chest pain*

Manage accordingly

Suspected stable angina

Suspected UA/ACS

Assessment of ischaemia
1. Stress ECG and or
2. Stress imaging (Pharmacological/Exercise)

NO ischaemia

Ischaemia

Confirmed stable angina

Evaluate prognosis on basis of clinical evaluation and non-invasive tests

Low risk

Intermediate risk

High risk

Medical therapy

Medical therapy ± Coronary arteriography

Medical therapy AND Coronary arteriography

*Refer to Table 4

Refer to CPG on UAVNSTEMI & CPG on Management of Acute ST-Segment-Elevation Myocardial Infarction (STEMI) 2007, 2nd edition

Figure 1. Algorithm for the initial evaluation of patients with clinical symptoms of angina.
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1. INTRODUCTION
Coronary Artery Disease (CAD) comprises a broad spectrum of manifestations ranging from asymptomatic atherosclerosis to symptomatic stable angina, acute coronary syndrome (ACS) and congestive heart failure (CHF).

Local data for the prevalence of patients with SAP is not available. However in 2008, cardiovascular disease (CVD) was the commonest cause of death in MOH hospitals at 25.19% of total deaths.1

Data from USA shows that SAP is the initial presenting manifestation in approximately half of patients with CAD.2,3

Reported annual incidence of angina is 213 per 100,000 population greater than 30 years old.2 Annual incidence of uncomplicated angina pectoris in western population aged > 40 years is approximately 0.5% with geographic variations.4-10

Prevalence of angina varies according to sex and age ranging from 0.1 - 1% in women aged 45 - 54 years, 10 - 15% in women aged 65 - 74 years to 2 - 5% in men aged 45 - 54 years and 10 - 20% in men aged 65 - 74 years.11-18

The management of SAP has not been extensively studied with large Randomised Clinical Trials (RCT) as other parts of the disease spectrum thereby hampering efforts to define an optimum strategy for management of SAP.

2. DEFINITION AND PATHOPHYSIOLOGY
2.1 DEFINITION

ANGINA
Clinical syndrome characterised by:
- Discomfort in chest, jaw, shoulder, back or arms
- Typically aggravated by exertion or emotional stress
- Relieved by rest or nitroglycerin (GTN)

Unstable Angina (UA) may present in the following ways:19

Table 1. Presentation of UA

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest angina</td>
<td>Pain of characteristic nature and location, but occurring at rest and for prolonged periods, up to 20 mins</td>
</tr>
<tr>
<td>Crescendo angina</td>
<td>Previously stable angina, which progressively increases in severity, intensity, and at lower threshold over a short period of 4 weeks or less</td>
</tr>
<tr>
<td>New-onset angina</td>
<td>Recent onset of severe angina, such that the patient experiences marked limitation of ordinary activity within 2 months of initial presentation</td>
</tr>
</tbody>
</table>
This CPG is a guide for the management of patients with angina who do not fulfill the criteria of UA.

2.2 PATHOPHYSIOLOGY
The syndrome is attributed to myocardial ischaemia, the most common cause being atherosclerotic CAD.

Other causes of myocardial ischaemia include:
- Hypertrophic cardiomyopathy
- Aortic stenosis
- Coronary vasospasm
- Coronary vasculitis from connective tissue disease
- Aortic aneurysms
- Coronary artery anomalies
- Anemia

Myocardial ischaemia is caused by an imbalance between myocardial oxygen supply and demand.

Coronary arterial flow which is dependant on luminal cross-sectional area and arteriolar tone, is a major determinant of myocardial oxygen supply.

Mismatch in myocardial oxygen supply and demand results in metabolic abnormalities, regional or global myocardial dysfunction, ECG changes and angina.

In SAP, angina threshold may vary from day to day or even within the same day.

Table 2. Canadian Cardiovascular Society Classification (CCS) of Angina

<table>
<thead>
<tr>
<th>Class</th>
<th>Severity of exertional stress inducing angina</th>
<th>Limitation of ordinary activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Strenuous, rapid or prolonged exertion at work or recreation</td>
<td>None</td>
</tr>
<tr>
<td>II</td>
<td>Walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, or in cold, or in wind, or under emotional stress, or only during the few hours after awakening</td>
<td>Slight</td>
</tr>
<tr>
<td>III</td>
<td>Walking one or two blocks on the level and climbing one flight of stairs in normal conditions and at a normal pace</td>
<td>Marked</td>
</tr>
<tr>
<td>IV</td>
<td>Inability to carry out any physical activity without discomfort or symptoms may be present at rest</td>
<td>Discomfort in all activity performed</td>
</tr>
</tbody>
</table>

Patients with SAP may become unstable. UA is characterised by angina which may be more prolonged, more frequent, more severe, occurring at a lower threshold or at rest²⁰ and patients may progress to non-ST-elevation or ST-elevation MI. (For
management of UA or MI, please refer to the Malaysia Clinical Practice Guidelines on UA/NSTEMI and Clinical Practice Guidelines on Management of Acute ST Segment Elevation Myocardial Infarction (STEMI) 2007

3. PROGNOSIS
European data estimates CAD mortality rates for men of 17.6 per 1,000 patient-years between age 70s and 90s. In the Framingham Heart Study, 2-year incidence rates for non-fatal MI and CAD death were 14.3% and 5.5% in men and 6.2% and 3.8% in women, respectively. Annual mortality rates from clinical trials on anti-anginal therapies and/or revascularisation ranges between 0.9 - 1.4%. However, the prognosis for each patient may vary considerably and the individual prognostic assessment is an integral part of management of patients with SAP.

4. DIAGNOSIS AND ASSESSMENT
- Diagnosis and assessment of angina involves clinical assessment, laboratory tests, and specific cardiac investigations.
- In practice, diagnostic and prognostic assessments are conducted in tandem rather than separately, and many of the investigations used for diagnosis also offer prognostic information.
- An algorithm for the initial evaluation of patients presenting with clinical symptoms suggestive of angina is depicted in Figure 1 (Page X).

4.1 SYMPTOMS AND SIGNS
- A careful history alone may be enough for the diagnosis of angina pectoris, and confirmation is made by physical examination and objective tests.
- The characteristics of discomfort related to myocardial ischaemia (angina pectoris) may be divided into four categories, summarised in Table 3 below:

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location</td>
<td>Classically retrosternal, but may be felt anywhere from the epigastrium to the jaw or teeth, between the shoulder blades or in either arm to the wrist and fingers.</td>
</tr>
<tr>
<td>Character</td>
<td>Pressure, tightness, or heaviness, sometimes strangling, constricting, or burning. The severity of the discomfort varies greatly and is not related to the severity of the underlying coronary disease. Shortness of breath may accompany angina.</td>
</tr>
<tr>
<td>Duration</td>
<td>Not more than 10 minutes in the majority of cases</td>
</tr>
<tr>
<td>Exacerbating and relieving factors</td>
<td>Symptoms classically get worse with increased levels of exertion, and rapidly disappear at rest within a few minutes. Exacerbations of symptoms after a heavy meal, during emotional stress or first thing in the morning are features of angina. Sublingual nitrates may rapidly relieve angina.</td>
</tr>
</tbody>
</table>
Definitions of typical and atypical angina have been previously published and are summarised in Table 4.

**Table 4. Clinical classification of chest pain**

<table>
<thead>
<tr>
<th>Type</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typical angina (definite)</td>
<td>Meets <em>three</em> of the following characteristics</td>
</tr>
<tr>
<td></td>
<td>• Retrosternal chest discomfort of characteristic quality and duration</td>
</tr>
<tr>
<td></td>
<td>• Provoked by exertion or emotional stress</td>
</tr>
<tr>
<td></td>
<td>• Relieved by rest and/or GTN</td>
</tr>
<tr>
<td>Atypical angina (probable)</td>
<td>Meets <em>two</em> of the above characteristics</td>
</tr>
<tr>
<td>Non-cardiac chest pain</td>
<td>Meets <em>one or none</em> of the above characteristics</td>
</tr>
</tbody>
</table>

Non-anginal pain lacks the characteristic qualities described above and non-cardiac causes of pain should be evaluated in such cases.

**Table 5. Causes of non-anginal chest pain**

<table>
<thead>
<tr>
<th>Underlying cause</th>
<th>System involvement</th>
<th>Specific condition</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Gastrointestinal system</td>
<td>Gastro-oesophageal reflux</td>
</tr>
<tr>
<td>Non-cardiovascular</td>
<td>Respiratory system</td>
<td>Peptic ulcer disease</td>
</tr>
<tr>
<td></td>
<td>Neurology</td>
<td>Oesophageal spasm</td>
</tr>
<tr>
<td></td>
<td>Psychiatry</td>
<td>Gallstones</td>
</tr>
<tr>
<td></td>
<td>Musculoskeletal</td>
<td>Pleurisy</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Cardiac</td>
<td>Pneumothorax</td>
</tr>
<tr>
<td>(not myocardial</td>
<td></td>
<td>Pulmonary embolism</td>
</tr>
<tr>
<td>ischaemia)</td>
<td>Non-cardiac</td>
<td>Pneumonia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Neuralgia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Psychosomatic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Costochondritis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Myalgia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mitral valve prolapse</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pericarditis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Aortic dissection</td>
</tr>
</tbody>
</table>

**Unstable Angina (UA)**

- It is important when taking the history to identify those patients with UA
- UA may present in one of three ways as defined in Table 1
The investigation and management of suspected UA are dealt within the guidelines for the management of ACS. (For management of ACS, please refer to the Malaysia Clinical Practice Guidelines on Management of Acute ST Segment Elevation Myocardial Infarction (STEMI) 2007[25])

Physical examination is directed at:
- looking for complications of CAD such as murmurs indicating mitral valvular regurgitation, septal defects, signs of cardiomegaly and CHF
- other sites of atherosclerosis – carotid bruises, peripheral vascular disease, aortic aneurysms
- risk factors for atherosclerosis such as hypertension, metabolic syndrome, etc.
- other causes of angina such as hypertrophic obstructive cardiomyopathy (HOCM), aortic stenosis

Investigations in stable angina may be divided broadly into 5 groups:
- 4.2 Laboratory tests
- 4.3 Chest X-Ray (CXR)
- 4.4 Non-invasive Cardiac Investigations
  - 4.4.1 Resting Electrocardiography (ECG)
  - 4.4.2 Exercise stress testing
  - 4.4.3 Stress testing in combination with imaging
    - 4.4.3.1 Exercise testing with echocardiography
    - 4.4.3.2 Exercise testing with myocardial perfusion scintigraphy
  - 4.4.4 Pharmacological stress testing with imaging techniques
  - 4.4.5 Stress Cardiac Magnetic Resonance (CMR)
  - 4.4.6 Echocardiography (Echo) at rest
  - 4.4.7 Ambulatory Electrocardiography (ECG) monitoring
- 4.5 Non-invasive Techniques to Assess Coronary Calcification and Coronary Anatomy
- 4.6 Invasive Techniques to Assess Coronary Anatomy

4.2 LABORATORY TESTS
The objectives of laboratory investigations are to:
- establish cardiovascular (CV) risk factors (e.g. fasting glucose level[31-34] fasting lipid profile,[35-37] homocysteine,[38] Lp(a), ApoA,[39] ApoB[40])
- provide information relating to possible causes of ischaemia (e.g. haemoglobin level[41])
- determine prognosis (e.g. hs-CRP,[38,41,42] serum creatinine[43])

<table>
<thead>
<tr>
<th>Recommendation of laboratory investigations</th>
<th>I, C</th>
<th>I, B</th>
<th>I, B</th>
<th>IIb, B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full blood count, serum creatinine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting glucose</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting lipid profile</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hs-CRP, homocysteine, Lp(a), ApoA, ApoB</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
4.3 CHEST X-RAY (CXR)
- In SAP, the CXR does not provide specific information for diagnosis or for risk stratification
- The test should be requested only in patients with suspected CHF, valvular disease, or pulmonary disease
- The presence of cardiomegaly, pulmonary congestion, atrial enlargement, and cardiac calcifications have been related to prognosis

<table>
<thead>
<tr>
<th>Recommendations for CXR for initial diagnostic assessment of angina</th>
</tr>
</thead>
<tbody>
<tr>
<td>CXR in patients with suspected CHF</td>
</tr>
<tr>
<td>CXR in patients with clinical evidence of significant pulmonary disease</td>
</tr>
</tbody>
</table>

4.4 NON-INVASIVE CARDIAC INVESTIGATIONS
This section describes investigations used in the assessment of angina and concentrate on recommendations for their use in diagnosis and evaluation of efficacy of treatment, whereas recommendations for risk stratification will be dealt with in the following section.

4.4.1 Resting Electrocardiography (ECG)
- All patients with suspected angina pectoris based on symptoms should have a resting 12-lead ECG recorded
- A resting ECG may show evidences of CAD such as previous MI or an abnormal repolarisation pattern
- A normal resting ECG does NOT exclude the diagnosis of ischaemia
- The ECG may assist in clarifying the differential diagnosis if taken in the presence of pain such as in vasospasm, allowing detection of dynamic ST-segment changes in the presence of ischaemia or by identifying features of pericardial disease.
- The ECG may also show other abnormalities such as left ventricular hypertrophy (LVH), bundle branch block, pre-excitation, arrhythmias, or conduction defects.
- Such information may be helpful in defining the mechanisms responsible for chest pain, in selecting appropriate further investigation or in tailoring individual patient treatment.

<table>
<thead>
<tr>
<th>Recommendations for resting ECG for initial diagnostic assessment of angina</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resting ECG while pain free</td>
</tr>
<tr>
<td>Resting ECG during episode of pain (if possible)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recommendations for resting ECG for routine re-assessment in patients with SAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Routine periodic ECG in the absence of clinical change</td>
</tr>
</tbody>
</table>
4.4.2 Exercise stress testing

- An exercise test should be carried out only after careful clinical evaluation of symptoms and a physical examination including resting ECG
- Exercise ECG is more sensitive and specific than rest ECG for detecting myocardial ischaemia
- Exercise ECG should not be carried out routinely in patients with known severe aortic stenosis or hypertrophic cardiomyopathy
- Interpretation of the exercise ECG test should be based on the pre-test probability of disease
- Exercise ECG testing is not of diagnostic value in the presence of:
  - Left bundle branch block (LBBB)
  - Paced rhythm
  - Wolff-Parkinson-White (WPW) syndrome
- The reasons for stopping the test are listed in Table 6
- In some patients, the exercise ECG may be non-conclusive if:
  - at least 85% of maximum heart rate (HR) is not achieved in the absence of symptoms or ischaemia
  - exercise is limited by orthopaedic or other non-cardiac problems
  - ECG changes are equivocal
- Inconclusive exercise test should then be followed by an alternative non-invasive diagnostic test, unless the patient has a very low pre-test probability (<10%) of disease
- For diagnostic purposes, the test should be conducted in patients without taking anti-ischaemic drugs provided it is safe to do so
- Exercise stress testing can also be useful to evaluate the efficacy of treatment after control of angina with medical treatment or revascularisation or to assist prescription of exercise after control of symptoms
- The effect of routine periodical exercise testing on patient outcomes has not been formally evaluated
- False positive results are more frequent in patients with abnormal resting ECG, in the presence of LVH, electrolyte imbalance, intraventricular conduction abnormalities, and use of digitalis
- Exercise ECG testing is also less sensitive and specific in women
Table 6. Reasons for terminating exercise stress test

<table>
<thead>
<tr>
<th>Reasons</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptom limitation</td>
<td>Pain, fatigue, dyspnoea, and claudication</td>
</tr>
<tr>
<td>Combination (symptoms and ECG)</td>
<td>Pain with significant ST-changes</td>
</tr>
<tr>
<td>Safety reasons</td>
<td>- Marked ST-depression (&gt; 2 mm as relative indication for termination and ≥ 4 mm as an absolute indication to stop the test)</td>
</tr>
<tr>
<td></td>
<td>- ST-elevation ≥ 1 mm</td>
</tr>
<tr>
<td></td>
<td>- Significant arrhythmia</td>
</tr>
<tr>
<td></td>
<td>- Sustained fall in systolic blood pressure (SBP) &gt; 10 mmHg</td>
</tr>
<tr>
<td></td>
<td>- Marked HPT (&gt; 250 mmHg systolic or &gt; 115 mmHg diastolic)</td>
</tr>
<tr>
<td>Achievement of maximum predicted HR</td>
<td>Decision to terminate the test is at the discretion of the physician</td>
</tr>
</tbody>
</table>

Recommendations for exercise ECG for initial diagnostic assessment of angina

Patients with angina and intermediate-to-high pre-test probability of CAD unless unable to exercise or displays ECG changes which make ECG non-evaluable I, B

Patients with ≥ 1 mm ST-depression on resting ECG or taking digoxin IIb, B

Patients with low pre-test probability (< 10%) of CAD IIb, B

a = based on age, gender and symptoms, see appendix 1.

Recommendations for exercise ECG for routine re-assessment in patients with SAP

Routine periodic exercise ECG in the absence of clinical change IIb, C

4.4.3 Stress testing in combination with imaging

- The most well-established stress imaging techniques are echo and perfusion scintigraphy and both may be used in combination with either exercise stress or pharmacological stress
- Novel stress imaging techniques also include stress CMR, which, for logistical reasons, is most frequently performed using pharmacological stress rather than exercise stress
• Stress imaging techniques have several advantages over conventional exercise ECG testing including superior diagnostic performance (Table 7) for the following reasons:
  o detection of obstructive CAD
  o the ability to quantify and localise areas of ischaemia
  o the ability to provide diagnostic information in the presence of resting ECG abnormalities
• Stress imaging techniques are often preferred in patients with previous PCI or CABG because of superiority in localising ischaemia
• In patients with angiographically confirmed intermediate coronary lesions (50% - 70% stenosis on angiography), evidence of anatomically appropriate ischaemia is predictive of future events, whereas a negative stress imaging test can be used to define patients with a low cardiac risk, who can be reassured

Table 7. Summary of test characteristics for investigations used in the diagnosis of SAP

<table>
<thead>
<tr>
<th>Test</th>
<th>Diagnosis of CAD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise ECG</td>
<td>Sensitivity (%)</td>
</tr>
<tr>
<td></td>
<td>Specificity (%)</td>
</tr>
<tr>
<td>Exercise echo</td>
<td>80 - 85</td>
</tr>
<tr>
<td>Exercise myocardial perfusion</td>
<td>85 - 90</td>
</tr>
<tr>
<td>Dobutamine stress echo</td>
<td>40 - 100</td>
</tr>
<tr>
<td>Vasodilator stress echo</td>
<td>56 - 92</td>
</tr>
<tr>
<td>Vasodilator stress myocardial perfusion</td>
<td>83 - 94</td>
</tr>
</tbody>
</table>

4.4.3.1 Exercise testing with echocardiography
• Exercise stress echo is an alternative to ‘classical’ exercise testing with ECG and provides additional information to establish the presence or location and extent of myocardial ischaemia during stress
• A resting echocardiogram is acquired before a symptom-limited exercise test is performed with further image acquisition at peak exercise
• Overall sensitivity and specificity of exercise echocardiography is 80 - 85% and 84 - 86% respectively
• Tissue Doppler and strain rate imaging are expected to improve the accuracy and reproducibility of stress echo in the broader clinical setting

4.4.3.2 Exercise testing with myocardial perfusion scintigraphy
• Thallium-201 and technetium-99m radiopharmaceuticals are the most commonly used tracers, employed with single-photon emission computed tomography (SPECT) in association with a symptom-limited exercise test on either a bicycle ergometer or a treadmill
• It produces images of regional tracer uptake that reflects relative regional myocardial blood flow. Myocardial hypoperfusion is characterised by reduced tracer uptake during stress in comparison with uptake at rest
• It is more sensitive and specific than exercise ECG (Table 7)
4.4.4 Pharmacological stress testing with imaging techniques

- Pharmacological stress may also be employed when the use of exercise imaging is not possible
- Pharmacological stress testing with either perfusion scintigraphy or echocardiography is indicated in patients who are unable to exercise adequately or may be used as an alternative to exercise stress
- Two approaches may be used to achieve this:
  - Infusion of short-acting sympathomimetic drugs (e.g. dobutamine)
  - Infusion of coronary vasodilators (e.g. adenosine and dipyridamole)
- The diagnostic performance of pharmacological stress perfusion and pharmacological stress echo is also similar to that of exercise imaging techniques (Table 7)\(^{30,\,91}\)
- Stress imaging has an important role to play in evaluating patients with a low pre-test probability of disease, particularly women,\(^{76-78}\) when exercise testing is inconclusive, in selecting lesions for revascularisation and in assessing ischaemia after revascularisation\(^{74-77}\)

### Recommendations for the use of exercise stress with imaging techniques (either echo or perfusion) in the initial diagnostic assessment of angina

| Patients with resting ECG abnormalities e.g. LBBB, > 1 mm ST depression, paced rhythm, or WPW which prevent accurate interpretation of ECG changes during stress | I, B |
| Patients with a non-conclusive exercise ECG but reasonable exercise tolerance, who do not have a high probability of significant coronary disease and in whom the diagnosis is still in doubt | I, B |
| Patients with prior revascularisation (PCI or CABG) in whom localisation of ischaemia is important | IIa, B |
| As an alternative to exercise ECG in patients where facilities, costs, and personnel resources allow | IIa, B |
| As an alternative to exercise ECG in patients with a low pre-test probability of disease | IIa, B |
| To assess functional severity of intermediate lesions on coronary arteriography | IIa, C |
| To localise ischaemia when planning revascularisation options in patients who have already had arteriography | IIa, C |

### Recommendations for the use of pharmacological stress with imaging techniques (either echo or perfusion) in the initial diagnostic assessment of angina

Class I, IIa, and IIb indications as mentioned earlier; if the patient is unable to exercise adequately
4.4.5 Stress Cardiac Magnetic Resonance (CMR)
- Stress CMR can be used to detect wall motion abnormalities induced by ischaemia or perfusion abnormalities
- Stress CMR, using either perfusion imaging or stress-induced wall motion abnormalities imaging, demonstrates good sensitivity 83 - 91% and specificity 81 - 86% for the diagnosis of CAD.\(^7\)\(^8\)
- High quality CMR perfusion has been shown to be at least as good as single photon emission computed tomography scan (SPECT) for the diagnosis of CAD. It also has a close correlation with invasive flow and pressure measurements.\(^7\)\(^8\)
- Dobutamine stress CMR has been shown to be superior to adenosine stress CMR to detect ischaemia in patients with suspected or known CAD but no history of prior MI\(^8\)\(^9\).

4.4.6 Echocardiography (Echo) at rest
- Two-dimensional and doppler echo is useful in patients with clinically detected murmurs,^8^\(^1\) \(^4\) history and ECG changes compatible with hypertrophic cardiomyopathy\(^8\)\(^5\)\(^6\) or previous MI\(^8\)\(^7\)\(^8\) and symptoms or signs of CHF\(^8\)\(^9\)\(^0\)
- Recent developments in tissue Doppler imaging and strain rate measurement have greatly improved the ability to study diastolic function\(^8\)\(^6\)\(^1\), \(^9\)

**Recommendations for echo for initial diagnostic assessment of angina**

Patients with abnormal auscultation suggesting valvular heart disease or hypertrophic cardiomyopathy I, B

Patients with suspected CHF I, B

Patients with prior MI I, B

Patients with LBBB, Q waves or other significant pathological changes on ECG, including left anterior hemiblock I, C

4.4.7 Ambulatory Electrocardiographic (ECG) monitoring
- Ambulatory ECG (Holter) monitoring may reveal evidence of myocardial ischaemia during normal ‘daily’ activities\(^8\)\(^2\)
- However, it rarely adds important diagnostic or prognostic information in chronic stable angina pectoris over and above that provided by an exercise test\(^8\)\(^3\), \(^8\)\(^4\)
- It may have a role in patients in whom vasospastic angina is suspected
- In patients with SAP and suspected major arrhythmias, Holter monitoring is an important method of diagnosing arrhythmias

**Recommendations for ambulatory ECG for initial diagnostic assessment of angina**

Angina with suspected arrhythmia I, B

Suspected vasospastic angina IIa, C
4.5 NON-INVASIVE TECHNIQUES TO ASSESS CORONARY CALCIFICATION AND CORONARY ANATOMY

There are 3 non-invasive modalities to define the coronary anatomy:
1. Electron beam computed tomography (EBCT) with/without angiogram
2. Multislice computed tomography (MSCT) angiogram
3. Cardiac magnetic resonance (CMR)

4.5.1 Electron Beam Computed Tomography (EBCT)
The EBCT is effective in quantifying the extent of coronary calcification. The coronary calcium score identifies a population at higher risk of significant coronary artery disease, and has been found to correlate well with overall burden of plaque. However, due to low spatial resolution and high image noise, EBCT angiogram is not an appropriate diagnostic tool for patients with SAP.

4.5.2 Multislice Computed Tomography (MSCT)
Cardiac CT is performed as a 2-part examination. Firstly, the coronary artery calcium score and secondly the coronary artery CT angiogram. The use of MSCT angiogram allows good diagnosis, accurate detection and quantification of stenosis of major segments of right and left coronary arteries. The 64 slice detector CT angiogram has a negative predictive value of 93 - 99% and sensitivities and specificities of 90 - 94% and 95 - 97% respectively.

**Recommendations for the use of CT angiography in SAP**

- Diagnosis of CAD when other modalities (e.g., stress testing or stress imaging) provide equivocal results, especially in patients with a low to intermediate probability of disease  
  IIA, C
- Patients who cannot undergo non-invasive testing due to disability, illness, or morbid obesity  
  IIb, C
- Patients with recurrent chest pain in whom a definite diagnosis is judged necessary  
  IIb, C

4.5.3 Cardiac Magnetic Resonance (CMR)
CMR is an emerging modality for cardiac imaging. It is an excellent modality for evaluation of myocardial structure, function, reversible ischaemia and viability, however the current MRI technology has limited diagnostic accuracy for assessment of coronary stenosis.

4.6 INVASIVE TECHNIQUES TO ASSESS CORONARY ANATOMY

4.6.1 Coronary angiography
Coronary angiography is defined as the radiographic visualisation of the coronary vessels after injection of radiopaque contrast media. Coronary angiography allows anatomical definition of the coronary arteries, degree of luminal obstruction and determination of prognosis. The risk of complications with routine angiogram is between 1 and 2% with the current methods. The composite rate of death, MI, or stroke is of the order of 0.1 - 0.2%.
## Recommendations for coronary angiography for establishing a diagnosis of SAP

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Level</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe SAP (Class 3 or greater of CCS Classification), with a high pre-test probability of disease, especially if symptoms are not responding to medical treatment</td>
<td>I, B</td>
<td></td>
</tr>
<tr>
<td>Survivors of cardiac arrest</td>
<td>I, B</td>
<td></td>
</tr>
<tr>
<td>Patients with serious ventricular arrhythmias</td>
<td>I, C</td>
<td></td>
</tr>
<tr>
<td>Patients previously treated by myocardial revascularisation (PCI, CABG) who develop early recurrence of moderate or severe angina pectoris</td>
<td>I, C</td>
<td></td>
</tr>
<tr>
<td>Patients with an inconclusive diagnosis on non-invasive testing, or conflicting result from different non-invasive modalities at intermediate to high risk of coronary disease</td>
<td>IIa, C</td>
<td></td>
</tr>
<tr>
<td>Patients with a high risk of restenosis after PCI if PCI has been done in a prognostically important site</td>
<td>IIa, C</td>
<td></td>
</tr>
<tr>
<td>Patients who cannot undergo non-invasive testing due to disability, illness, or morbid obesity</td>
<td>IIa, C</td>
<td></td>
</tr>
<tr>
<td>Patients with a high pre-test probability of left main or 3-vessel CAD</td>
<td>IIa, C</td>
<td></td>
</tr>
<tr>
<td>Patients with significant LV dysfunction (left ventricular ejection fraction (LVEF) &lt; 45%), CCS class I or II angina, and demonstrable ischaemia but less than high-risk criteria on non-invasive testing</td>
<td>IIa, C</td>
<td></td>
</tr>
<tr>
<td>Patients with recurrent chest pain in whom a definite diagnosis is judged necessary</td>
<td>IIb, C</td>
<td></td>
</tr>
<tr>
<td>Patients with significant co-morbidity in whom the risk of coronary arteriography outweighs the benefit of the procedure</td>
<td>III, C</td>
<td></td>
</tr>
</tbody>
</table>

Adjunctive invasive techniques with coronary angiography for assessment of CAD include intravascular ultrasound (IVUS), fractional flow reserve (FFR) and coronary angioscopy.

### 5. RISK STRATIFICATION

The process of risk stratification serves 2 purposes:
- To provide information regarding prognosis
- To assist in choosing appropriate treatment, e.g. revascularisation in high risk groups

While clear risk stratification exists for primary prevention, absolute levels of what constitutes high risk and low risk are not clearly defined for those with established CVD. Risk stratification primarily refers to the risk of cardiovascular death. However, there is no systematic predictive method to determine what constitutes high risk or low risk. The Euro heart angina score probably provides the simplest and most objective way to discriminate extremely low risk
group and those at high risk. Comorbidity, diabetes, severity of angina, duration of symptoms, left ventricular function and ST segment changes on resting ECG independently predict outcome, i.e. non-fatal MI and death.  

For the purposes of these guidelines, an individual with SAP is deemed:
• high risk - if he has annual CV mortality of > 2%  
• intermediate risk - if he has annual CV mortality of 1 - 2%  
• low risk - if he has annual CV mortality of < 1%  

Information required to stratify a patient’s risk:
A. Clinical evaluation  
B. Non-invasive assessment of ischaemia  
C. Quantification of ventricular function  
D. Extent of CAD (angiography)  

5.1 CLINICAL EVALUATION  

5.1.1 Clinical history
Important predictors of adverse outcome in patients with established CAD:
• DM  
• HPT  
• Metabolic syndrome  
• Current smoker  
• Increasing age  
• Prior MI  
• Symptoms and signs of CHF  
• Pattern of occurrence of angina (recent onset or progressive)  
• Severity of angina, particularly if unresponsive to therapy  
• Dyslipidaemia  

5.1.2 Physical examination
The presence of the following assists in determining risk:
• peripheral vascular disease (PVD) - either lower limb or carotid  
• signs related to CHF  

5.2 RESTING ECG
Resting ECG abnormalities can predict patients at greater risk of future CV events than those with a normal ECG. The abnormalities are:
• Evidence of prior MI  
• LBBB  
• Left anterior hemiblock  
• LVH  
• Second or third degree AV block  
• Atrial fibrillation (AF)  

Recommendations for risk stratification by clinical evaluation, including ECG and laboratory tests, in SAP

| Detailed clinical history and physical examination - including | I, B |
| BMI and/or waist circumference and CV risk profile | I, B |
| Resting ECG | I, B |
5.3 STRESS TESTING

Risk stratification using stress testing
- Stress testing can be in the form of exercise or pharmacological stress, with or without imaging.
- Prognostic information that can be obtained from stress testing:
  o detection of ischaemia
  o ischaemic threshold
  o extent and severity of ischaemia (for imaging techniques)
  o functional capacity (for exercise testing)
- The choice of initial stress test should be based on the patient’s resting ECG, physical ability to perform exercise, local expertise, and available technologies.
- Commonly used stress testing modalities are:
  1. Exercise stress test
  2. Stress echo
  3. Stress perfusion scintigraphy

5.3.1 Exercise stress test
- Prognostic exercise testing markers include exercise capacity and exercise-induced ischaemia (clinical and ECG).
- Maximum exercise capacity is a consistent prognostic marker. It may be measured by
  o maximum exercise duration
  o maximum MET level achieved
  o maximum HR
  o double (rate-pressure) product
- In patients with known CAD and normal or mildly impaired LV function, the 5-year survival is higher in patients with a better exercise tolerance.\(^{45, 56, 124-126}\)
- An early positive exercise test (ST depression > 1 mm within stage 1 or 2 of standard Bruce protocol) identifies a high risk population.\(^{125}\)
- The Duke treadmill score (DTS) is a well-validated score which combines exercise time, ST deviation, and angina during exercise to calculate the patient’s risk (Figure 2).\(^{124, 127}\)

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**Figure 2. DTS score.**\(^{127}\)

<table>
<thead>
<tr>
<th>Duke treadmill score</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Exercise time (in minutes)</td>
<td>(-n)</td>
</tr>
<tr>
<td>b. ST-depression (mm x 5)</td>
<td>(-n)</td>
</tr>
<tr>
<td>c. Angina (non-limiting) OR</td>
<td>(-4)</td>
</tr>
<tr>
<td>d. Angina (limiting)</td>
<td>(-8)</td>
</tr>
<tr>
<td>Total score = a + b + (c OR d)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Risk</th>
<th>Total score</th>
<th>1-year mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>(\geq 5)</td>
<td>0.25%</td>
</tr>
<tr>
<td>Intermediately</td>
<td>4 to -10</td>
<td>1.25%</td>
</tr>
<tr>
<td>High</td>
<td>(\leq -11)</td>
<td>5.25%</td>
</tr>
</tbody>
</table>
Recommendations for risk stratification according to exercise stress ECG in SAP in patients who can exercise

All patients without significant resting ECG abnormalities undergoing initial evaluation I, B
Patients with stable coronary disease after a significant change in symptom level I, C
Patients post-revascularisation with a significant deterioration in symptomatic status IIa, B

5.3.2 Stress Echocardiography (Echo)

- May be used to risk stratify patients at risk of CV events\(^{82, 126}\)
- Has an excellent negative predictive value in patients with a negative test having an event rate (death or MI) of < 0.5% per year\(^{125, 130}\)
- Risk of future events is influenced by the number of
  - Resting regional wall motion abnormalities
  - Inducible wall motion abnormalities on stress echo\(^{69}\)
- Identification of a high risk cohort allows for appropriate further investigation and/or intervention

Recommendations for risk stratification according to exercise stress imaging (perfusion or echo) in SAP in patients who can exercise

Patients with resting ECG abnormalities e.g. LBBB, > 1 mm ST-depression, paced rhythm, or WPW which prevent accurate interpretation of ECG changes during stress I, C
Patients with a non-conclusive exercise ECG, but intermediate or high probability of disease I, B
Patients with a deterioration in symptoms post-revascularisation IIa, B
As an alternative to exercise ECG in patients, in which facilities, cost, and personnel resources allow IIa, B

5.3.3 Pharmacological stress echocardiography

- Dobutamine and vasodilators (e.g. dipyridamole) at appropriately high doses are equally potent ischaemic stressors and have similar accuracies and specificities to exercise\(^{132-134}\)
- The presence (or absence) of inducible wall motion abnormalities separates patients with different prognosis\(^{129, 135-147}\)
- Normal stress echocardiogram yields a cardiac event risk of 0.4% to 0.9%\(^{150}\)

Recommendations for risk stratification according to pharmacological stress imaging (perfusion or echo) in SAP

Patients who cannot exercise I, B
Other class I and II indications as for exercise stress imaging (perfusion or echocardiography) in SAP in patients who can exercise, but where local facilities do not include exercise imaging
5.3.4 Stress perfusion scintigraphy

- Normal stress myocardial perfusion images carries a benign prognosis, with an event rate of < 1% per year, which is nearly as low as that of the general population.\textsuperscript{151-153}

- The only exceptions would appear to be patients with normal perfusion images with either a high-risk treadmill ECG score or severe resting LV dysfunction.\textsuperscript{154}

- In contrast, abnormal findings have been associated with severe CAD and subsequent cardiac events.

- Large stress-induced perfusion defects, defects in multiple coronary artery territories, transient post-stress ischaemic LV dilatation, and in patients studied with thallium-201, increased lung uptake\textsuperscript{155} on post-exercise or pharmacologic stress images are all adverse prognostic indicators.\textsuperscript{62, 66, 153, 154}

- Exercise stress imaging offers greater prognostic information than pharmacological stress imaging because of the information regarding symptoms, exercise tolerance and haemodynamic response to exercise, which is additive to that obtained from perfusion or echo data alone.

5.3.5 Stress Cardiac Magnetic Resonance (CMR)

- In patients with known or suspected CAD, myocardial ischaemia detected by adenosine and dobutamine stress CMR can be used to identify patients at high risk for subsequent cardiac death or non-fatal MI. For those with normal stress CMR, the 3-year event-free survival was 99.2%.\textsuperscript{156}

- Adenosine stress CMR imaging is safe to perform early after acute STEMI and can identify patients with significant coronary stenosis more accurately than exercise stress test.\textsuperscript{157}

- Adenosine stress CMR may help to identify patients at risk who would benefit from intensified medical treatment and close follow-up.\textsuperscript{158}

5.4 VENTRICULAR FUNCTION\textsuperscript{45, 84, 105, 110-112}

- Risk stratification using ventricular function

- Strongest predictor of long-term survival is LV function.

- Prevalence of asymptomatic ventricular dysfunction has been reported to be as high as twice that of clinical CHF, with the presence of IHD a major risk factor for its occurrence.\textsuperscript{159-161}

- In patients with SAP, as LVEF declines, mortality increases.

- Resting LVEF of < 35% is associated with an annual mortality rate > 3% per year\textsuperscript{45, 48, 111, 162}

- An estimation of ventricular function is desirable in risk stratifying patients with SAP, and an assessment for ventricular hypertrophy (by echo or MRI) and of ventricular function is particularly pertinent in patients with HPT\textsuperscript{163} or DM.

<table>
<thead>
<tr>
<th>LVEF</th>
<th>12-year survival rate$^8$ ( (P &lt; 0.0001) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 35%</td>
<td>21%</td>
</tr>
<tr>
<td>35 - 49%</td>
<td>54%</td>
</tr>
<tr>
<td>&gt; 50%</td>
<td>73%</td>
</tr>
</tbody>
</table>
Recommendations for risk stratification by echo evaluation of ventricular function in SAP

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resting echo in patients with prior MI, symptoms or signs of CHF, or resting ECG abnormalities</td>
<td>I, B</td>
</tr>
<tr>
<td>Resting echo in patients with HPT</td>
<td>I, B</td>
</tr>
<tr>
<td>Resting echo in patients with DM</td>
<td>I, C</td>
</tr>
<tr>
<td>Resting echo in patients with a normal resting ECG without prior MI who are not otherwise to be considered for coronary arteriography</td>
<td>IIa, C</td>
</tr>
</tbody>
</table>

5.5 CORONARY ARTERIOGRAPHY

Risk stratification using coronary arteriography

- Despite the recognised limitations of coronary arteriography to identify vulnerable plaques which are likely to lead to acute coronary events, the following have been convincingly demonstrated to be important prognostic indicators in patients with angina.46, 101, 164, 165
  - extent of CAD (number of vessels involved)
  - severity of luminal obstruction
  - location of coronary disease (left main stem (LMS) and proximal left anterior descending artery (LAD)

- In the CASS registry of medically treated patients, the 12-year survival rate of patients with normal coronary arteries was 81% compared with 74% for those with single vessel disease, 59% for those with two-vessel disease (2VD), and 50% for those with three-vessel disease (3VD) (P < 0.001).162

- The 5-year survival rate for patients with 3VD including a > 95% proximal LAD stenosis was 54% compared with a rate of 79% for patients with 3VD without LAD stenosis.165

- The use of coronary arteriography to identify patients whose prognosis can be improved is likely to be appropriate in high but not low risk groups.

- In the intermediate risk group, the decision should be guided by a variety of factors including the patient's symptoms, functional status, lifestyle, occupation, co-morbidity, and response to initial medical therapy.

- It is the duty of the physician to ensure that the patient is fully informed of their risk and the potential benefits or lack of benefit of any particular procedure and to guide their decision appropriately.

- Coronary arteriography should NOT be performed in patients
  - with angina who refuse invasive procedures
  - who prefer to avoid revascularisation
  - who are not candidates for PCI or CABG
  - in whom PCI/CABG will not improve quality-of-life
Recommendations for risk stratification by coronary arteriography in patients with SAP

- Patients determined to be at high risk for adverse outcome on the basis of non-invasive testing even if they present with mild or moderate symptoms of angina: I, B
- Severe SAP (Class 3 or greater of CCS Classification), particularly if the symptoms are inadequately responding to medical treatment: I, B
- SAP in patients who are being considered for major non-cardiac surgery, especially vascular surgery (repair of aortic aneurysm, femoral bypass, carotid endarterectomy) with intermediate or high risk features on non-invasive testing: I, B
- Patients with an inconclusive diagnosis on non-invasive testing, or conflicting results from different non-invasive modalities: IIa, C
- Patients with a high risk of restenosis after PCI, if PCI has been performed in a prognostically important site: IIa, C

A summary of the recommendations for the routine use of investigations in the evaluation of SAP, with corresponding levels of evidence related to diagnosis and prognosis, is presented in Appendix 2.

6. TREATMENT
6.1 AIMS OF TREATMENT:
Generally treatment is aimed to:
- prevent MI and death
- minimise or abolish symptoms of angina thereby improving quality of life (QoL)

6.2 GENERAL MANAGEMENT
Lifestyle modification should be emphasised to all patients with SAP in addition to pharmacological measures and revascularisation. Symptoms can be improved in most patients with appropriate measures.

Upon comprehensive risk stratification (see section 5):
- patients and close relatives should be well-informed of the nature and prognosis of the disease as well as the implication of the diagnosis
- treatment goals and strategies should be discussed to improve compliance
- lifestyle risks should be identified and managed accordingly

6.2.1 Lifestyle modification
6.2.1.1 Smoking cessation
Smoking is strongly discouraged. This is the most important reversible risk factor. Smoking cessation greatly improves symptoms and prognosis. There was a 36% relative reduction in mortality and a 32% relative reduction in non-fatal MI for patients with CHD who quit smoking compared with those who continue to smoke.166

Nicotine replacement therapy is safe and helpful.167 If possible, patient should be referred to centres with expertise in smoking cessation because a structured smoking cessation program has a higher success rate than brief office advice.168
Table 8 below provides the list of available nicotine replacement therapy available in Malaysia.

Varenicline tartrate is now available and effective in smoking cessation. It has proven efficacy and safety in general population.\textsuperscript{166,170} The same treatment regime is advocated for CAD patients.\textsuperscript{171} However, there has been some safety concerns by Food and Drug Administration in the United States regarding the risk of depression and suicidal thoughts.

Clinicians may want to refer to Malaysia Clinical Practice Guidelines on Treatment of Tobacco Use and Dependence.\textsuperscript{172}

### Table 8. Nicotine replacement therapy available in Malaysia\textsuperscript{172}

<table>
<thead>
<tr>
<th>Nicotine Replacement Therapy</th>
<th>Recommended Regime</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicotine gum</td>
<td></td>
</tr>
<tr>
<td>• Nicorette® 2 mg</td>
<td>Use 2 mg gum for patients smoking less than 20 cigarettes per day</td>
</tr>
<tr>
<td>• Nicorette® 4 mg</td>
<td>Use 4 mg gum for patients smoking 20 or more cigarettes per day</td>
</tr>
<tr>
<td></td>
<td>Generally, the gum should be used for up to 12 weeks with no more than 24 pieces/day</td>
</tr>
<tr>
<td></td>
<td>Clinicians should tailor the dosage and duration of therapy to fit the needs of each patient</td>
</tr>
<tr>
<td>Nicotine patch 1. Nicorette®</td>
<td>Applied on skin as soon as the patient wakes on their quit day</td>
</tr>
<tr>
<td>2. Nicotinell®</td>
<td>Use 15 mg x 8 weeks, then 10 mg x 2 weeks and finally 5 mg x 2 weeks</td>
</tr>
<tr>
<td>• TTS10 (7 mg)</td>
<td>Applied on skin as soon as the patient wakes on their quit day</td>
</tr>
<tr>
<td>• TTS20 (14 mg)</td>
<td>For patient smokes &gt; 20 cig/day, use:</td>
</tr>
<tr>
<td>• TTS30 (21 mg)</td>
<td>• TTS30 for 1 - 4 weeks</td>
</tr>
<tr>
<td></td>
<td>• TTS20 for 5 - 8 weeks</td>
</tr>
<tr>
<td></td>
<td>• TTS10 for 9 - 12 weeks</td>
</tr>
<tr>
<td></td>
<td>For patient smokes &lt; 20 cig/day, use:</td>
</tr>
<tr>
<td></td>
<td>• TTS20 for 1 - 4 weeks</td>
</tr>
<tr>
<td></td>
<td>• TTS20 for 5 - 8 weeks</td>
</tr>
<tr>
<td></td>
<td>• TTS10 for 9 - 12 weeks</td>
</tr>
<tr>
<td>Nicotine inhaler (4 mg/cartridge)</td>
<td>6 - 16 cartridges/day up to 6 months of treatment</td>
</tr>
<tr>
<td></td>
<td>Taper dosage during the final 3 months of treatment</td>
</tr>
<tr>
<td>Varenicline tartrate</td>
<td>Day 1 - 3: 0.5 mg once daily</td>
</tr>
<tr>
<td></td>
<td>Day 4 - 7: 0.5 mg bd</td>
</tr>
<tr>
<td></td>
<td>Day 8 - end of treatment: 1 mg bd</td>
</tr>
<tr>
<td></td>
<td>Duration: 12 weeks. If successful stopped at 12 weeks, an additional course of 12 weeks treatment may be considered</td>
</tr>
<tr>
<td></td>
<td>Quit date is set 1 - 2 weeks before taking varenicline</td>
</tr>
</tbody>
</table>
6.2.1.2 Dietary control and fibre intake
Dietary intervention is an effective adjunct measure if properly implemented.\textsuperscript{173, 174} Healthy eating and appropriate dietary intervention have favourable effects on many CAD risk factors\textsuperscript{175} notably HPT, hypercholesterolaemia, obesity and DM.

Patients should be encouraged to adopt a healthy eating habit,\textsuperscript{176} which includes
- Eating a variety of fruits, vegetables, legumes, nuts, soy products, low-fat dairy products, and whole grain breads, cereals and pastas
- Minimising the intake of foods high in saturated and trans-fats, such as red meat, whole milk products, and pastries

Polyunsaturated fat is preferable to monounsaturated fat because it is associated with lower CV mortality in patients after MI.\textsuperscript{177-179} However, there has been no direct study on patients with stable CAD. Food high in polyunsaturated fat include:
- oily fish
- walnuts
- sesame and pumpkin seeds
- vegetable oils such as sunflower oil

The intensity of dietary changes is guided by abnormality of patients’ lipid profile, weight, DM and blood pressure (BP) control. An ideal body weight and waist circumference should be aimed for if achievable with appropriate calorie intake.

Clinicians may want to refer to the respective clinical practice guidelines for CV risk factors management.

\textit{Table 9. Targets for BMI}\textsuperscript{160}

<table>
<thead>
<tr>
<th>Group</th>
<th>BMI (kg/m\textsuperscript{2})</th>
<th>Risk of co-morbidities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight</td>
<td>&lt; 18.5</td>
<td>Low (but increased risk of other clinical problems)</td>
</tr>
<tr>
<td>Ideal</td>
<td>18.5 - 22.9</td>
<td>Average: target for BMI</td>
</tr>
<tr>
<td>Pre-obese</td>
<td>23.0 - 27.4</td>
<td>Increased</td>
</tr>
<tr>
<td>Obese I</td>
<td>27.5 - 34.9</td>
<td>Moderate</td>
</tr>
<tr>
<td>Obese II</td>
<td>35.0 - 39.9</td>
<td>Severe</td>
</tr>
<tr>
<td>Obese III</td>
<td>&gt; 40.0</td>
<td>Very severe</td>
</tr>
</tbody>
</table>

Targets for waist circumference (Malaysia Clinical Practice Guideline Clinical Practice Guidelines on Management of Obesity, 2003):\textsuperscript{160}
- Men < 85 cm
- Women < 80 cm

Increase intake of soluble fibres is encouraged because it has been shown to have a small but significant reduction in total cholesterol and LDL cholesterol level in meta-analysis among healthy subjects and high risk patients for CAD.\textsuperscript{161} Soluble fibre is found in oats, peas, beans, legumes (dhall, chickpeas, red beans and
green beans), apples, citrus fruits, carrots, and barley. High fibre intake was also associated with reduced risk of MI and death from CAD in cohort studies among healthy subjects.\textsuperscript{182, 183} Patients should be advised to increase total fibre intake by including 3 servings of vegetables and 2 servings of fruits daily. They should also increase whole grains such as brown rice, whole wheat breads and chapatti.\textsuperscript{184}

The benefit of soluble fibres should not be denied for patients with stable CAD despite insufficient evidence on the benefit of increasing fibre intake among patients with CAD.

6.2.1.3 Alcohol restriction
Alcohol intake at moderation may be beneficial in reducing the population risk of CV events.\textsuperscript{185} There is insufficient evidence to recommend alcohol consumption among patients with stable CAD. It is also generally difficult to quantify units of alcohol intake by general public.\textsuperscript{185, 187}

6.2.1.4 Physical activity
Patients should be encouraged to engage in physical activities within their limits. The minimal goal should be 30 mins, 3 - 4 days per week. Moderate intensity aerobic activities are recommended e.g. brisk walking.

Physical activity is beneficial on weight reduction, BP control, lipid abnormalities, glucose tolerance and insulin sensitivity. Several randomised control trials and meta-analysis have demonstrated improvement in mortality, symptoms and exercise tolerance with exercise programs.\textsuperscript{188-190}

Regular exercise is recommended, but individual fitness and severity of symptoms should be taking into consideration. Exercise stress test can assist in prescription of an appropriate exercise program.

<table>
<thead>
<tr>
<th>Recommendations for lifestyle modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking cessation: I, C</td>
</tr>
<tr>
<td>Dietary control &amp; fibre intakes:</td>
</tr>
<tr>
<td>• Healthy dietary choices: I, B</td>
</tr>
<tr>
<td>• Use of polyunsaturated fat: I, C</td>
</tr>
<tr>
<td>• Fibre intake: I, C</td>
</tr>
<tr>
<td>Moderate alcohol intake: I, C</td>
</tr>
<tr>
<td>Physical activity 30 mins 3 - 4 days per week: I, A</td>
</tr>
</tbody>
</table>

6.2.2 Health supplements
6.2.2.1 Omega-3 fatty acids
Omega-3 fatty acids are generally found in fish oil. Epidemiological studies in the populations showed that men who ate at least some fish weekly had a lower CAD mortality than men who ate none.\textsuperscript{191} Large control trials using up to 1 g of omega-3 fatty acids daily reduced the risk of sudden death in patients with recent MI.\textsuperscript{192, 193} However, there is no clear evidence of benefit among stable CAD patients.\textsuperscript{194}
6.2.2.2 Vitamins, anti-oxidants and other health supplements
Generally the use of vitamins, anti-oxidants, garlic and co-enzyme Q10 for stable CAD patient is not encouraged. There is generally lack of evidence for CV mortality benefit from these supplements. Morbidity benefit from co-enzyme Q10 was shown only among patients with CHF.

Recommendations for health supplements

<table>
<thead>
<tr>
<th>Use of omega-3 fatty acids</th>
<th>II, C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use of vitamins, anti-oxidants and other health supplements</td>
<td>III, A</td>
</tr>
</tbody>
</table>

6.2.3 Others
6.2.3.1 Psychological factors
Diagnosis of CAD often leads to excessive anxiety and depressions. Psychological factors may provoke attacks of angina and are associated with a higher risk of coronary mortality. Anxiety and depression should be actively screened for and treated. Cardiac rehabilitation and self-management empowerment has been shown to improve psychological, physical symptoms and functional status.

The patients should be properly educated on:
- Characteristic of their disease
- Personal risk factors
- Therapeutic lifestyle changes to address the risk factors
- Treatment goals and prognosis
- Action plan during an anginal attack

6.2.3.2 Sexual activity
Sexual activity is no more stressful to the heart than a number of other natural daily activities e.g. walking one mile (1.6 km) on the level in 20 minutes (Table 28). Patients who can engage in activities requiring METs score rating between 3 - 4 can safely resume non vigorous sexual activities because they have low cardiac risk. Patients who do not fulfill this criterion should be referred for further assessment by a specialist.

Sexual intercourse may trigger angina. GTN may be helpful prior to intercourse. Phosphodiesterase-5 (PDE-5) inhibitors can be prescribed safely but should not be used in those receiving any nitrates.

Table 9. METs score rating of some daily activities

<table>
<thead>
<tr>
<th>Daily activity</th>
<th>METs Score Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sexual intercourse with regular partner</td>
<td>2 - 3</td>
</tr>
<tr>
<td>• lower range (&quot;normal&quot;)</td>
<td>5 - 6</td>
</tr>
<tr>
<td>• upper range (vigorous activity)</td>
<td>4 - 5</td>
</tr>
<tr>
<td>Lifting and carrying objects (9 - 20 kg)</td>
<td>3 - 4</td>
</tr>
<tr>
<td>Walking one mile in 20 minutes on the level</td>
<td>4 - 5</td>
</tr>
<tr>
<td>Golf</td>
<td>3 - 5</td>
</tr>
<tr>
<td>Gardening (digging)</td>
<td>4 - 5</td>
</tr>
<tr>
<td>DIY, wallpapering, etc.</td>
<td>4 - 5</td>
</tr>
<tr>
<td>Light housework (e.g. ironing, polishing)</td>
<td>2 - 4</td>
</tr>
<tr>
<td>Heavy housework (e.g. making beds, scrubbing floors)</td>
<td>3 - 6</td>
</tr>
</tbody>
</table>
6.2.3.3 Employment
Patient should be encouraged to continue their occupation with appropriate adjustment as necessary to avoid angina episodes.

6.2.3.4 Heavy vehicle driving
Patients are prohibited to drive commercial public transport/heavy vehicles if they are symptomatic or suffer from complications of CAD like CHF and arrhythmias.²⁰⁴

<table>
<thead>
<tr>
<th>Recommendations for others</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychological factors</td>
<td>I, B</td>
</tr>
<tr>
<td>Sexual activity</td>
<td>I, B</td>
</tr>
<tr>
<td>Heavy vehicle driving</td>
<td>III, C</td>
</tr>
</tbody>
</table>

6.2.4 Hypertension (HPT), Diabetes Mellitus (DM) and other disorders
Concomitant HPT, DM and other features of metabolic syndrome should be addressed as these are major risk factors to CAD.²⁰⁵

The target BP for patients with CAD is < 130/80 mmHg.²¹,²² Beta-blockers, ACEIs²⁰⁹-²¹³ and long acting CCBs,²⁸ are the drugs of choice. Pharmacological intervention is necessary if target is not achieved upon diagnosis.

DM should be managed carefully with the target HbA1c < 6.5%.²³⁹ The target level for HbA1c must be individualised based on risks of hypoglycaemia and quality of life.²³⁹,²¹⁰ Hypoglycaemia must be avoided as it may precipitate anginal attack and increase mortality.²¹¹

Hypercholesterolaemia should be controlled to target (Table 10). Please refer to Clinical Practice Guidelines on Dyslipidaemia 2003.²¹²

<table>
<thead>
<tr>
<th>Table 10. Targets for cholesterol levels²⁷²</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL cholesterol</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>HDL cholesterol</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Triglyceride</td>
</tr>
</tbody>
</table>

Note:
- In patients with triglyceride of > 2.3 mmol/l, a non-HDL cholesterol of ≤ 3.4 mmol/l should be aimed for.
- It should be emphasised that LDL-cholesterol is the primary target of therapy. HDL-C and triglyceride are the secondary targets.

Anaemia and hyperthyroidism, if present should be corrected.
6.3 PHARMACOLOGICAL TREATMENT OF STABLE ANGINA PECTORIS (SAP)

The goals of:
1. Acute treatment are:
   - Relieve symptoms
   - Prevent provokable angina
2. Long-term treatment are:
   - Improve prognosis (Reduction in CV events)
   - Improve QoL by reducing severity and frequency of anginal attacks

6.3.1 Acute treatment

Self-management during an acute attack of angina:
During an acute attack of angina, patient is advised to
- rest and refrain from provoking activities
- take sub-lingual/buccal GTN (tablet or spray)
- sit in order to protect against potential harm of hypotension upon use of GTN and should be warned of possible side effect of headache

Patient can be encouraged to use prophylactic GTN to prevent predictable episodes. Medical advice should be sought if symptoms persist > 10 minutes after resting and/or is not relieved by three GTN.

6.3.2 Long-term treatment
Pharmacological strategies are:
6.3.2.1 Anti-thrombotic agents

6.3.2.1.1 Low dose Aspirin
Aspirin inhibits COX-1 and thromboxane production and remains the main pharmacological prevention of arterial thrombosis. Use of low dose Aspirin (75 mg)\(^{22}\) in stable angina and silent ischaemia are associated with lower incidence of MI, cardiac death or stroke.\(^{218}\)

Dosage of Aspirin should be the lowest effective to optimise the balance between therapeutic gains and gastrointestinal side effects during chronic therapy. The optimal anti-thrombotic dosage of aspirin appears to be 75 - 150 mg/day. The SAPAT trial showed a 34% reduction of MI or cardiac death with aspirin 75 mg/day compared with placebo in sotalol-treated patients with stable angina pectoris.\(^{26}\)

6.3.2.1.2 Thienopyridines
Clopidogrel and Ticlopidine are thienopyridines which act as non competitive ADP receptor antagonist with similar antithrombolic effects of aspirin.\(^{229}\)

**Clopidogrel**

Clopidogrel 75 mg daily is more effective compared to aspirin alone in preventing CV complication in high risk patient especially in the peripheral vascular disease arm.\(^{29}\) Combination of aspirin and Clopidogrel is not warranted in SAP.
Ticlopidine
Ticlopidine efficacy has been documented in stroke and PCI. However, there are no large clinical trials to support the use of Ticlopidine in SAP. Ticlopidine has 1-2% risk of neutropenia and thrombocytopenia and other symptomatic side effects.

6.3.2.1.3 Other anti-thrombotic agents
Dipyridamole
Dipyridamole is not recommended for anti-thrombotic treatment in SAP due to poor anti-thrombotic efficacy and the risk of worsening angina symptoms due to coronary steal phenomena. 222, 223

Anticoagulation
Anticoagulant drugs (warfarin or thrombin inhibitor) are not indicated in SAP without a separate indication such as AF.

6.3.2.2 Lipid Lowering Therapy
Statin therapy has been shown to reduce CV events and mortality by 20-30%. 224 There has been no statin trials specifically for patients with SAP. However, the HPS trial 226 has shown a reduction in chest pain and the need for revascularisation in patients with stable CAD. These benefits were seen irrespective of age, gender and baseline LDL-C levels.

Many of the statin benefits could not be explained by LDL-C lowering alone and is thought to be due to the pleiotropic effects of statins. 226-228

The NCEP ATP III guidelines 229 and the Malaysia Lipid CPG 2004 230 recommended target LDL-C of <2.6 mmol/l in CAD or CAD-risk equivalent patients. The updated ATP III guideline in 2004 229, recommended a target of LDL-C < 1.8 mmol/l in high risk CAD patients. The 2007 update of the ACC/AHA guideline for the management of patients with SAP 236 recommends this level as reasonable for all patients with SAP.

Recent trials 231, 232 have shown aggressive LDL-C reduction with high-dose statin could halt plaque progression and induce plaque regression respectively.

If the LDL-C target is not achieved with the maximum tolerable dose of statins, the addition of a cholesterol absorption inhibitor, ezetimide may be useful.

Many statin-treated patients continue to have recurrent CV events. This residual risk could partly be explained by other dyslipidaemic parameters e.g. low-HDL-C and high TG, especially in patients with metabolic syndrome and T2DM. Improvement in these non-LDL-C fractions and possible reduction of CAD events 235, 236 could be achieved with the addition of a fibrate or nicotinic acid. Combination therapy with fibrates may increase adverse effect 235, 236 There is insufficient data to recommend a target HDL-C or triglyceride level in patients with SAP.
6.3.2.3 ACE-Inhibitors (ACEIs)

There are benefits of ACEIs in secondary prevention especially in post-MI patients with depressed LV function (LVEF < 40%).

Recent trials have investigated the use of ACEI in CAD patients without LVD. The HOPE trial (using Ramipril 10 mg daily against placebo) and EUROPA trial (using Perindopril 8 mg daily against placebo) showed 20% reduction in composite primary endpoints (CV death, MI + stroke/cardiac arrest).

The PEACE trial utilising Trandolapril 4 mg against placebo did not show benefit in low risk patients (normal LVEF in whom CV risk factors are well controlled and revascularisation has been performed).

However 2 large meta-analyses have shown favourable effect of ACEIs on the outcome in CAD patients with preserved LV systolic function.

Therefore, ACEI is recommended for all patients with CAD especially when there is concomitant LV dysfunction or DM.

6.3.2.4 Angiotensin Receptor Blockers (ARBs)

The effects of ARB on prognosis in IHD is less well studied and more controversial. There has been no specific ARB-intervention trial for patients with SAP.

The significant incidence of ACEI-induced cough (up to 20% especially in Asian and Black populations) has encouraged the use of ARBs in patients with CVD.

In the landmark ONTARGET trial involving 25,260 patients aged 55 years and above with CAD or DM plus additional risk factors with no evidence of CHF, telmisartan was “non-inferior” to ramipril in achieving the composite endpoints of CV death, MI, stroke, or hospitalisation for CHF. The combination of the two drugs was associated with more adverse events without an increase in benefit.

In the TRANSCEND trial involving 5,926 patients with CV disease or high-risk DM without CHF who were intolerant to ACEI, telmisartan was no better than placebo in improving the primary composite end point of CV death, MI, stroke, or admission to the hospital for CHF events. There was however benefits in the prespecified secondary outcome of CV death, MI, and stroke.

Based on current evidence, ARBs may be considered as secondary prevention therapy in CAD patients with HPT, CHF, post MI with left ventricular dysfunction (LVD) and diabetics when ACE-Inhibition is indicated but not tolerated.

6.3.2.5 Heart Rate (HR) reducing agents

Beta-blockers and HR-reducing non-dihydropyridine calcium channel blockers (CCB) have been the mainstay of pharmacological treatment to achieve HR reduction. We also know that almost two-thirds of patients continue to experience an average of two angina episodes per week despite simultaneous use of multiple anti-anginal drugs.
6.3.2.5.1 Beta-Blockers

Beta-blockers are the first line treatment in patients with SAP. Beta-blockers act by competitively inhibiting catecholamines from binding to β1, β2 and β3 receptors. The risk of CV death or MI was reduced by 30% with the use of beta-blockers in post-MI trials. It has been extrapolated that beta-blockers may be cardioprotective in patients with stable CAD.

A meta-regression analysis of effects of different beta-blockers on mortality found non significant benefits of acute treatment. However, a 24% relative risk reduction of mortality was noted with long-term secondary prevention.

β1 blockade by metoprolol or bisoprolol reduces cardiac events in CHF patients while carvedilol, a non-selective beta-blocker also reduces risks of death and CV hospitalisations in CHF. There is a lack of evidence showing benefits in this group of patients using atenolol.

6.3.2.5.2 Ivabradine

Several studies have shown a compelling correlation between elevated HRs and both all-cause as well as CV mortality in the general population and CAD patients. This relationship is independent of other risk markers.

HR reduction may reduce angina by reducing myocardial oxygen consumption and by increasing diastolic perfusion time.

Ivabradine is a first in its class of agent that acts primarily on the SA node via blockade of the ‘funny’ If current. It achieves HR reduction without significant negative inotropic effect and other adverse effects associated with beta-blocker use. Common side effects include sinus bradycardia and reversible visual disturbances. There is no significant interaction with various cardiac drugs e.g. ACEIs, ARBs, warfarin, amiodarone, anti-platelet agents, cholesterol lowering agents, digoxin and diuretics.

The INITIATIVE study showed that ivabradine is as effective as atenolol in improving ischaemia endpoints in patients with SAP. In the BEAUTIFUL study, ivabradine significantly reduced ischaemic end-points of hospitalisation for fatal and non-fatal MI and the need for coronary revascularisation in patients with stable CAD, moderate LV dysfunction and HR > 70 bpm.

Ivabradine may be considered for symptomatic treatment of SAP in patients with normal sinus rhythm, especially in those who have a contraindication to or intolerance to beta-blockers. It may also be used in combination with beta-blockers in patients whose resting HR remains high.

6.3.2.5.3 Non-dihydropyridine Calcium Channel Blockers (CCBs)

HR-lowering CCBs - diltiazem and verapamil may be used as an alternative to beta-blockers in patients without CHF who do not tolerate beta-blockers.
The APSIS trial comparing metoprolol CR against verapamil SR showed similar CV event rates in both groups of patients with SAP especially in females without DM.  

6.3.2.6 Calcium Channel Blockers (CCBs)
CCBs act by blocking calcium channels in muscle cells of the heart and blood vessel, resulting in vasodilatation, increasing coronary blood flow and decreasing the myocardial oxygen demand. The non-dihydropyridine CCBs have an additional effect of reducing HR.

Randomised clinical trials comparing CCB and beta-blockers have demonstrated that CCB are generally as effective as beta blockers in relieving angina and improving exercise time to onset of ischaemia or angina.

6.3.2.6.1 Dihydropyridine Calcium Channel Blockers (CCBs)
Earlier trials of short acting nifedipine showed no prognostic benefit regarding in CAD patients. In the ABCD trial, the use of nisoldipine, a short acting dihydropyridine CCB, was associated with a higher incidence of fatal and nonfatal MI compared with enalapril. A meta-analysis of 16 trials using immediate release and short acting nifedipine in MI and UA reported a dose related influence on excess mortality. The use of short acting dihydropyridine CCB as monotherapy is discouraged.

Long acting dihydropyridine CCB may be safe as shown in the ACTION trial, with less coronary interventions in the CCB group but no reduction in the composite endpoints of death, MI, refractory angina, debilitating stroke CHF.

6.3.2.6.2 Non-dihydropyridine Calcium Calcium Channel Blockers (CCBs)
See section 6.3.2.5.3

6.3.2.7 Nitrates
Nitrates are both venous and arterial dilators. It reduces myocardial oxygen demand via its reduction of LV volume and arterial pressure via preload reduction. The vasodilatory effect on epicardial arteries and collateral vessels improves the oxygen supply.

The clinical benefits of nitrates are mainly seen in symptom improvement e.g. reduction of angina episodes, improvement in exercise tolerance and increase in time to onset of ischaemia. It has no prognostic benefit.

Rapidly acting formulation of nitroglycerin provides effective symptoms relief of angina pectoris and maybe used for situational prophylaxis.

The anti-ischaemic effect is additive when used in combination with other antianginal medications e.g. beta-blockers and CCB.

Long-acting nitrates reduces the frequency and severity of anginal attacks and may increase exercise tolerance. These drugs failed to show prognostic benefit and are
only for symptomatic relief of angina, e.g. isosorbide-5-mononitrate. The long acting-nitrates come in tablet, transdermal patch and ointment formulations.

Nitrate tolerance may develop if used continuously resulting in breakthrough angina. Hence, nitrate-free periods (8 - 12 hours) are encouraged. Rebound angina may happen during this nitrate-free interval.

Nitrates should be used with caution in patients with severe hypertrophic obstructive cardiomyopathy and severe aortic stenosis. PDE5-inhibitor use is contraindicated in patients who are on nitrate therapy. The most common side effect is headache.

6.3.2.8 Trimetazidine
Trimetazidine inhibits 3-KAT (3-ketoacyl CoA thiolase) enzyme in myocardial cells. This optimises cardiac metabolism by switching energy substrate preference from fatty acid oxidation to glucose oxidation which is a more efficient pathway for ATP production. This promotes a favourable demand versus (vs) supply balance in myocardial oxygen need.

Trimetazidine has been shown to be effective in providing angina symptom relief, reduction in the need for nitrates and improving functional capacity in patients with angina. It is useful whether as monotherapy or in combination with other anti-ischaemic agents.

It is also safe and effective in patients with ED. Therefore, it allows angina symptom relief and concomitant treatment with PDE5-inhibitor for the Erectile Dysfunction (ED).

### Recommendations for pharmacological therapy to improve prognosis in SAP

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Level of evidence</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin 75 mg daily in all patients, if not contraindicated</td>
<td>I, A</td>
<td></td>
</tr>
<tr>
<td>Clopidogrel as alternative to those intolerant to Aspirin</td>
<td>IIa, B</td>
<td></td>
</tr>
<tr>
<td>ACEIs for all patients with CAD</td>
<td>IIa, A</td>
<td></td>
</tr>
<tr>
<td>ACEIs in CAD patients with other indications for ACEIs (HPT, HF, LVD, prior MI with LVD, DM)</td>
<td>I, A</td>
<td></td>
</tr>
<tr>
<td>ACEIs in all CAD patients with preserved LV systolic function</td>
<td>IIa, B</td>
<td></td>
</tr>
<tr>
<td>ARBs in CAD patients when ACEIs is indicated but not tolerated (HPT, CHF, post MI with preserved LVD, DM)</td>
<td>IIa, A</td>
<td></td>
</tr>
<tr>
<td>Oral beta-blockers (Bisoprolol, Carvedilol, Metoprolol) in post MI or CHF</td>
<td>I, A</td>
<td></td>
</tr>
<tr>
<td>Statins for all CAD patients</td>
<td>I, A</td>
<td></td>
</tr>
<tr>
<td>High dose statins in high risk patients</td>
<td>IIa, B</td>
<td></td>
</tr>
<tr>
<td>Fibrate or nicotinic acid as adjunct to statin for improvement of non LDL-C fractions</td>
<td>IIb, C</td>
<td></td>
</tr>
</tbody>
</table>
Recommendations for pharmacological therapy to improve symptoms and/or reduce ischaemia in patient with SAP

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Level</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short acting nitroglycerin for acute treatment/situational prophylaxis</td>
<td>I, B</td>
<td></td>
</tr>
<tr>
<td>Beta1-blocker: titrate according to symptoms and HR</td>
<td>II, A</td>
<td></td>
</tr>
<tr>
<td>If intolerant to beta-blocker, attempt monotherapy with</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Non-dihydropyridine CCB</td>
<td>I, A</td>
<td></td>
</tr>
<tr>
<td>- Long acting nitrates</td>
<td>I, C</td>
<td></td>
</tr>
<tr>
<td>- Ivabradine</td>
<td>IIa, B</td>
<td></td>
</tr>
<tr>
<td>If beta-blockers monotherapy insufficient add</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Long acting dihydropyridine CCB</td>
<td>I, B</td>
<td></td>
</tr>
<tr>
<td>- Ivabradine</td>
<td>IIa, B</td>
<td></td>
</tr>
<tr>
<td>Trimetazidine (add on/substitution)</td>
<td>IIb, B</td>
<td></td>
</tr>
</tbody>
</table>

6.3.3 Other medical therapy

6.3.3.1 NSAIDS and COX 2 inhibitors

NSAIDS and selective COX 2 inhibitors may increase the risk of CV complications. They should be used in the lowest effective dose and for the shortest possible duration. If analgesia is needed, it is recommended to use Non NSAIDS analgesics e.g. paracetamol or opiates. If NSAIDS and COX 2 are unavoidable, they should be used in combination with low dose Aspirin.

6.4 MYOCARDIAL REVASCULARISATION

Revascularisation in patients with stable CAD confers prognostic benefit in the following high risk group of patients, and therefore should be considered as a first line treatment, along with optimal medical therapy.185, 280

1. Significant Left main stem (LMS) disease (> 50% stenosis).
2. Significant proximal multi-vessel disease with angina symptoms or in which large area of ischaemia has been demonstrated on functional testing.
3. Multi-vessel disease with impaired LV function with proven viable myocardium.

In all other conditions, revascularisation may be offered following failure of optimal medical therapy to control symptoms.281, 282 In asymptomatic patients, revascularisation may be offered in the presence of extensive inducible ischaemia or viable myocardium on functional tests.283

Revascularisation in patients with stable CAD may be accomplished by

- Percutaneous Coronary Intervention (PCI)
- Coronary Artery Bypass Grafting (CABG)
6.4.1 Percutaneous Coronary Intervention (PCI)

PCI is established as the less invasive procedure compared to CABG with lower procedure-related mortality (0.3 - 1.0%). The advance in drug-eluting stents (DES) has led to improved long-term results. Reported rate of 9-month major adverse cardiac events range between 7.1 to 10.3% in patients treated with DES, in contrast to bare metal stents rate between 13.3 to 18.9%. There has been some concerns regarding the safety of DES, in particular late stent thrombosis. However, Sheishanbor et al. reported in a prospective PCI patient registry at Cleveland Clinic involving over 8,000 patients implanted with DES or bare metal stent (BMS), there was a significantly lower mortality in the DES group (8% vs. 17%) at an average follow-up of 4.5 years. This recent findings served as a reassurance on the safety of DES, though experts still advise caution on the small but real risk of late stent thrombosis.

6.4.2 Coronary Artery Bypass Grafting (CABG)

CABG is known for its long-term established data on outcome in the above high risk groups especially in the presence of DM or concurrent valvular disease. This is particularly true when arterial grafts are used. Typically, the internal mammary graft has a patency rate of about 90% at ten years post-CABG. As for vein grafts, the patency rate ranges between 60 - 70% at 10 years. Patients who are deemed suitable for surgery must be thoroughly evaluated and informed of the risk. In uncomplicated patients with normal LV function and no other co-morbidity, the reported mortality rate is under 3%.

6.4.3 Percutaneous Coronary Intervention (PCI) vs. Coronary Artery Bypass Grafting (CABG)

Meta-analysis comparing PCI with CABG demonstrated similar mortality rates in both groups. In the CABG group, there was a significantly higher proportion of patients who remained symptom-free. There was also lower requirement for repeat revascularisation. The BARI trial showed significantly lower 5-year mortality in diabetics undergoing CABG compared to PCI. Recent Registry Data (New York State) comparing DES vs. CABG also showed a mortality difference in favour of CABG in patients with multi-vessel disease. SYNTAX randomised 1,800 patients with documented multi-vessel CAD including LM stenosis to CABG or PCI. One year follow-up from the study demonstrated comparable outcomes in composite end points between the two strategies including the subset of patients with LMS. PCI resulted in a higher rate of repeat revascularisation (13.7% vs. 5.9%). CABG resulted in a higher rate of stroke (2.2% vs. 0.6%).

Evidence is now emerging regarding efficacy and safety of LMS stenting, particularly with DESs. In low risk patients with ostial or body of LMS stenosis, PCI may be offered as an alternative (IIb, B). In LMS bifurcation, CABG should be preferred except when patients refused surgery following thorough explanation, or when the risk of surgery is unacceptable. Overall, there is still limited long-term data regarding PCI in LMS. Therefore, PCI of LMS cannot be routinely recommended. In patients with significant LMS disease who decline surgery (after a thorough consultation), PCI with complete revascularisation may be offered. PCI of LMS should only be carried out at experienced centres by experienced interventional cardiologists.
In all cases of decision making in revascularisation, centre expertise in PCI and CABG procedure must be taken into account with the emphasis on collaboration between cardiologists and cardiothoracic surgeon. Prior to revascularisation procedures, patients must be thoroughly informed of the associated risk of mortality and morbidity, as well as long-term results.19

It should be emphasised that optimal medical therapy should be offered to all patients regardless whether or not they undergo revascularisation. In patients who have undergone PCI, antiplatelet therapy should be maintained according to the standard guidelines.298

The following table summarises the recommendations:281, 282, 283, 286, 300

<table>
<thead>
<tr>
<th>Indication for PCI</th>
<th>For symptom</th>
<th>For prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angina with one vessel disease</td>
<td>I, A</td>
<td></td>
</tr>
<tr>
<td>Angina with multi-vessel disease (non-DM)</td>
<td>I, A</td>
<td></td>
</tr>
<tr>
<td>Angina with minimal symptom but inducible ischaemia proven</td>
<td>Iib, B</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Indication for CABG</th>
<th>For symptom</th>
<th>For prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angina with LMS disease</td>
<td>I, A</td>
<td>I, A</td>
</tr>
<tr>
<td>Angina with 3VD and:</td>
<td>I, A</td>
<td>I, A</td>
</tr>
<tr>
<td>1) Inducible ischaemia or</td>
<td>I, A</td>
<td>I, A</td>
</tr>
<tr>
<td>2) Poor LV function or</td>
<td>I, A</td>
<td>I, A</td>
</tr>
<tr>
<td>3) Involving proximal LAD</td>
<td>I, A</td>
<td>I, A</td>
</tr>
<tr>
<td>Angina and multi-vessel disease (DM)</td>
<td>I, A</td>
<td>Ila, B</td>
</tr>
<tr>
<td>Angina and multi-vessel disease (no DM)</td>
<td>I, A</td>
<td></td>
</tr>
</tbody>
</table>

6.4.4 Revascularisation vs. medical therapy

Review of data from earlier trials suggested that whenever revascularisation was compared to optimal medical therapy, there were no significant difference in the outcome, with the exception of CABG in diabetic patients with multi-vessel disease.294, 301, 302 Two recently published trials have again reaffirmed the importance of optimal medical therapy. The COURAGE trial concluded that initial strategy of PCI in patients with proven coronary artery disease did not provide incremental clinical benefit over optimal medical therapy.267 BARI 2D trial in diabetic patients with multi-vessel disease concluded that medical therapy offered similar survival advantage comparing to revascularisation; with the only exception of CABG - showing lower incidents of non-fatal reinfarction.303

This data provides strong evidence on the importance of optimal medical therapy in all CAD patients - which should include antiplatelet, statin, beta-blocker and RAAS inhibitors. In a majority of patients optimal medical therapy is an excellent initial treatment strategy, particularly those with less severe disease.
6.5 SPECIAL SUBGROUPS

6.5.1 Women
6.5.2 Diabetes Mellitus (DM)
6.5.3 Elderly
6.5.4 Chronic refractory angina

6.5.1 Women

CVD is the main cause of death among women both worldwide and in Malaysia. In Malaysia it accounts for 25% of all female deaths in government hospitals. There are also numerous differences in the epidemiology of CAD between men and women. There is a significantly lower age-specific risk of CAD in women than men. Risk of death due to CAD in women is roughly similar to that of men 10 years younger. Despite their marked advantage in age-specific risk of CAD death, the greater likelihood of survival of women to advanced ages produces nearly equal numbers of actual deaths due to CAD in men and women.

SAP is the most common presentation in women as compared to ACS and sudden death in men. However, women suffering from MI have a higher mortality and morbidity compared to men. This poorer prognosis is most likely due to severity of illness, increased age at presentation, and co-morbidity in women. In-hospital mortality was 13% for women vs. 7% for men. Cumulative mortality at 48 months was 36% for women vs. 21% for men.

6.5.1.1 Clinical evaluation

Evaluation of chest pain in women is less straightforward due to:
- Gender differences in presentation and disease manifestation
- SAP being the most frequent initial manifestation of CAD in women
- MI or sudden death is the most frequent initial manifestation in men
- Incidence of angina in women being higher than men in the post-menopausal age group
- Incidence of fatal CAD being higher in men with angina than women with angina
- Preponderance of male specific data in literature

6.5.1.2 Diagnosis

6.5.1.2.1 Clinical evaluation

The diagnosis of angina in women is more difficult for the following reasons:
- Atypical symptoms are more common in women
- Correlation between symptoms and ‘significant’ luminal obstruction at coronary angiography is weaker in women
- Angina may be associated with ischaemia in Syndrome X, in the absence of obstructive coronary lesion
- Microvascular disease and coronary vasospasm are more common in women
- Ischaemia may be shown by ECG, perfusion study or other methods in these patients

6.5.1.2.2 Stress testing

- Exercise ECG testing has higher false positive rates in women (38 - 67%) than in men (7 - 44%)
• However exercise ECG testing has lower false-negative rates in women resulting in a higher negative predictive value
• Only 30% of women need to be referred for further testing
• Stress echo is an independent predictor of cardiac events in women with known or suspected CAD
• Sensitivity of Thallium radionuclide perfusion scan may be lower in women

These patients may respond to anti-ischaemic therapy without angiographic evidence of epicardial stenosis.

6.5.1.3 Treatment
• Women tend to present at an older age and have a higher morbidity and mortality after MI than men
• Less vigorous treatment in women may impact on reduced survival
• Women should be treated no less aggressively than men

(For further information, please refer to Clinical Practice Guidelines on Prevention of Cardiovascular Disease in Women 2008)\textsuperscript{307}

6.5.2 Diabetes Mellitus (DM)
Diabetes Mellitus (DM) is associated with an increased risk of CVD. CAD mortality is increased by three fold in diabetic men and two to five fold in diabetic women.\textsuperscript{308-310} Prevalence of asymptomatic ischaemia is increased in patient with DM.\textsuperscript{311}

Symptoms occur at an earlier age in diabetics. In symptomatic diabetic patients, risk stratification strategy should follow that of non-diabetics. Diabetics may have subclinical ventricular dysfunction which negatively impacts on exercise capacity.\textsuperscript{312}

In patients with diabetes, the higher the blood glucose the greater the incidence of CVD.\textsuperscript{313, 314} There is firm evidence of prognostic power of perfusion imaging in diabetic patients.\textsuperscript{315}

Conventional therapies for CAD with nitrates, beta-blockers, CCBs, statins, anti-platelets and coronary revascularisation have similar indications in diabetic and non-diabetic patients.\textsuperscript{19}

Due to the chronic metabolic disturbances, patients have continuous progression of native atherosclerotic disease. This leads to extensive CAD with high rates of multi-vessel disease and restenosis.\textsuperscript{316, 317}

DM management should include:
• lifestyle and pharmacotherapy measures to achieve a near-normal HbA1c (l, B)\textsuperscript{226}
• long-term maintenance of near-normal blood glucose levels which substantially reduces complications and mortality in both DM types\textsuperscript{316-321}
• vigorous modification of other risk factors (e.g. physical activity, weight management, BP control, and cholesterol management) (l, B)\textsuperscript{230}
• ACEI unless contraindicated (l, A)\textsuperscript{113}
Even after successful invasive procedures, good management of CVD risk factors and a tight glycaemic control are essential for good long-term outcome.\(^{310}\)

### 6.5.3 Elderly

After the age of 75 there is equal prevalence of CAD in men and women.\(^{202}\)

Complaints of chest discomfort, weakness and dyspnoea are common and evaluation of chest pain can be difficult. Co-morbidities that mimic SAP are common (e.g. gastroesophageal reflux disease).

#### 6.5.3.1 Exercise stress ECG in the elderly

- Exercise testing may be problematic due to muscle weakness and deconditioning
- Less challenging exercise stress ECG protocols may be more appropriate\(^{220}\)
- Arrhythmias are more common at higher exercise stress ECG workload\(^{924}\)
- Higher false negative rates due to higher prevalence of disease
- Higher false positive rates due to higher prevalence of confounders including prior MI, conduction disturbances, HPT and LVH from valvular diseases

However exercise testing remains important in the elderly despite these differences.

#### 6.5.3.2 Coronary angiography

- Elderly patients with objective evidence of moderate to severe ischaemia at non-Invasive testing should have similar access to coronary arteriography as younger patients\(^{19}\)
- Diagnostic coronary arteriography has relatively little increased risk in elective evaluation\(^{101}\)
- The disease is more likely to be diffuse and severe
- LMS stenosis, 3VD and impaired LV function are more prevalent
- Age > 75 years is an important predictor of contrast-induced nephropathy\(^{225}\)

#### 6.5.3.3 Treatment

Issues in medical treatment are dose modification, drug interactions, polypharmacy and compliance.\(^{226}\) Elderly patients have the same benefit from medical therapy, angioplasty and bypass surgery as younger patients.\(^{227-229}\)

Management of the elderly should be individualised taking into account co-morbidities and not based on age alone.

#### 6.5.4 Chronic refractory angina

Chronic stable refractory angina can be defined as a clinical diagnosis based on the symptoms of SAP, caused by ischaemia due to advanced CAD which is not controlled by a combination of maximal medical therapy, CABG and PCI.

Most common reasons why revascularisation is not considered:
- Unsuitable anatomy
- One or several previous CABG and/or PCI
- Lack of available graft conduits
- Extra-cardiac diseases with increased perioperative morbidity and mortality
- Advanced age, in combination with the above factors
Treatment requires optimisation of medical treatment including the use of different drugs in maximal tolerated doses.

New treatment modalities under extensive evaluation:
- Neuromodulation techniques (transcutaneous electric nerve stimulation and spinal cord stimulation)
- Thoracic epidural anaesthesia
- Endoscopic thoracic sympathectomy
- Stellate ganglion blockade
- Angiogenesis
- Enhanced external counterpulsation (EECP)
- Extracorporeal shockwave myocardial revascularisation (ESMR)
- Transmyocardial (TMR) or percutaneous laser revascularisation
- Heart transplantation
- Drugs that modulate metabolism

Neuromodulation techniques have a favourable analgesic effect with increased exercise time on treadmill but the clinical trials are small and long-term effects unknown.\textsuperscript{330-332}

EECP has been evaluated for safety and effectiveness in two multi-centre registries and anginal symptoms improved in 75 - 80% of patients.\textsuperscript{333-334}

ESMR has also been evaluated for safety and symptom relief in a few small studies with promising results.\textsuperscript{335-337}

TMR shown conflicting results in various studies with a recent randomised controlled trial showing no benefit\textsuperscript{338} and no evidence of increased perfusion by PET in another study.\textsuperscript{339}

Chelation therapy (intravenous infusion of ethylenediamine tetraacetic acid or EDTA is not recommended for the treatment of chronic angina or atherosclerotic cardiovascular disease and may be harmful because of its potential to cause hypocalcaemia.\textsuperscript{340}
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### Appendix 1

**Table 11. Probability of coronary disease in symptomatic patients based on (a) age, gender, and symptom classification and (b) modified by exercise test result**

(a) Pre-test likelihood of CAD in symptomatic patients according to age and sex

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Typical angina</th>
<th>Atypical angina</th>
<th>Non-anginal chest pain</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
<td>Male</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
<td>Male</td>
</tr>
<tr>
<td>30 - 39</td>
<td>69.7 ± 3.2</td>
<td>25.8 ± 6.6</td>
<td>21.8 ± 2.4</td>
</tr>
<tr>
<td></td>
<td>5.2 ± 0.8</td>
<td>0.8 ± 0.3</td>
<td>0.8 ± 0.3</td>
</tr>
<tr>
<td>40 - 49</td>
<td>87.3 ± 1.0</td>
<td>55.2 ± 6.5</td>
<td>46.1 ± 1.8</td>
</tr>
<tr>
<td></td>
<td>14.1 ± 1.3</td>
<td>2.8 ± 0.7</td>
<td>0.8 ± 0.3</td>
</tr>
<tr>
<td>50 - 59</td>
<td>92.0 ± 0.6</td>
<td>79.4 ± 2.4</td>
<td>58.9 ± 1.5</td>
</tr>
<tr>
<td></td>
<td>21.5 ± 1.7</td>
<td>8.4 ± 1.2</td>
<td>7.6 ± 1.9</td>
</tr>
<tr>
<td>60 - 69</td>
<td>94.3 ± 0.4</td>
<td>90.1 ± 1.0</td>
<td>67.1 ± 1.3</td>
</tr>
<tr>
<td></td>
<td>28.1 ± 1.9</td>
<td>18.6 ± 1.9</td>
<td>7.6 ± 1.9</td>
</tr>
</tbody>
</table>

(b) CAD post-test likelihood (%) based on age, sex, symptom classification, exercise-induced electrocardiographic ST-segment depression

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>ST-Depression (mv)</th>
<th>Typical angina</th>
<th>Atypical angina</th>
<th>Non-anginal chest pain</th>
<th>Asymptomatic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
<td>Male</td>
<td>Female</td>
<td></td>
</tr>
<tr>
<td>30 - 39</td>
<td>0.00 - 0.04</td>
<td>25</td>
<td>7</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>0.05 - 0.09</td>
<td>68</td>
<td>24</td>
<td>21</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>0.00 - 0.14</td>
<td>83</td>
<td>42</td>
<td>38</td>
<td>9</td>
</tr>
<tr>
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### Recommendations for routine non-invasive investigations in evaluation of SAP

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<td>Fasting lipid profile</td>
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<td>Suspected vasospastic angina</td>
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<td>Suspected CHF or abnormal cardiac auscultation</td>
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<td>Previous MI</td>
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<td>Intermediate or low risk patient not due to have alternative assessment of LV function</td>
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<td><strong>Exercise ECG</strong></td>
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<td>First line for initial evaluation, unless unable to exercise/ECG not evaluable</td>
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<td>Patients with known CAD and significant deterioration in symptoms</td>
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<td>Routine periodic testing once angina controlled</td>
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<td><strong>Exercise imaging technique (echo or radionuclide)</strong></td>
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<td>Initial evaluation in patients with uninterpretable ECG</td>
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<td>Angina post-revascularisation</td>
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<td>To identify location of ischaemia in planning revascularisation</td>
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<td>Assessment of functional severity of intermediate lesions on arteriography</td>
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<td><strong>Pharmacological stress imaging technique</strong></td>
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<td>Patients unable to exercise</td>
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<td>I, B</td>
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<td>Patients with non-conclusive exercise test due to poor exercise tolerance</td>
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<tr>
<td>To evaluate myocardial viability</td>
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<tr>
<td>Other indications as for exercise imaging where local facilities favour pharmacological rather than exercise stress</td>
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<tr>
<td><strong>Non-invasive CT arteriography</strong></td>
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<tr>
<td>Patients with low probability of disease and non-conclusive or positive stress test</td>
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The following free text terms or MeSH terms (in alphabetical order) were used either singly or in combination:

### ABBREVIATIONS

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<td>3-KAT</td>
<td>3-ketoacyl CoA thiolase</td>
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<tr>
<td>3VD</td>
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<td>ACC</td>
<td>American College of Cardiology</td>
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<tr>
<td>ACEI</td>
<td>angiotensin converting enzyme-inhibitor</td>
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<tr>
<td>ACS</td>
<td>acute coronary syndrome</td>
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<tr>
<td>ADP</td>
<td>adenosine diphosphate</td>
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<td>AF</td>
<td>atrial fibrillation</td>
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<td>AHA</td>
<td>American Heart Association</td>
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<td>ARB</td>
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<td>BMI</td>
<td>body mass index</td>
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<td>BMS</td>
<td>bare metal stent</td>
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<tr>
<td>BP</td>
<td>blood pressure</td>
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<td>CABG</td>
<td>coronary artery bypass graft</td>
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<td>CCB</td>
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<td>CCS</td>
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<td>CHF</td>
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<td>CMR</td>
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<td>cyclooxygenase 1</td>
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<td>DES</td>
<td>drug eluting stent</td>
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<td>DTS</td>
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<td>ECG</td>
<td>electrocardiography</td>
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<td>Echo</td>
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<td>ED</td>
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<tr>
<td>EECP</td>
<td>enhanced external counterpulsation</td>
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<td>ESC</td>
<td>European Society of Cardiology</td>
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<td>FFR</td>
<td>fractional flow reserve</td>
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<td>GTN</td>
<td>nitroglycerin</td>
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<td>HCM</td>
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<td>hypertension</td>
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<td>HTA</td>
<td>Health Technology Assessment</td>
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<td>HR</td>
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<td>IHD</td>
<td>ischaemic heart disease</td>
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<td>IVUS</td>
<td>intravascular ultrasound</td>
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<td>LAD</td>
<td>left anterior descending artery</td>
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<td>LBBB</td>
<td>left bundle branch block</td>
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<td>LMS</td>
<td>left main stem</td>
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<td>LV</td>
<td>left ventricle</td>
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<td>LVEF</td>
<td>left ventricular ejection fraction</td>
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<td>LVH</td>
<td>left ventricular hypertrophy</td>
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<td>MET</td>
<td>metabolic equivalent</td>
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<td>MI</td>
<td>myocardial infarction</td>
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<td>MOH</td>
<td>Ministry of Health</td>
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<td>MSCT</td>
<td>multislice computed tomography</td>
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<td>PCI</td>
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<td>PDE-5</td>
<td>phosphodiesterase-5 inhibitor</td>
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<td>PVD</td>
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<td>QoL</td>
<td>quality of life</td>
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<td>SBP</td>
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<td>SPECT</td>
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<td>TMR</td>
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<td>UA</td>
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<td>Heart Protection Study</td>
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ACKNOWLEDGMENT
The committee of this guideline would like to express their gratitude and appreciation to the following for their contribution:

- European Society of Cardiology (of which the National Heart Association of Malaysia is an affiliate member) - for allowing the Committee to adopt the European Society of Cardiology (ESC) Guidelines on the Management of Stable Angina, 2006 as a basis for these guidelines

- Panel of external reviewers who reviewed the draft

- Technical Advisory Committee, Clinical Practice Guidelines, Ministry of Health for their valuable input and feedback

- Health Technology Assessment Section, Ministry of Health

STATEMENT OF DISCLOSURE
The panel members have completed disclosure forms. No member holds shares in pharmaceutical firms or acts as consultants to such firms. Details of the disclosure are available upon request from the CPG Secretariat.

SOURCES OF FUNDING
This CPG was made possible by an unrestricted educational grant from Servier (M) Sdn Bhd. However, the views or interests of the funding body have not influenced in any way the contents of this CPG.