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Clinical Practice Guidelines of

Stable Coronary Artery Disease 2018

2nd Edition

Ministry of Health Malaysia
Academy of Medicine Malaysia
National Heart Association of Malaysia

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Stable Coronary Artery Disease 2018

(2nd Edition)

STATEMENT OF INTENT

This guideline was developed to be a guide for best clinical practice, based on the best available evidence at the time of development. Specific attempts were made to use local data and publications to ensure local relevance. Adherence to this guideline does not necessarily lead to the best clinical outcome in individual patient care. Every health care provider is responsible for the management of his/her unique patient based on the clinical presentation and management options available locally.

REVIEW OF THE GUIDELINE

This guideline is issued in 2018 and will be reviewed in 2023 or earlier if important new evidence becomes available.

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Available on the following websites:
http://www.moh.gov.my
http://www.acadmed.org.my
http://www.malaysiaheart.org

This is an update to the Clinical Procedure Guidelines of Management of Stable Angina Pectoris published in 2010. This CPG supersedes the previous CPG.

MESSAGE FROM THE DIRECTOR GENERAL OF HEALTH

The previous clinical practice guidelines for the management of stable angina were issued in 2010. Since then, there have been advances in both diagnostic and therapeutic strategies in the management of this progressive disease. Therefore, it is timely for the publication of this CPG, with a title that is now evolved from stable angina to that of stable coronary artery disease (SCAD).

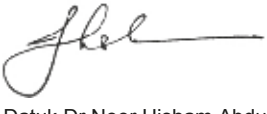
Atherosclerosis is a systemic vascular disease, but it is in the coronary arteries where this progressive disease exerts its most serious effects which can significantly affect morbidity and mortality.

Clinical manifestation of SCAD, by means of stable angina, has long been the point whereby an individual begins to seek medical attention. However, the combination of earlier screening by an increasingly greater number of the general population at risk of coronary artery disease has seen more patients being diagnosed with the subclinical SCAD. The high prevalence of risk factors of cardiovascular disease in Malaysia, including diabetes, hypertension, dyslipidaemia and smoking, and the emergence of better diagnostic equipment have both contributed to this effect.

In both subclinical and clinically evident SCAD, there are now new drugs and non-drug interventions available, which are now more readily available compared to when this last CPG was published. In addition, new clinical evidence have emerged on these new therapies. In this respect, the publication of this CPG, which reviews published research on these new therapies and strategies, is timely.

The management of SCAD has to be tailored carefully to an individual, as the right therapeutic strategies often improves symptoms. This CPG reviews most available treatment options in Malaysia and makes recommendations on strategies that can improve both the patients' clinical outcomes and quality of life.

Finally, I would like to thank Dr Jeyamalar Rajadurai and the multidisciplinary team on the expert panel who have worked hard to put this CPG together, as well as the external reviewers of this CPG. I believe this CPG will be a relevant document for every practicing healthcare professional who manages patients with SCAD.



Datuk Dr Noor Hisham Abdullah
Director General of Health Malaysia

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CONTENTS

ABBREVIATIONS

3-KAT	3-ketoacyl CoA Thiolase
ACEi	Angiotensin Converting Enzyme Inhibitor
ACS	Acute Coronary Syndrome
AF	Atrial Fibrillation
AHA/ACC	American Heart Association/american College Of Cardiology
ARB	Angiotensin Receptor Blocker
ATP	Adenosine Triphosphate
BMI	Body Mass Index
BMT	Behavioural Modification Therapy
BP	Blood Pressure
CABG	Coronary Artery Bypass Surgery
CAD	Coronary Artery Disease
CAC	Coronary Calcium Score
CASS	Coronary Artery Surgery Study
CCB	Calcium Channel Blockers
CCS	Canadian Cardiovascular Society
CHF	Congestive Heart Failure
CHO	Carbohydrate
CKD	Chronic Kidney Disease
CMR	Cardiac Magnetic Resonance
CPG	Clinical Practice Guidelines
CT	Computerised Tomographic
CTA	Computerised Tomographic Angiography
CV	Cardiovascular
CVD	Cardiovascular Disease
DAPT	Dual Antiplatelet Therapy
DASH	Dietary Approaches To Stop Hypertension
DHP	Dihydropyridine
DSE	Dobutamine Stress Echocardiogram
DTS	Duke Treadmill Score
ECG	Electrocardiogram
ED	Erectile Dysfunction
EECP	Enhanced External Counterpulsation
eGFR	Estimated Glomerular Filtration Rate
ESC	European Society of Cardiology
ESMR	Extracorporeal Shockwave Myocardial Revascularisation
FFR	Fractional Flow Reserve

ABBREVIATIONS

GFR	Glomerular Filtration Rate
GTN	Glyceryl Trinitrate
HbA1c	Glycated Haemoglobin
HDL-C	High Density Lipoprotein Cholesterol
HIV	Human Immunodeficiency Virus
HOCM	Hypertrophic Obstructive Cardiomyopathy
HR	Heart Rate
HRT	Hormone Replacement Therapy
ICA	Invasive Coronary Angiogram
iFR	Instantaneous Wave-Free Ratio
ISCHEMIA-CKD	International Study Of Comparative Health Effectiveness With Medical And Invasive Approaches-Chronic Kidney Disease
ISDN	Isosorbide Dinitrate
ISMN	Isosorbide Mononitrate
K(ATP)	Adenosine Triphosphate Sensitive Potassium
LAD	Left Anterior Descending
LBBB	Left Bundle Branch Block
LDL-C	Low Density Lipoprotein Cholesterol
LV	Left Ventricle
LVEF	Left Ventricular Ejection Fraction
LVH	Left Ventricular Hypertrophy
MET	Metabolic Equivalent
MI	Myocardial Infarction
MPI	Myocardial Perfusion Imaging
MRI	Magnetic Resonance Imaging
MUFA	Monounsaturated Fatty Acid
NCVD	National Cardiovascular Disease Registry
NOAC	Newer Oral Anticoagulant
NSTEMI	Non-ST Elevation Myocardial Infarction
OMT	Optimal Medical Therapy
OSA	Obstructive Sleep Apnea
PA	Physical Activity
PCI	Percutaneous Coronary Intervention
PDE5	Phosphodiesterase Type 5 Inhibitor
PET	Positron Emission Tomography
PTP	Pre-Test Probability
PUFA	Polyunsaturated Fatty Acid

ABBREVIATIONS

SCAD	Stable Coronary Artery Disease
SCD	Sudden Cardiac Death
SFA	Saturated Fatty Acid
SLE	Systemic Lupus Erythematosus
SPECT	Single-Photon Emission Computed Tomography
STEMI	ST Elevation Myocardial Infarction
TIA	Transient Ischemic Attack
TFA	Trans Fatty Acid
TMR	Transmyocardial Revascularization
UA	Unstable Angina

RATIONALE AND PROCESS OF GUIDELINE DEVELOPMENT

Rationale:
Coronary Artery Disease (CAD) covers a wide spectrum from asymptomatic individuals to patients with stable CAD, Acute Coronary Syndromes (ACS) and Sudden Cardiac Death (SCD). This Clinical Practice Guidelines (CPG) on Stable CAD is directed at individuals:

- with stable chest pain or other symptoms (e.g. dyspnea) which are known or suspected to be due to CAD.
- who had a previous episode of ACS but who are now stable and need regular follow up and monitoring.
- post revascularization by Coronary Artery Bypass Surgery (CABG) or Percutaneous Coronary Intervention (PCI) who are at present asymptomatic or have stable symptoms due to CAD.
- who are asymptomatic but are suspected or known to have CAD on non-invasive testing. This may occur in the absence or presence of ischemia and/or left ventricular (LV) dysfunction.

This CPG on Stable CAD has been drawn up by a committee appointed by the National Heart Association of Malaysia, Ministry of Health (MOH) and the Academy of Medicine. It comprises cardiologists, endocrinologists, general and family physicians and consultant internal medicine physicians and pharmacists from the Public Health Division, government and private hospitals and the universities. This is the 2nd edition of the CPG, the first being published in 2010.

Objectives:
The objectives of this CPG are to provide guidance on:

- the diagnosis of CAD in individuals presenting with stable chest symptoms.
- the risk stratification of individuals who are diagnosed with CAD. This helps determine the need for revascularization guided by the patient's preferences.
- optimal medical therapy (OMT) in all individuals with CAD.
- revascularization strategies.

Process:
A review of current medical literature on Stable CAD for the last 10 years was performed. Literature search was carried out using the following electronic databases - PubMed and Cochrane Database of Systematic Reviews.The search was conducted for the period January 2006 till 31st August 2016. The following MeSH terms or free text terms were used either singly or in combination:

1"angina", "stable angina", "stable coronary artery disease", "stable ischemic heart

disease", "refractory angina", "epidemiology of CAD", "pathophysiology of CAD", "diagnostic testing of CAD", "exercise stress ECG", "stress echocardiogram", "magnetic perfusion imaging", "cardiac magnetic resonance imaging", "coronary calcium score", "CT coronary angiogram", "Invasive coronary angiogram", "fractional flow reserve", "iFR", "coronary revascularization", "optimal medical therapy", "percutaneous coronary intervention in stable CAD", "coronary artery bypass grafting in Stable CAD".

The search was filtered to clinical trials and reviews, involving humans and published in the English language. The relevant articles were carefully selected from this huge list. In addition, the reference lists of all relevant articles retrieved were searched to identify further studies. Local CPGs were also studied. Experts in the field were also contacted to obtain further information. International guidelines mainly that from the American Heart Association/ American College of Cardiology (AHA/ACC) and the European Society of Cardiology (ESC) were used as main references.

All literature retrieved were appraised by members of the Expert Panel and all statements and recommendations made were collectively agreed by the group. The grading of evidence and the level of recommendation used in this CPG was adapted from the AHA/ACC and the ESC (pg 15).

After much discussion, the draft was then drawn up and submitted to the Technical Advisory Committee for Clinical Practice Guidelines, MOH Malaysia and key health personnel in the major hospitals of the MOH and the private sector for review and feedback.

Clinical Questions Addressed:
There were several topics and subtopics that were formulated using the patient, intervention, comparison, outcome (PICO) method, addressing diagnosis, prognosis and management of Stable CAD.

The topics and subtopics were as follows:

P: Population- Persons:

- who are asymptomatic with no previous history of CAD
- with chest pain suspected to be due to CAD
- with known CAD
- with diabetes
- with chronic kidney disease
- who are elderly
- women

I: Intervention:

For diagnosis and Prognosis:

- Resting electrocardiogram (ECG)
- Chest X-Ray
- 2D echocardiogram
- Exercise stress ECG
- Stress echocardiogram
- Myocardial perfusion imaging(MPI)
- Cardiac Magnetic Resonance (CMR) Imaging
- Coronary Calcium (CAC) Score
- CT coronary angiogram
- Invasive coronary angiogram
- Fractional Flow Reserve (FFR) and iFR

For management:

- Optimal medical therapy - including diet, exercise
- Percutaneous coronary intervention (PCI)
- Coronary Artery Bypass Grafting (CABG)

C: Comparison:

- Different diagnostic modalities
- Optimal medical therapy vs PCI vs CABG in Stable CAD

O: Outcome:

- Accuracy of the test in making a diagnosis of CAD - i.e. its validity, reliability
- Reduction in Cardiovascular (CV) Disease- CV Events, vascular mortality
- Reduction in All cause mortality

Type of Question- Involves:

- Diagnosis - Diagnosis of CAD
- Therapy - optimal medical therapy, PCI, CABG
- Harm - Increase in CV Event Rate, mortality
- Prognosis - Reduction in CV events and mortality
- Prevention of CV Disease

Type of Study:

- Systematic review and meta analysis
- Randomised Controlled Studies
- Cohort studies

Thus, there were numerous clinical questions formulated.
E.g. of some of these Clinical Questions:

- What is the validity (sensitivity, specificity and predictive value) of an Exercise ECG in an asymptomatic individual with no previous medical illness, in the diagnosis of CAD?
- What is the validity (sensitivity, specificity and predictive value) of an Exercise ECG in diagnosing CAD in an individual with chest pain suspected to be due to CAD?
- What is the validity (sensitivity, specificity and predictive value) of an Exercise ECG when compared to a stress echocardiogram in diagnosing CAD in an individual with chest pain suspected to be due to CAD?
- What is the prognostic value of an abnormal Exercise ECG in an individual with chest pain suspected to be due to CAD?
- In an individual with known stable CAD, does optimal medical therapy as compared to PCI, lead to a reduction in CV events and all cause mortality?

Target Group:
These guidelines are directed at all healthcare providers - all medical practitioners, and allied health personnel.

Target Population:
These guidelines are directed at individuals with stable CAD.

Period of Validity of the Guidelines:
These guidelines need to be revised at least every 5 years to keep abreast with new developments and knowledge.

Implementation of the Guidelines:
The implementation of the recommendations of a CPG is part of good clinical governance. To ensure successful implementation of this CPG we suggest:

- Continuous medical education and training of healthcare providers on diagnosis and management of Stable CAD. This can be done by road shows, electronic media, and in-house training sessions.

- Performance measures that include:
  - Percentage of patients with Stable CAD on optimal medical therapy with aspirin (or clopidogrel or ticlid if aspirin intolerance) and statin therapy?

Applicability of the Guidelines and Resource Implications:
This guideline was developed taking into consideration our local health resources. Almost all the investigations and most of the medications recommended are available in public hospitals or at the cardiac centres in Malaysia.

This guideline aims to educate health care professionals on strategies to optimize existing resources in the diagnosis and management of stable CAD.

Facilitators and Barriers:
The main barrier for the successful implementation of this CPG is the lack of knowledge of the public and healthcare providers on the:

- role/limitations of the available non-invasive investigations in the diagnosis and risk stratification of individuals with CAD.
- benefits of optimal medical therapy in the management of persons with stable CAD.
- role/limitations of PCI in the management of individuals with stable CAD-the fallacies of the "oculostenotic reflex".
- "commercialization" of the medical industry in promoting expensive and sometimes unnecessary investigations and PCIs.

GRADES OF RECOMMENDATION AND LEVEL OF EVIDENCE

GRADES OF RECOMMENDATION	
I	Conditions for which there is evidence and/or general agreement that a given procedure/therapy is beneficial, useful and/or effective.
II	Conditions for which there is conflicting evidence and/or divergence of opinion about the usefulness/efficacy of a proce dure/therapy.
II-a	Weight of evidence/opinion is in favour of its usefulness/efficacy.
II-b	Usefulness/efficacy is less well established by evidence/opinion.
III	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.

LEVELS OF EVIDENCE	
A	Data derived from multiple randomized clinical trials or meta analyses.
B	Data derived from a single randomized clinical trial or large non randomized studies.
C	Only consensus of opinions of experts, case studies or standard of care.

Adapted from the American College of Cardiology Foundation / American Heart Association and the European Society of Cardiology

(Available at: http://assets.cardiosource.com/Methodology_Manual_for_ACC_AHA_Writing-_Committees and at http://www.escardio.org/guidelines-surveys/escguidelines/about/Pages /rules-writing.aspx).

SUMMARY

- Coronary Artery Disease (CAD) covers a wide spectrum - from persons who are asymptomatic to those presenting with acute coronary syndromes (ACS) and sudden cardiac death (SCD).
- Stable CAD includes individuals:
  - with stable chest pain or other symptoms (e.g. dyspnoea) which are known to be due to CAD.
  - who had a previous episode of ACS but who are now stable.
  - post revascularization (by CABG or PCI).
  - who are asymptomatic but are known to have CAD on non-invasive testing. This may occur in the absence or presence of ischemia and/or Left Ventricular (LV) dysfunction.
- Stable CAD may present as:
  - Chest pain
  - Dyspnea
  - Palpitations, near syncope and syncope.
- In Stable CAD, angina is due to myocardial ischemia resulting from a transient and reversible imbalance (mismatch) between myocardial oxygen demand and supply. In contrast, in an ACS, the thrombotic component of the ruptured plaque dominates the overall pathophysiological process and clinical picture.

In the ***DIAGNOSIS*** of CAD in patients presenting with stable chest symptoms (Fig 1, pg 23)

- A detailed history and physical examination are of paramount importance.
- Clinical investigations are necessary for:
  - detection of myocardial ischemia and/or
  - confirmation of the diagnosis and/or
  - prognostication.
- **Exercise stress ECG** is the non-invasive test of choice in patients who can exercise and have interpretable ECGs.
- **Stress imaging tests** are useful in individuals who have intermediate Pre-test probability (PTP) of CAD (Table 1, pg 22) and who:
  - are unable to exercise adequately and/or
  - have uninterpretable resting ECG and/or
  - have exercise stress ECG with equivocal results or which are abnormal at moderate to high workloads.
- **Coronary Calcium (CAC) Score** - This is more important in risk stratification than in the diagnosis of CAD.

- **Computerised Tomographic Coronary Angiogram (CTA)** - may be considered in individuals with low to intermediate risk PTP of CAD and who have mild or equivocal changes of ischemia in the exercise stress test or stress imaging tests and who are asymptomatic or mildly symptomatic with good exercise capacity.
- **Invasive Coronary Angiogram (ICA)** - This is not commonly used for the diagnosis of CAD. It is important in risk stratification and in determining the optimal mode of revascularization.

The ***RISK STRATIFICATION*** of patients with CAD who have stable symptoms of at least 2 months duration involves:
- Clinical evaluation
- Resting ECG
- Assessment of LV function by echocardiography
- Non-invasive assessment for myocardial ischemia - (Table 2, pg 24)
- Where indicated, evaluation of coronary anatomy and physiological assessment of the significance of the coronary lesion by Fractional Flow Reserve (FFR).

Risk may be defined as:
- high risk - annual mortality of >3%
- intermediate risk - annual mortality of 1-3%
- low risk - annual mortality of <1%

In general, individuals with no ischemia demonstrated by non-invasive testing and/or have no or minimal plaque in the coronary arteries by CTA have an excellent prognosis with a rate of cardiovascular (CV) death/non-fatal Myocardial Infarction(MI) of <0.5% and an annual mortality of <1%.

- **Low risk individuals** can be managed with risk factor reduction and/or anti anginal medications as necessary. Revascularization has not been shown to improve their long-term CV outcomes. Thus, no further intervention is required. This includes individuals who are:
  - asymptomatic or minimally symptomatic.
  - have no demonstrable or minimal ischemia on non-invasive testing. (Table 2, pg 24)
- **Intermediate risk individuals** may be managed with risk reduction strategies +/- anti anginal therapy or considered for invasive coronary angiogram and revascularization depending on the clinical condition, ischemic burden and patient preferences.
- **High risk individuals**, in addition to risk reduction strategies, should be considered for invasive coronary angiography with view to revascularization. This includes individuals who:

- continue to have troubling angina/angina equivalents despite OMT.
- Have significant ischemia on non-invasive testing. (Table 2, pg 24)

All individuals with CAD who are at Intermediate and High Risk should be referred to tertiary cardiology centers for further evaluation and revascularization as indicated. Individuals at low risk can be managed both at the hospital and also in general outpatient clinics with Family Medicine Specialists.

Following stabilization and revascularization, intermediate and high risk individuals can be transferred back to the general outpatient clinics with Family Medicine Specialists after a period of 1 - 2 years or at the discretion of the attending doctor.

Management (Fig 2, pg 25) should be multifaceted and involves OMT which includes both behavioural modification therapy and pharmacological therapy.

- Behavioral modification therapy (BMT) - patient education and lifestyle modification.
- Pharmacological therapy - This aims at:
  - Prevention of CV events.
    - All patients should receive aspirin and a statin (+/- non-statin therapy) with the aim of achieving a LDL-C <1.8 mmol/l - the lower the better.
    - All CV risk factors should be treated to target.
    - Patients with depressed LV function (LVEF <40%) should receive ACEi/ARB, β-blockers and mineralocorticoid antagonists as tolerated. Angiotensin-receptor-neprilysin inhibitors may also be considered.
  - Relieving symptoms
    - β-blockers and/or calcium channel blockers (CCBs) should be prescribed as first-line treatment to reduce angina because they are widely available.
    - Ivabradine, trimetazidine, long-acting nitrates and ranolazine are recommended as add-on therapy in patients who remain symptomatic.
- Myocardial revascularization - OMT should be instituted prior to revascularization procedures. The decision to revascularize will depend on:
  - symptoms - presence of angina affecting quality of life.
  - extent of ischemia as determined by non-invasive testing
  - extent of coronary disease and where applicable physiological functional testing using FFR. Individuals with:
    - FFR <0.75 - benefit from revascularization as compared to OMT.
    - FFR between >0.75 but <0.8 - have intermediate benefit with revascularization and management should be based on clinical judgement.
    - FFR >0.8 - do not benefit from revascularization.
- Wherever possible, a discussion with the patient and Heart Team should be encouraged prior to revascularization to determine the best strategy - PCI or CABG.

KEY RECOMMENDATIONS

A) Diagnosis of CAD in persons having stable chest pain/angina equivalent of more than 2 months' duration

Recommendation 1:
In making a diagnosis of CAD:

- A detailed history and a thorough physical examination are important.
- Relevant laboratory investigations to assess the general health status of the individual and to look for co-morbidities.
- A resting ECG, preferably during an episode of chest pain/angina equivalent.
- An echocardiogram is not a routine investigation but is indicated in the:
  - Presence of abnormal auscultatory findings and/or
  - Presence of abnormal resting ECG and/or
  - Assessment of LV function/regional wall motion abnormalities in patients with shortness of breath and/or known CAD.
- A chest radiograph is not a routine investigation but may be helpful in assessing cardiac size, pulmonary vasculature and excluding certain non-cardiac causes of chest pain.

Recommendation 2:
In persons with suspected CAD and undergoing non-invasive cardiac testing, it is important to determine the:

- Pre-Test Probability (PTP) of CAD of that individual. (Table 1, pg 22). In the Euro model for assessing PTP, which this writing group has adopted, (Table 1, pg 22) patients with a:
  - low PTP of <15% can be assumed to have no significant obstructive CAD. In these individuals, CV risk factors should be treated to target. Other causes of chest pain should be looked for. (Table 5, pg 35)
  - intermediate PTP (≥15-≤ 85%) require further non-invasive evaluation.
  - high PTP >85% can be assumed to have significant obstructive CAD and nvasive coronary angiography maybe a more appropriate investigation.
- Sensitivity and specificity of the different diagnostic modalities. (Table 6, pg 39)

Recommendation 3:
In non-invasive cardiac testing: (Fig 1, pg 23)

- Exercise stress ECG is the non-invasive test of choice in patients who can exercise and have interpretable ECGs.
- Stress imaging tests are used in individuals who have intermediate PTP of CAD and who:
  - are unable to exercise adequately and/or
  - have uninterpretable resting ECG and/or
  - have exercise stress ECG with equivocal results or which are abnormal at moderate to high workloads depending upon the clinical condition.
- Coronary Calcium has been used to detect CAD but is more useful for CV risk assessment.
- CTA may be considered in individuals with low to intermediate risk PTP of CAD and who have mild or equivocal changes of ischemia in the exercise stress test or stress imaging tests and who are asymptomatic or mildly symptomatic with good exercise capacity.
- Invasive Coronary Angiogram (ICA) is rarely necessary in stable patients with suspected CAD for the sole purpose of establishing the diagnosis of CAD. It is indicated, following non-invasive risk stratification, to determine the most appropriate mode of revascularization.

B) Risk Stratification of patients with suspected or known CAD

Recommendation 4:

- This is done by: (section 7, pg 53-61)
  - Clinical evaluation
  - Resting ECG
  - Non-invasive assessment of myocardial ischaemia (Table 2, pg 24)
  - Assessment of Left ventricular function
  - Where indicated, evaluation of coronary anatomy and physiological assessment of the significance of the coronary lesion by Fractional Flow Reserve (FFR).
- Low risk individuals (annual mortality of <1%) should be managed with risk factor reduction and/or anti anginal medications as necessary. No further intervention is required.
- Intermediate risk individuals (annual mortality of 1-3%) may be managed with risk reduction strategies +/- anti anginal therapy or considered for invasive coronary angiogram and revascularization depending on the clinical condition and patient preferences.
- High risk individuals (annual mortality of >3%) in addition to risk reduction strategies, should be considered for invasive coronary angiography with view to revascularization.

Recommendation 5
- Low risk individuals can be managed in the general outpatient clinics with Family Medicine Specialists.
- Intermediate and high risk individuals should be referred to tertiary cardiac centers for further evaluation and revascularisation as indicated.

C) Management of Stable CAD

Recommendation 6:
- All patients should be on Optimal Medical Therapy (Behavioural modification therapy and appropriate pharmacotherapy). (Fig 2, pg 25)
- Appropriate pharmacotherapy includes:
  - aspirin (or clopidogrel/ticlopidine if aspirin intolerant) and
  - statin (+/- non- statin therapy) with the aim of achieving LDL-C targets and
  - at least 2 anti anginal agents.
- In addition:
  - All CV risk factors should be treated to target.
  - Patients with depressed LV function (LVEF <40%) should receive ACEi/ARB, β-blockers and mineralocorticoid antagonists.
- Optimal medical therapy should be instituted prior to revascularization procedures.

Recommendation 7:
- The decision to revascularize patients with stable CAD on OMT will depend on:
  - Symptoms
  - Extent of ischemia
  - Extent of coronary disease and where applicable physiological functional testing using FFR.
- Wherever possible, a discussion with the patient and Heart Team should be encouraged prior to revascularization to determine the best strategy.

Recommendation 8:
- All patients with Stable CAD with no change in symptoms and medications over a period of 1-2 years, can be discharged from the speciality cardiac clinics.
- When there is a change in the patient's clinical condition, they should be referred to tertiary cardiac centres for optimization of management.

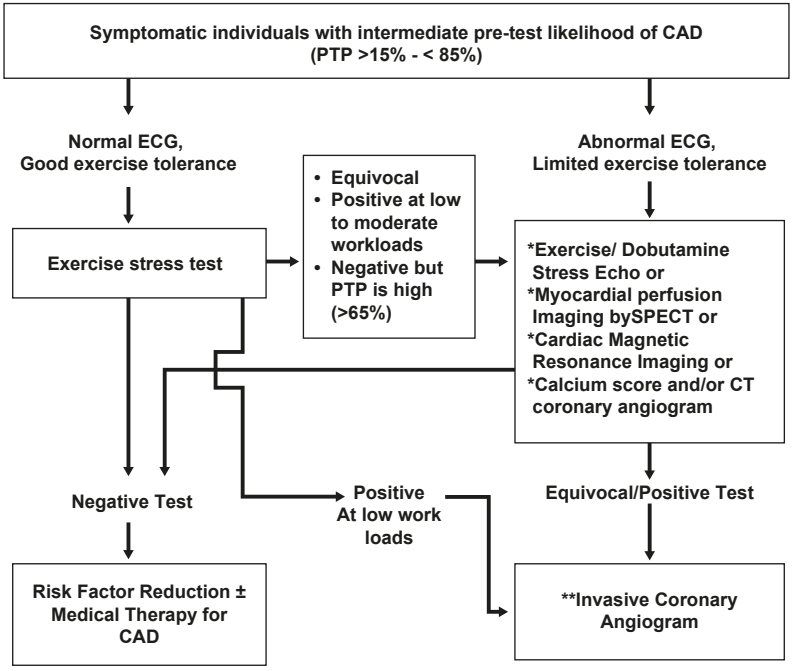
Table 1: Pre-Test Probability (PTP) of CAD in patients with stable Chest Pain*

Age	Pre-test Probability of CAD					
	Typical Angina		Atypical Angina		Non-anginal Pain	
	Men	Women	Men	Women	Men	Women
30-39	59	28	29	10	18	5
40-49	69	37	38	14	25	8
50-59	77	47	49	20	34	12
60-69	84	58	59	28	44	17
70-79	89	68	69	37	54	24
>80	93	76	78	47	65	32

Red boxes: High PTP >85%; Yellow boxes: Intermediate PTP >15-<85%; Green box: Low PTP <15%

**Adapted from Montalescot G, Sechtem U, Achenbach S, Andreotti F, Arden C et al. The Task Force on the management of stable coronary artery disease of the European Society of Cardiology. 2013 ESC guidelines on the management of stable coronary artery disease. Eur Heart J 2013: 34, 2949-3003*

Figure 1: Algorithm for the investigation of individuals with stable chest symptoms suspected to be due to CAD



**The choice of non-invasive tests will depend on the patient's ability to exercise, ECG interpretability, obesity and the presence of good echo windows and availability of local services and expertise*

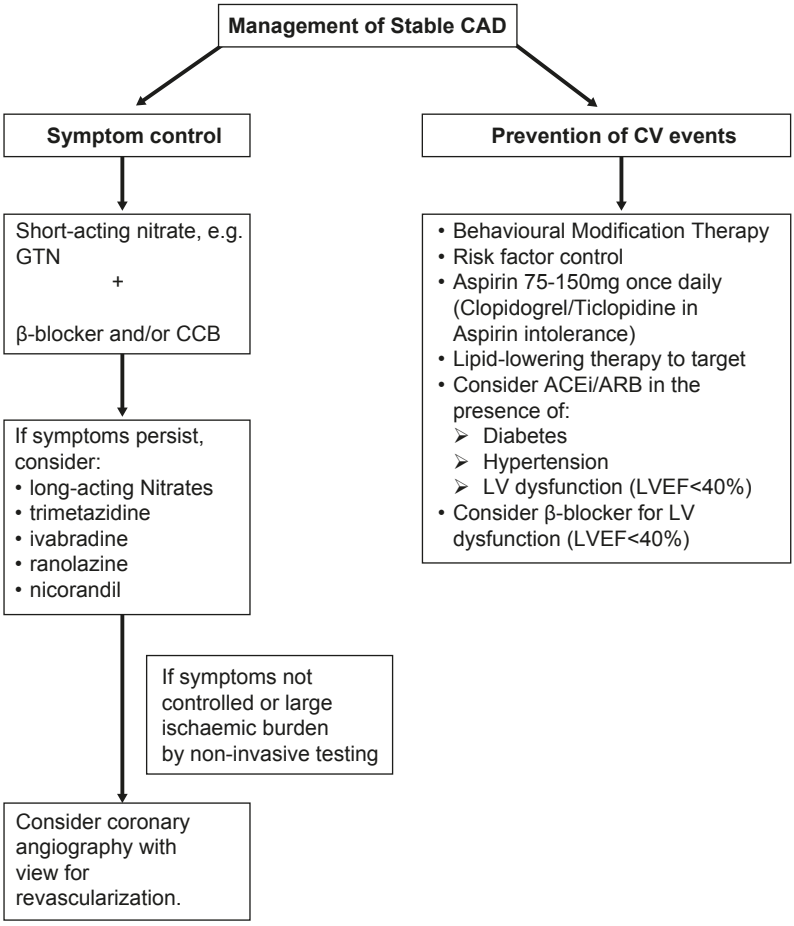
***In individuals with typical symptoms and a high pre-test likelihood of CAD (PTP>85%), an invasive coronary angiogram may be the initial investigation of choice (please refer to Appropriate Use Criteria for Investigations and Revascularization in CAD 2015 (1st edition): available at www.acadmed.org.my)*

Table 2: Prognostic indicators for Adverse CV outcomes on Non-Invasive testing[1–9]

Modality	Definition of Risk	Risk
Exercise Stress Test based on Duke Treadmill Score (DTS) (Table 7, pg 44)	DTS: ≤ -11: High risk	Annual mortality >5%
	DTS: +4 to -10: Moderate Risk	Annual mortality 0.25-5%
	DTS: ≥ +5: Low risk	Annual mortality <0.25%
Stress Echocardiogram	Low risk: No inducible ischemia (negative test)	Annual rate of CV death /MI 0.54%, annual mortality <1%
	High Risk: inducible wall motion abnormalities in ≥3 segments of the standard LV model	Annual rate of CV death/MI: 4.5% (range: 3.8% to 5.9% /yr)
Exercise MPI (nuclear)	No inducible ischemia (Negative test)	Annual rate of CV death/MI: 0.45% per year
	High risk: stress induced reversible perfusion defect (≥10% of total LV myocardium	Annual rate of CV death/MI: 4.9% (interquartile range: 3.7% to 5.3%/year)
Stress CMR	No inducible ischemia (Negative test)	The 3-year event-free survival: 99.2%.
	≥4 of 32 stress perfusion defects or ≥ 3 dysfunctional dobutamine induced segments	Annual risk of CAD death/ MI: ~5%
CT coronary Angiography (CTA)	Absence of any plaque	CV event rate is low - 0.24% for CV death/non-fatal MI; annual mortality: 0.28%.
	Coronary plaque but without stenosis*	Annual mortality rate is higher but remains < 0.5%
	Left main stenosis or proximal triple vessel disease	HR for all-cause mortality: 3.70

**Non- obstructive < 50% stenosis* [8,9]

Figure 2: Management of Stable CAD



1. INTRODUCTION

Coronary Artery Disease (CAD) is an important cause of morbidity and mortality in Malaysia.[10-12] It has been the main cause of death in both gender for over a decade although in recent years, the mortality trend has shown a small decrease.[10-12] In most Western countries however, mortality due to CAD has been on a significant downward trend due to appropriate primary prevention strategies, improved diagnosis and early treatment.[13-15]

CAD covers a wide spectrum - from persons who are asymptomatic to those presenting with ACS and sudden cardiac death (SCD).

This CPG on Stable CAD is directed at individuals:

- with stable chest pain or other symptoms (e.g. dyspnoea) which are known or suspected to be due to CAD.
- who had a previous episode of ACS but who are now stable and need regular follow up and monitoring.
- post revascularization (by CABG or PCI) who are at present asymptomatic or have stable symptoms due to CAD.
- who are asymptomatic but are suspected or known to have CAD on non-invasive testing. This may occur in the absence or presence of ischemia and/or Left Ventricular (LV) dysfunction.

It provides guidance on:

- diagnosis of CAD in individuals presenting with stable chest symptoms.
- risk stratification of individuals who are diagnosed with CAD. This helps determine the need for revascularization guided by the patient's preferences.
- optimal medical therapy in all individuals with CAD.
- revascularization strategies.

Individuals with CAD, even with minimal or absent symptoms, including those post-revascularization, are at high risk for recurrent cardiovascular (CV) events.[16-18] In a large multinational registry, the 4-year rate of CV death, MI or stroke in patients with stable CAD but no previous ischemic events was 12.2% and in those with previous ischemic events, it was 18.3%.[19] Almost 20% of individuals continue to have angina one year after their MI.[20]

In a more recent registry of patients with stable CAD who were enrolled 1-year post ACS and managed in the contemporary era with optimal medical therapy, the prognosis was much better.[21]

This CPG does not address individuals who do not have CAD but who are at risk for CAD. This is covered in the CPG Primary and Secondary Prevention of CVD, 2017.[22]

Key Messages:

- CAD covers a wide spectrum – from individuals who are asymptomatic to those presenting with ACS and SCD.
- Individuals with CAD, even with minimal or absent symptoms, including those post-revascularization, are at high risk for recurrent CV events.

2. CLINICAL SPECTRUM OF STABLE CAD

Stable CAD may present as:
- chest pain
- dyspnoea
- palpitations, near syncope and syncope

2.1 Chest pain

Stable CAD often manifests as chest pain. Occasionally the individual may be asymptomatic or may have atypical symptoms e.g. pain in the jaw, shoulder or epigastrium precipitated by stress - physical and/or emotional (angina equivalent).

Chest pain may be categorized into:
- **Stable angina** (typical/definite angina) - This is a clinical syndrome of retrosternal chest discomfort with the following characteristics and fulfilling these 3 criteria:[23–25] (Table 3, pg 29)
  1. predictable and with possible radiation to jaw, shoulders, arms and/or back.
  2. provoked by physical exertion and/or emotional stress.
  3. relieved by rest and/or with glyceryl trinitrate (GTN).
- **Atypical angina** (probable) - chest pain or discomfort which meets 2 out of the above 3 criteria.
- **Non-anginal chest pain** or discomfort - this meets one or none of the typical angina criteria.

Chest pain is more likely to be due to CAD in the older individual, in males, in those with a family history of premature CAD and in the presence of CV risk factors or a previous cardiac event.

Chest pain may also occur at rest due to:
- coronary vasospasm (de novo or superimposed on a fixed stenosis) of an epicardial vessel (variant/Printzmetal angina) and/or
- microvascular dysfunction.

These individuals are managed as stable CAD.

Chest pain with the following features may be due to an ACS: (Section 5.1, pg 33-34)
- of recent onset (<2 months) and/or
- occurring at rest and/or
- associated with other features such as sweating and dyspnoea.

Management of these individuals are in the CPGs on ST Elevation Myocardial Infarction (STEMI) and Unstable Angina/Non-ST Elevation Myocardial Infarction (UA/NSTEMI).[26,27]

The prevalence of angina is dependent upon age and sex and is often under estimated.[24,28] The Health Survey for England (2006) reported that 3% of women and 8% of men aged 55 to 64 years have or had angina.[25]

In the United States, the prevalence of angina in adults ≥20 years was 3.4% and was higher in the older age groups.[29] Among individuals aged 55-64 years, the prevalence was about 7% in both gender.[29]

In the Malaysian National Cardiovascular Disease Registry (NCVD) ACS 2014-15 report, 9.2% of patients admitted with ACS had a history of chronic angina.[30] In this registry, this was defined as onset of chest pain more than 2 weeks prior to admission.[30]

2.2 Dyspnoea / LV dysfunction

Individuals with stable CAD may also present with dyspnoea. This may be due to either:
- myocardial ischemia (angina equivalent) and/or
- LV dysfunction from a hibernating but viable myocardium or from previously infarcted muscle (scar tissue).

2.3 Palpitations/near syncope/syncope

A less common presentation is palpitations due to arrhythmia. The presence of syncope/near syncope may be due to:
- tachyarrhythmia - atrial fibrillation, ventricular tachycardia
- bradyarrhythmia from drug therapy, conduction disturbances and/or co existing sick sinus syndrome and/or
- hypotension from drug therapy particularly diuretic use.

Table 3: Definition of Typical/Definite Angina

Typical/definite angina - is retrosternal chest discomfort characterized by the following 3 criteria:

1. predictable and with possible radiation to jaw, shoulders, arms and/or back.
2. provoked by physical exertion and/or emotional stress.
3. relieved by rest and/or with GTN.

Key messages:

Stable CAD may present as:

- Chest pain- This may be categorized into:
  - Stable angina (typical/definite angina) - This is a clinical syndrome of retrosternal chest discomfort with the following characteristics and fulfilling the 3 criteria listed in Table 3, pg 29:
  - Atypical angina (probable) - chest pain or discomfort which meets 2 out of the above 3 criteria.
  - Non-anginal chest pain or discomfort - this meets one or none of the typical angina criteria.
- Dyspnoea - This may be due to either:
  - myocardial ischemia (angina equivalent) and/or
  - LV dysfunction from a hibernating but viable myocardium or from previous infarcted muscle (scar tissue).
- Palpitations, near syncope and syncope

3. PATHOPHYSIOLOGY

Angina is due to myocardial ischemia resulting from a transient and reversible imbalance (mismatch) between myocardial oxygen demand and supply. This may occur in the presence of a fixed stenosis or the result of a dynamic stenosis (vasospasm) of the coronary arteries. In contrast, in an ACS, the thrombotic component of the ruptured plaque dominates the overall pathophysiological process and clinical picture.

Myocardial ischemia may also occur in the absence of chest pain or with atypical symptoms (angina equivalent) such as dyspnoea, unexplained sweating, extreme fatigue, or pain at a site other than the chest. This is more common in diabetics, the elderly and in women.

Myocardial ischemia may occur in the presence of:[31]

- Atherosclerotic obstructive CAD (coronary lesions >50% luminal narrowing)
- Non-obstructive CAD (≥20% and <50% luminal narrowing). The prognosis of these patients is worse if myocardial ischemia is documented.
- Normal coronary arteries (Cardiac Syndrome X) - (<20% luminal narrowing) The commonest cause of myocardial ischemia is atherosclerotic plaque related obstructive CAD. Generally, in stable CAD, a stenosis of ≥50% in the left main coronary artery and ≥70% in one or several of the major epicardial coronary arteries is necessary to cause myocardial ischemia. In an ACS, lesser degrees of coronary stenosis may give rise to angina.

The pathophysiology of myocardial ischemia in patients with non-obstructive CAD and normal coronaries is not clear. Postulated mechanisms include:

- coronary vasospasm
- microvascular dysfunction. About 50% of women with chest pain have evidence of microvascular dysfunction,[32-34] but only about 20% to 25% showed signs of ischaemia[33,35,36] There are no gender differences in the prevalence of coronary microvascular dysfunction.[37]
- myocardial bridging - At autopsy, the incidence has been reported to be between 40-80% although functional myocardial bridging is less common (0.5% to 16.0% of cases).[38,39] The left anterior descending coronary artery is most commonly involved. These patients are generally asymptomatic but may present with exertional angina, syncope, and even sudden death. Medical therapy with β-blockers and CCBs remain the mainstay of treatment.[38,39] If medical therapy fails, surgery may be considered.[39] Stent implantation may be complicated by stent fracture, perforation, thrombosis and restenosis.[39]
- enhanced pain perception.[40,41]

Other common causes of myocardial ischemia include:

- hypertrophic obstructive cardiomyopathy
- aortic stenosis
- coronary vasculitis from connective tissue disease
- aortic aneurysms
- anaemia - this may be a precipitating cause for the angina

Key messages:

- Angina in Stable CAD is due to myocardial ischemia from a transient and reversible imbalance (mismatch) between myocardial oxygen demand and supply.
- It may occur in the presence of:
  - Atherosclerotic obstructive CAD (coronary lesions >50% luminal narrowing)
  - Non-obstructive CAD (≥20% and <50% luminal narrowing). The prognosis of these patients is not benign. It is worse if myocardial ischemia is documented.
  - Normal coronary arteries (Cardiac Syndrome X) – (<20% luminal narrowing)

4. NATURAL HISTORY AND PROGNOSIS OF STABLE CAD

The natural history of Stable CAD is marked by episodes of sudden deterioration due to plaque fissuring, ulceration or erosion with superimposed thrombosis resulting in an acute decrease in myocardial oxygen supply and the clinical picture of ACS. The episodes of chest pain become more frequent, occurring at rest or with minimal exertion and with no obvious trigger. Accelerated chest pain may also occur due to an episode of increased myocardial oxygen demand as in periods of emotional or strenuous physical stress/exertion.

Earlier studies reported that the annual rate of MI in persons with stable angina was 3.0-3.5%.[42,43] Generally, the annual mortality has been estimated to be in the range of 1.2-2.4% per annum, cardiac death 0.6-1.4% per annum and non-fatal MI 0.6-2.7%.[44]

However, in a recent registry of patients with stable CAD managed in the contemporary era and who had their ischemic events and/or revascularization 4 to 5 years earlier, the incidence of MI occurred linearly at a rate of 0.8% per year and about a third of these were STEMI.[21] About 20% of the MIs in this registry were due to very late stent thrombosis.[21]

Prognosis in any individual patient however, will depend on the nature and extent of the underlying disease, the LV function, the age of the patient, the presence of CV risk factors and other co-morbidities. In the registry study mentioned earlier, baseline predictors of MI were: [21]

- CV risk factors such as active smoking, poorly controlled diabetes and/or lipids,
- persistent angina and
- multivessel disease

Previous CABG was inversely associated with the risk of MI.[21]

The most important predictors of adverse CV outcomes are LV function and the extent of myocardial ischemia (total ischemic burden).[45–51] This is not necessarily equivalent to the number of vessels diseased.

The association between angina and the combined CV end points of CV death, MI or stroke is weak.[52–54] Individuals with angina are, however, at increased risk for heart failure, CV hospitalizations, coronary revascularization and death than individuals without angina.[52,55]

In a large registry of outpatients with stable CAD, about half of CV events (CV deaths and non-fatal MI) occurred in individuals without angina or ischemia.56 Unlike earlier studies, in this large registry, patients with angina and myocardial ischemia fared worse than those who only had silent ischemia.[47,48,56]

This highlights the importance of optimal medical therapy in all patients with CAD irrespective of the presence of symptoms

Key messages:

- The natural history of Stable CAD is marked by episodes of sudden deterioration due to plaque fissuring, ulceration or erosion with superimposed thrombosis resulting in ACS.
- In patients with Stable CAD on OMT, the incidence of MI occurs at a rate of 0.8% per year.
- Predictors of MI are CV risk factors such as active smoking, poorly controlled diabetes and/or lipids, persistent angina and multivessel disease.
- The most important predictors of adverse CV outcomes are LV function and the extent of myocardial ischemia (total ischemic burden).

5. DIAGNOSIS OF CAD -BASIC ASSESSMENT

In the management of individuals with suspected or known CAD, the following need to be performed concurrently:

- Establishing a diagnosis of stable CAD by clinical assessment and appropriate investigations.
- Risk stratification and prognostication.
- Initiating Optimal Medical Therapy (OMT).
- Determining if the patient would benefit from revascularization.

Clinical assessment and relevant investigations are necessary for:

- diagnosis and
- prognosis

5.1 Clinical Assessment

I, C

In making a diagnosis of stable angina, a detailed history and physical examination are of paramount importance. Clinical investigations are necessary for confirmation of the diagnosis, detection of myocardial ischemia and for prognostication.

- **History**
  - Detailed history of angina i.e. character of the pain, location, radiation and severity (Table 3, pg 29)
    - Character - heaviness, pressure, tightness, constricting or burning.
    - Location - typically present in the retrosternal area but may also be felt in the epigastrium with radiation to neck/jaw, shoulders, back and arm.
    - Duration - not more than 20 min.
    - Precipitating factors - exertion, heavy meal, emotional stress.
    - Relieving factors - rapidly relieved by rest and/or GTN.
    - Severity of chest pain can be graded according to the Canadian Cardiovascular Society (CCS) Classification.[57] (Table 4, pg 34)
  - Presence of CV risk factors i.e. diabetes mellitus, hypertension, dyslipidaemia, smoking, family history of premature CAD, (father, male sibling or son <55 years of age or mother, female sibling or daughter <65 years of age).
  - Previous history of MI and coronary revascularization.
  - Women and the elderly can present with atypical symptoms.

Angina of less than 2 months duration is classified as recent onset or unstable angina (UA).[58] In the presence of a good effort tolerance, normal cardiac biomarkers and LV function and absence of ischemia at low to moderate workloads, these individuals (low risk UA) can be managed as stable CAD. All other individuals should be managed as in the Clinical Practice Guidelines (CPG) on UA/NSTEMI.[26]

- **Physical examination**

This involves:

- inspection of the general habitus of the patient, looking for signs of anaemia, polycythaemia and stigmata of hyperlipidaemia.
- examination of the peripheral pulses.

- measurement of the blood pressure.
- auscultation of the precordium for additional heart sounds and murmurs and the carotid and renal arteries for bruit.
- excluding non-coronary causes of angina such as severe aortic stenosis, hypertrophic obstructive cardiomyopathy, and hyperthyroidism.

If the history of chest pain is not suggestive of angina, then other causes should be considered. (Table 5, pg 35)

Table 4: Canadian Cardiovascular Society (CCS) Classification of Angina[57]

Class	Severity of Exertional Stress Inducing Angina	Limitation of Ordinary Activity
I	Strenuous, rapid or prolonged exertion at work or recreation	None
II	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	Slight
III	Walking one or two blocks on the level* and climbing one flight of stairs in normal conditions and at a normal pace	Marked
IV	Inability to carry out any physical activity without discomfort or symptoms may be present at rest	Discomfort in all activity performed

Table 5: Other causes of non-ischaemic chest pain

System Involvement	Condition
Gastrointestinal system	Gastro-oesophageal reflux Oesophageal spasm Peptic Ulcer Disease Gallstone disease Pancreatitis
Respiratory system	Pleurisy Pneumothorax Pulmonary Embolism Pneumonia
Neurology	Neuralgia
Psychiatry	Anxiety disorder Psychosomatic disorder
Musculoskeletal	Costochondritis Myalgia
Cardiovascular	Pericarditis

5.2 Biochemistry

Relevant laboratory investigations are performed to assess the general health status of the individual and to look for co-morbidities. These include:

I, C • Full Blood Count

I, C • Fasting glucose and/or A1c

I, C • Lipid profile - fasting or non-fasting

I, C • Renal profile - electrolyte, serum creatinine and/or glomerular filtration rate (eGFR)

IIa, C • Liver enzymes

5.3 Resting ECG

I, C — All patients with chest pain/ angina equivalent should have a baseline resting 12-lead ECG performed.

I, B — Preferably, the ECG should be done during an episode of chest pain.

The resting 12 lead ECG:

- is usually normal - A normal resting ECG does not rule out CAD or myocardial ischemia.
- may show evidence of CAD such as pathological Q waves, left bundle branch block (LBBB), ST-T abnormalities.
- may help to identify other causes of chest discomfort such as pericardial disease, dynamic ST-T changes of coronary vasospasm, hypertrophic obstructive cardiomyopathy (HOCM).

5.4 Echocardiography (at rest)

Echocardiography is not a routine investigation in individuals suspected of having CAD. In most of these individuals, the study is normal. The echocardiogram, however, provides valuable information on LV function which is important in risk stratification.

It is indicated in the:

I, C
- Presence of abnormal auscultatory findings and/or

I, C
- Presence of abnormal resting ECG and/or

I, C
- Assessment of LV function/regional wall motion abnormalities in patients with shortness of breath and/or known CAD.

It is a useful test to assess LV function in individuals with:

IIa, C
- hypertension and/or diabetes.

IIa, C
- chest pain suspected to be due to CAD

5.5 Chest radiography

The diagnostic yield of a chest radiograph in individuals with stable CAD is low.

IIa, C Where indicated, it may be helpful in assessing cardiac size, pulmonary vasculature and excluding certain non-cardiac causes of chest pain.

IIb, C It is not a routine investigation in individuals with suspected or known stable CAD.

Key messages:

- In the management of individuals with suspected or known CAD, the following need to be performed concurently:
  - Establishing a diagnosis of stable CAD by clinical assessment and appropriate investigations.
  - Risk stratification and prognostication.
  - Initiating Optimal Medical Therapy (OMT).
  - Determining if the patient would benefit from revascularization.
- A detailed history and physical examination are of paramount importance in making the diagnosis of Stable CAD.
- Clinical investigations are necessary for the confirmation of diagnosis, detection of myocardial ischemia and for prognostication.

Recommendation 1:

In making a diagnosis of CAD:

- A detailed history and a thorough physical examination are important.
- Relevant laboratory investigations to assess the general health status of the individual and to look for co-morbidities.
- A resting ECG, preferably during an episode of chest pain/angina equivalent
- An echocardiogram is not a routine investigation but is indicated in the:
  - Presence of abnormal auscultatory findings and/or
  - Presence of abnormal resting ECG and/or
  - Assessment of LV function/regional wall motion abnormalities in patients with shortness of breath and/or known CAD.
- A chest radiograph is not a routine investigation but may be helpful in assessing cardiac size, pulmonary vasculature and excluding certain non-cardiac causes of chest pain.

6. OTHER NON-INVASIVE INVESTIGATIONS FOR THE DIAGNOSIS OF CAD

6.1 Principles of diagnostic testing

Additional non-invasive investigations help in the diagnosis of CAD and its prognostication. Important considerations are availability of resources, costs and the potential harm of any procedure including avoiding, wherever possible, false positive or false negative results. A false positive result can result in unnecessary, expensive further downstream investigations and anxiety while a false negative result can result in a missed diagnosis and opportunity for appropriate treatment.

In addition to a resting ECG, chest radiograph and echocardiogram, other non-invasive tests may be:

- Functional - for myocardial ischemia or
- Anatomical - for visualization of the epicardial coronary arteries

In symptomatic patients with **suspected CAD**, functional testing as compared to an initial strategy of anatomical testing with CTA did not result in an improvement in clinical outcomes.[59] A meta-analysis found a small decrease in the incidence of MI but no improvement in mortality or cardiac death at the cost of greater downstream invasive procedures.[60] CTA, however, provided better prognostic information than functional testing by identifying patients at risk due to non-obstructive CAD.[61]

I, C In patients with **known CAD** presenting with atypical symptoms, a functional test for myocardial ischemia is a more appropriate initial investigation.

The interpretation of these diagnostic investigations will depend on:

- the pre-test probability (PTP) i.e. the likelihood of CAD in that patient. The PTP can be estimated using different models based on the patient's age, sex and clinical history of chest pain.[28,44,62–64]
- the diagnostic accuracy of the test which is represented by its sensitivity and specificity. (Table 6, pg 39) Sensitivity is the frequency of a true positive while specificity is the frequency of a true negative. In addition, the positive predictive value is the frequency that a patient with a positive test does have CAD and the negative predictive value is the frequency that a patient with a negative test truly does not have CAD. The predictive value of a test is dependent on the prevalence of CAD in the population being studied. As the prevalence of CAD in the population decreases, the positive predictive value declines and the negative predictive value increases.

Diagnostic testing is most valuable when the pre-test probability of CAD is intermediate. The precise definition of intermediate probability (i.e. between 15% and 85%) is somewhat arbitrary. An accurate model to assess PTP of CAD ensures to some extent, the most appropriate test for the patient at that level of risk.

In patients presenting with stable chest pain of more than two months duration and suspected to be due to CAD, the writing group had adapted the Euro model for assessing the PTP and the cut offs proposed by the ESC.[44] (Table 1, pg 22) This model has however not been validated in the local population.

Patients with a:

- low PTP of <15% can be assumed to have no significant obstructive CAD. In these individuals, the presence of CV risk factors should be determined, and these treated to target. Other causes of chest pain should be looked for.
- intermediate PTP (≥15-≤85%) - require further non-invasive testing.
- high PTP >85% can be assumed to have significant obstructive CAD and invasive coronary angiography maybe a more appropriate initial investigation.

In patients with intermediate PTP, the choice of non-invasive tests will depend on the patient's ability to exercise, ECG interpretability, obesity and the presence of good echo windows and the local availability of services and expertise.

Table 6: Sensitivity and Specificity of the Various Non-Invasive Diagnostic tests for CAD*

	Diagnosis of CAD	
	Sensitivity (%)	**Specificity (%)**
Exercise ECG	45 - 50	85 - 90
Exercise stress echocardiography	80 - 85	80 - 88
Exercise stress SPECT	73 - 92	63 - 87
Dobutamine stress echocardiography	79 - 83	82 - 86
Dobutamine stress MRI	79 - 88	81 - 91
Vasodilator stress echocardiography	72 - 79	92 - 95
Vasodilator stress SPECT	90 - 91	75 - 84
Vasodilator stress MRI	67 - 94	61 - 85
Coronary CTA	95 - 99	64 - 83
Vasodilator stress PET	81 - 97	74 - 91

**Montalescot G, Sechtem U, Achenbach S, Andreotti F, Arden C et al. The Task Force on the management of stable coronary artery disease of the European Society of Cardiology. 2013 ESC guidelines on the management of stable coronary artery disease. European Heart Journal (2013) 34, 2949–3003*

Key messages:

- In the diagnosis of CAD in patients presenting with stable chest pain, non-invasive tests may be:
  - Functional – for myocardial ischemia or
  - Anatomical – for visualization of the coronary arteries
  - It is important to determine the:
  - Pre-Test Probability (PTP) of CAD of that individual.
  - Sensitivity and specificity of the different diagnostic modalities.

Recommendation 2:

In persons with suspected CAD and having stable chest pain/angina equivalent of more than 2 months and undergoing non-invasive cardiac testing, it is important to determine the:

- Pre-Test Probability (PTP) of CAD of that individual. (Table 1, pg 22) In the Euro model for assessing PTP, (Table 1, pg 22) which this writing group has adopted, patients with a:
  - low PTP of <15% can be assumed to have no significant obstructive CAD. In these individuals, CV risk factors should be treated to target. Other causes of chest pain should be looked for.
  - intermediate PTP (≥15-≤ 85%) require futher non-invasive evaluation
  - high PTP >85% can be assumed to have significant obstructive CAD and invasive coronary angiography maybe a more appropriate investigation.

- Sensitivity and specificity of the different diagnostic modalities. (Table 6, pg 39)

6.2. Functional Tests for Myocardial ischemia in the Diagnosis of CAD

6.2.1 Diagnostic Accuracy of Exercise stress ECG

Exercise stress ECG is an important investigative tool in the diagnosis of CAD and in risk stratification. The sensitivity and specificity vary from 70-77% depending on the prevalence of CAD in the population being studied.[28] It is lower in females.

I, A

Despite its pitfalls, exercise stress ECG is a useful first line strategy in both gender in the evaluation of individuals with chest pain.[28,65-68] (Fig 1, pg 23) This recommendation differs from that of the NICE guidelines where CTA is recommended as a first line strategy in individuals with typical or atypical angina or if clinical assessment indicates non anginal pains, but the resting ECG is abnormal.[24]

Patient selection for exercise stress ECG is important. The individual should be:

- able to perform moderate physical activity (e.g. household chores, gardening or recreational work, activities of daily living). In these instances, exercise stress testing is superior to pharmacological stress because it will allow correlation with the patient's symptoms on exercise and the assessment of functional capacity.
- without disabling comorbidities such as frailty, marked obesity, peripheral arterial disease, chronic obstructive airways disease or orthopaedic limitations.

Before ordering an exercise stress ECG, the following should be evaluated:

- The individual's PTP of CAD (Table 1, pg 22, Section 6.1, pg 38-39) - The most suitable candidates are those with an intermediate PTP of CAD.
- The resting ECG - An interpretable ECG should not have any resting ST segment depression (>0.1mV), LBBB, LV hypertrophy with repolarization abnormalities, pre-excitation, paced rhythm or digoxin effect.

If the exercise stress ECG is being done for **diagnostic** reasons, it is best to stop all anti-anginal medications for at least 48 hours.

If it is being done for **prognosis**, then anti-anginal medications should be continued.

A positive exercise stress ECG includes:

- horizontal or down-sloping ST segment depression of ≥1mm (at 60-80 ms after the J point) in two contiguous leads.

- ST segment elevation of ≥1mm (at 60-80 ms after the J point) in leads that do not have Q wave(s) - This is an important marker of a high grade coronary stenosis and severe transmural ischemia.
- ST segment elevation in lead aVR, particularly if higher than lead V1, is reflective of high risk CAD, including significant left main CAD, multivessel disease or ostial/proximal left anterior descending (LAD) artery occlusion.[69,70]
- symptoms - chest pain or other ischemic equivalents.

The timing and magnitude of the ST segment changes/symptoms is an important prognostic indicator. The ST segment changes may sometimes only occur during recovery.

In addition to the ST segment changes, other important parameters that enhance the interpretation and predictive value of the exercise stress ECG include:

- Duke treadmill score - there is good correlation with mortality and the extent of CAD.[1,2] (Table 7, pg 44)
- Exercise capacity - metabolic equivalent (MET) or exercise duration. (Fig 3, pg 45)
- Presence of ventricular arrhythmias.
- Heart rate and blood pressure response.

The Duke treadmill scoring system allows a method for risk stratification:[1,2]

- Low-risk - the predicted 4-year survival was 99%, annual mortality 0.25%. Thus, in this group, no further testing is required.
- High-risk - the predicted 4-year survival was 79%, annual mortality: 5%. This group should be considered for invasive coronary angiography.
- Intermediate-risk - these patients require further evaluation using stress imaging techniques and/ or CTA

I, C The patient should be made to attain maximal symptom limited exercise level.

Achieving 85% of age-predicted maximal heart rate might not indicate sufficient stress.[71] This should not be used as criteria to terminate an exercise stress ECG. Should the patient have inadequate levels of stress, use of pharmacological stress imaging may help in further evaluation.

In the diagnosis of chest pain:

A negative stress test does not necessarily indicate absence of obstructive CAD.

If the exercise stress test is **negative** and there is:[44]

I, C
- intermediate to high probability of CAD (PTP >65%), the patient should be referred for further evaluation

I, C
- low probability of CAD, (PTP 15-65%) appropriate risk reduction therapy (lifestyle modification) should be advised. These individuals, even if obstructive CAD is present, are generally at low risk and have a good prognosis. Their long-term survival has not been shown to be improved further by interventional strategies as compared to optimal medical therapy (OMT).[72–76]

If the exercise stress test is **positive**:

I, C
- at low workloads, the patient should be referred for an invasive coronary angiogram (ICA).
- at moderate to high workloads, depending on the clinical condition, the patient may be:

I, C
  - ➢ treated conservatively with OMT if the PTP is low

I, C
  - ➢ referred for a non-invasive stress imaging test, C TA or ICA

If the exercise stress test is **inconclusive or equivocal**, depending on the clinical condition, the patient may be referred for a non-invasive stress imaging test or CTA.

Following the initiation of treatment, an exercise stress ECG may be repeated to:

- assess the efficacy of OMT +/- revascularisation
- guide an exercise regime
- reassess the clinical condition if there is a change in symptoms

I, C The benefits of routine periodic exercise stress testing in the asymptomatic individual with stable CAD is unknown.

Table 7: Duke Treadmill Score (DTS)*[1,2]

DTS	: Exercise Time - (5 x max ST) - (4 x Angina Index)
Exercise Time	: Treadmill exercise time (minutes) by Bruce protocol
Maximum ST	: Maximum net ST deviation (except aVR) (mm) **
Angina Index	: Treadmill angina index 1. No angina during exercise 2. Non-limiting angina 3. Exercise induced angina
DTS Risk	: Duke Treadmill Score **> +5:** Low risk **+4 to -10:** Moderate risk **< -11:** High risk

**Using standard Bruce protocol*
***At 80msc after the J point*

Figure 3: Nomogram of the percentage of Predicted Exercise capacity for Age in asymptomatic Individuals

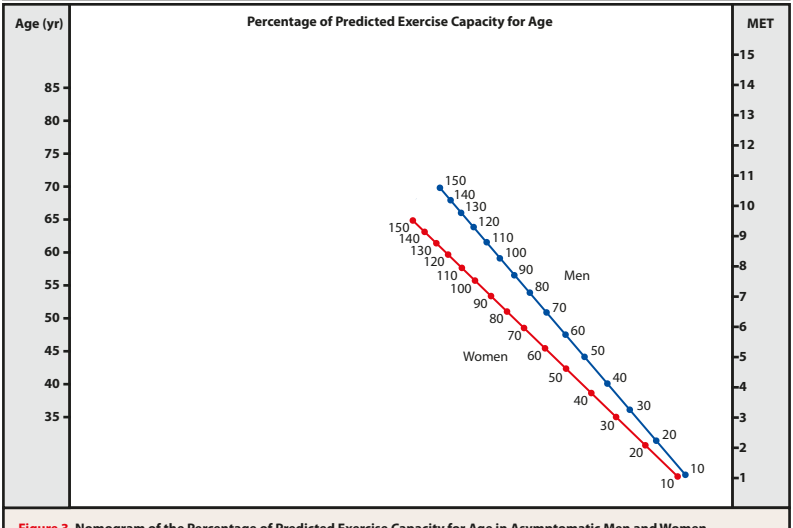


Figure 3. Nomogram of the Percentage of Predicted Exercise Capacity for Age in Asymptomatic Men and Women.
A line drawn from the patients's age on the lefthand scale to the MET value of the righthand scale will cross the percentage line at the point corresponding to the patients's percentage of predicted exercise capacity for age. The nomogram for men was modified from Morris et al.[6]

Adapted from:
Gulati M, Black HR, Shaw LJ, Arnsdorf MF, Merz NB et al. The Prognostic Value of a Nomogram for Exercise Capacity in Women. N Engl J Med 2005; 353: 468-75
Morris CK, Myers J, Froelicher VF, Kawaguchi T, Ueshima K, Hideg A. Nomogram based on metabolic equivalents and age for assessing aerobic exercise capacity in men. J Am Coll Cardiol 1993; 22: 175-182.

6.2.2 Stress testing in combination with imaging in the detection of myocardial ischemia and diagnosis of CAD

Stress testing may be performed in combination with:

- echocardiography or
- Myocardial perfusion imaging (MPI) via single photon emission computed tomography (SPECT) or positron emission tomography (PET) or
- Cardiac magnetic resonance (CMR) imaging

The stressor agent is either:

- an exercise treadmill or
- pharmacologic agents such as:
  - dobutamine in the case of echocardiography and CMR imaging or
  - vasodilators like adenosine and dipyridamole for MPI and CMR imaging

Stress imaging techniques have better diagnostic sensitivity and specificity compared to exercise stress ECG because they identify ischemia prior to changes in ECG and prior to onset of symptoms (the ischemic cascade).[77,78] They can localize the territory of ischemia and are also superior in the presence of myocardial scarring. In a study in low risk women who had good exercise capacity, both exercise ECG and stress MPI resulted in similar CV outcomes.[65] An initial strategy of exercise ECG was also more cost effective than an initial strategy of stress MPI.[65,79]

Stress echocardiogram, however, was found to be superior to exercise ECG as an initial strategy for the prediction of CAD in individuals presenting with chest pain.[80] It was also found to be cost-beneficial.[80]

These imaging techniques have the advantage that they allow better localization of ischemic areas especially in patients with prior MI, PCI or CABG. The diagnostic performance of these modalities is almost similar and the preference to use one imaging modality or the other depends on local expertise and availability.[3,81]

The choice of stress imaging technique will depend on:

- the patient - ability to exercise, obesity, lung problems which may affect image quality.
- local resources and expertise.

Prior to performing the test, the following should be considered:

- the modality is performed and interpreted by adequately trained personnel.
- each modality of testing has its own inherent risk e.g. radiation, contrast sensitivity, bodily injury and interpretation error which should be explained to the patient.

In the diagnosis of CAD, these modalities are used in individuals who have intermediate PTP of CAD and who:

- are unable to exercise adequately or
- have exercise stress ECG with equivocal results or abnormal at moderate to high workloads, or
- have un-interpretable ECG that makes interpretation of exercise stress ECG test difficult.

In the presence of LBBB and ventricular paced rhythms, stress imaging techniques are the non-invasive tests of choice although the diagnostic accuracy in these situations, is reduced.[82]

In patients with multivessel disease, imaging tests especially Stress MPI can sometimes underestimate the amount of myocardial ischemia. This is because these tests are based on the principle of perfusion differences between different myocardial territories and therefore require at least one non-ischemic myocardial territory as a "normal" reference to be able to detect inducible myocardial ischemia in another territory. If all 3 vessels are significantly narrowed or there is a combination of left main and multivessel CAD, uniform tracer uptake due to "balanced" ischemia may lead to a rather homogeneous tracer uptake and result in a false negative result.[83-85]

6.2.2.1 Diagnostic Accuracy of Stress echocardiogram - exercise or pharmacological stress (dobutamine)

This is one of the least expensive and most widely available stress imaging techniques.

I, B An exercise stress echocardiogram is more physiological than pharmacological stress and is the stress of choice wherever possible.[86,87]

Pharmacological stress is preferred if the patient is unable to exercise or if there are wall motion abnormalities seen at rest. The pharmacological stressor most often used is dobutamine. The increase in cardiac workload seen with dobutamine is less than that with exercise. The addition of atropine augments the sensitivity of the dobutamine stress echocardiogram (DSE).[86,88] With the use of dobutamine, viability can also be assessed.[89]

The marker for ischemia in stress echocardiogram is absence of wall thickening and inducible new or worsening wall motion abnormalities before, during and

after the stress.[86,87] If severe, there is also a decrease in LV ejection fraction and LV enlargement on stress.[86,87] The presence of inducible wall motion abnormalities implies significant limitation of blood flow at peak stress, and usually corresponds to a functionally significant stenosis, although the anatomic severity and physiologic consequences are poorly related.[86]

DSE has good sensitivity and specificity especially in the setting of multivessel disease and previous MI.[81,87,90-92] The interpretation is dependent on the adequacy of stress. In the diagnosis of CAD, the sensitivity of DSE is reduced in the presence of single vessel disease, small vessels and distal disease.[86] It has greater use in prognostication of CAD and for the prediction of myocardial viability.[86,87,91,93]

DSE has also a long learning curve and is relatively subjective relying on the human eye for the accurate assessment of myocardial motion. With the usage of myocardial contrast agents or microbubbles, endocardial border delineation is enhanced, and image quality and diagnostic accuracy improved.[94-96]

6.2.2.2. Diagnostic Accuracy of Myocardial Perfusion Imaging (MPI) via SPECT

MPI most commonly uses technetium-99m sestamibi as the radiotracer and SPECT for imaging. Stress can be either by exercise or pharmacological agents - adenosine, dipyridamole or dobutamine.

Ischemia is indicated by reduced radiotracer uptake during stress when compared with the uptake at rest. Transient ischaemic dilatation and reduced post-stress LV ejection fraction are important predictors of severe CAD.

SPECT detects a relative reduction in myocardial blood volume that occurs earlier than wall thickening abnormality in the ischaemic cascade. Despite this, SPECT has not been shown to be significantly superior to stress echocardiography in terms of sensitivity and detecting the extent of CAD.[97] This is due to the poorer spatial resolution of SPECT (12mm) as compared to stress echocardiography (2mm).[91]

In the diagnosis of CAD, MPI with SPECT has good sensitivity and specificity.[98] The diagnostic image quality is affected in obese patients, as well as in women with large breasts. The diagnostic accuracy is also reduced in the presence of LBBB and ventricular pacing.[82,99] Other disadvantages are the use of ionizing radiation and its cost.

6.2.2.3 Diagnostic Accuracy of Stress Cardiac Magnetic Resonance (CMR)

Stress CMR with the use of dobutamine can be used to look at regional wall motion abnormalities similar to DSE and with a similar safety profile.[100-102] In studies on patients with high disease prevalence, stress CMR demonstrated overall good sensitivity and specificity for the diagnosis of CAD.[103-105] It is particularly useful in patients where it is difficult to acquire good echocardiographic images due to poor acoustic windows.

Perfusion CMR (with adenosine) also has good diagnostic accuracy as compared to MPI (nuclear studies).[101,105-107] It has also demonstrated good correlation with Pressure wire (Fractional Flow Reserve) measurements.[108]

6.3. Anatomical testing in the Diagnosis of CAD

6.3.1 Coronary Calcium Score (CAC)

Calcium accumulates in coronary arteries in an age-related manner. Thus, all scores must be adjusted for age, as well as for sex.[109] The relationship of arterial calcification, like that of angiographic coronary artery stenosis, to the probability of plaque rupture is unknown. Vulnerable plaques are frequently present in the absence of calcification.[109]

Coronary calcium score has been used to detect CAD. Most studies demonstrated a high sensitivity but a much lower specificity, and an overall predictive accuracy of ≈ 70% in typical CAD patient populations.[109] CAC was found not to be superior to other non-invasive diagnostic modalities for the detection of CAD.[109] In general, a negative test (CAC =0):[109]

- makes the presence of atherosclerotic plaques, including unstable plaques, very unlikely.
- is highly unlikely in the presence of significant luminal obstructive disease.
- occurs in most patients who have angiographically normal coronary arteries.

CAC score is more useful in CV risk assessment. (Section 7.5.1, pg 56)

In the emergency room, CAC may be used in the triage of patients with a negative resting ECG and normal cardiac biomarkers. A CAC=0 has a high sensitivity and a very high negative predictive value for CAD.[110,111]

6.3.2 Diagnostic Accuracy of Computed Tomography Angiography (CTA)

CTA allows visualization of the coronary arteries non-invasively. It can also determine the extent of coronary calcification, degree of luminal stenosis, degree of luminal remodelling and plaque characteristics.

It is usually done as a 2-stage procedure. The first being the quantification of coronary calcium (CAC) and the second is the CTA. The 64-slice detector is the minimum machine requirement. It has a negative predictive value of 93-99% and sensitivity and specificity of 90-94% and 95-97% respectively.[112-120] It is most useful in the diagnostic assessment of individuals with low or intermediate PTP of CAD.[112–115]

Careful patient selection and preparation is integral to obtaining good images. These include:

- patients with adequate breath holding capabilities.
- absence of severe obesity.
- a favourable calcium score (<400 Agatston score) and distribution.
- presence of sinus rhythm (absence of ectopics).
- heart rate of less than 65 beats per minute.

A high coronary calcium score reduces the accuracy of the test.[112] However, per-segment calcification (circumferential extent of calcium - arc calcium) has a stronger influence on diagnostic accuracy than the total calcium score.[121] Coronary CTA interpretation is less reliable in the presence of coronary stents of <3mm.[122] In situations where the clinical presentation suggests low-to-intermediate probability for restenosis and in the presence of larger stents, coronary CTA may be a reasonable alternative to invasive angiography to rule out significant in-stent restenosis.[123]

It is highly accurate in the assessment of coronary artery bypass grafts.[124] The interpretation of native coronary vessels in post bypass patients is however, more difficult.[124]

I, A

CTA may be considered in:

- individuals with low to intermediate PTP of CAD and who have mild or equivocal changes of ischemia in the exercise stress test or stress imaging tests and who are asymptomatic or mildly symptomatic with good exercise capacity.[112–115]

III, C CTA should not be used as a screening test for CAD in the asymptomatic individual.

Due to the low prevalence of disease in most individuals undergoing health screening, there tends to be too many false-positive lesions. Also, many minor lesions not causing ischemia may be found, potentially resulting in unnecessary downstream invasive procedures and intervention.

6.3.3 Diagnostic Accuracy of Invasive Coronary Angiography (ICA)

Invasive Coronary angiography has been the “gold standard” for the diagnosis of CAD. It can detect obstructive lesions with negative remodelling accurately but unlike CTA, it may not be able to detect non-obstructive lesions with positive remodelling where the lumen diameter may be maintained.

I, C ICA is rarely necessary in stable patients with suspected CAD for the sole purpose of establishing the diagnosis of CAD. It is indicated, following non-invasive risk stratification, to determine the most appropriate mode of revascularization.

Key messages:

In the **diagnosis** of CAD in patients presenting with stable chest pain:

- Exercise stress ECG is the non-invasive test of choice in patients who can exercise and have interpretable ECGs.
  - If the exercise stress test is negative and there is:
    - intermediate to high probability of CAD (PTP >65%), the patient should be referred for further evaluation.
    - low probability of CAD, (PTP 15-65%) appropriate risk reduction therapy and treatment of CV risk factors to target should be advised. These individuals, even if obstructive CAD is present, are generally at low risk and have a good prognosis. Their long-term survival has not been shown to be improved further by interventional strategies as compared to OMT.
  - If the exercise stress test is **positive** at:
    - low workloads, the patient should be referred for an invasive coronary angiogram (ICA).
    - moderate to high work loads, depending on the clinical condition, the patient may be:
      - treated conservatively with OMT.
      - referred for a non-invasive stress imaging test, CTA or ICA.
- Stress imaging tests are used in individuals who have intermediate PTP of CAD and who:
  - are unable to exercise adequately and/or
  - have uninterpretable resting ECG and/or
  - have exercise stress ECG with equivocal results or which are abnormal at moderate to high workloads depending upon the clinical condition.
- Coronary Calcium has been used to detect CAD but is more useful for CV risk assessment.
- CTA:
  - May be considered in individuals with low to intermediate risk PTP of CAD and who have mild or equivocal changes of ischemia in the exercise stress test or stress imaging tests and who are asymptomatic or mildly symptomat ic with good exercise capacity.
  - It should not be used as a screening tool for CAD in the asymptomatic individual.

Recommendation 1:

In the diagnosis of CAD in patients having stable chest pain/angina equivalent:

- Exercise stress ECG is the non-invasive test of choice in patients who can exercise and have interpretable ECGs.
- Stress imaging tests are used in individuals who have intermediate PTP of CAD and who:
  - are unable to exercise adequately and/or
  - have uninterpretable resting ECG and/or
  - have exercise stress ECG with equivocal results or which are abnormal at moderate to high workloads depending upon the clinical condition.
- Coronary Calcium has been used to detect CAD but is more useful for CV risk assessment.
- CTA:
  - May be considered in individuals with low to intermediate risk PTP of CAD and who have mild or equivocal changes of ischemia in the exercise stress test or stress imaging tests and who are asymptomatic or mildly symptomatic with good exercise capacity.
- Invasive Coronary Angiogram (ICA)
- ICA is rarely necessary in stable patients with suspected CAD for the sole purpose of establishing the diagnosis of CAD. It is indicated, following non-invasive risk stratification, to determine the most appropriate mode of revascularization.

7. RISK STRATIFICATION IN STABLE CAD

The objectives of risk stratification in stable CAD are for:

- prognosis
- choosing the appropriate management strategy (e.g. revascularisation in high risk groups)

Absolute levels of what constitutes high risk and low risk are not clearly defined for those with stable CAD. There are several risk assessment scores for individuals with stable CAD using different CV end points.[1,2,64,125-128]
The ESC guidelines define risk as:[44]

- high risk - annual mortality of >3%
- intermediate risk - annual mortality of 1-3%
- low risk - annual mortality of <1%

Patients with stable CAD should be risk stratified using the following parameters:

- clinical evaluation
- resting ECG
- assessment of left ventricular function
- non-invasive assessment of myocardial ischemia
- where indicated, evaluation of coronary anatomy and physiological assessment of the significance of the coronary lesion

7.1 Risk Stratification of Stable CAD by Clinical Evaluation

I, B

Important predictors of adverse outcomes in patients with stable CAD are:[28,63,129–142]

- 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
- presence of atherosclerotic disease in other vascular beds - peripheral vessels, cerebral and/or aorta
- presence of CV risk factors:
  - Diabetes
  - Hypertension
  - Metabolic syndrome
  - Current smoking
  - Dyslipidaemia
  - Family history of premature CAD
- co-existing medical conditions:
  - Diabetes
  - Chronic Kidney Disease (CKD)
- psychosocial factors
  - Depression
  - Poor social support

The above adverse clinical predictors especially the severity of angina help modulate decisions made based on non-invasive tests of ischemia and where indicated, physiological testing by Fractional Flow Reserve (FFR).

7.2 Risk Stratification of Stable CAD by Resting ECG

I, B Resting ECG abnormalities can predict patients at greater risk of future CV events than those with a normal ECG. These abnormalities include:[63,127,133,135,143-145]

- evidence of prior MI
- LBBB
- left anterior hemiblock,
- Left ventricular hypertrophy (LVH)
- second or third-degree AV block
- atrial fibrillation (AF)

7.3 Risk Stratification of Stable CAD by Left Ventricular Function

LV function is the strongest predictor of survival. Patients with an LVEF of <50 % are already at high risk of CV death (annual mortality rate of >3%) without incorporating other risk factors.[45,46,133,134,146,147]

I, B In the presence of a depressed LV function, it is important to determine if this is due to infarcted (scar) tissue or viable but stunned ischemic myocardium. This can be done by stress imaging techniques. In the presence of ischemic but viable myocardium, coronary revascularisation can result in an improvement in LV function and survival.[148]

7.4 Risk Stratification of Stable CAD by Non-invasive Testing

Non-invasive tests provide useful information for prognostication. (Table 2, pg 24) A negative test carries a good prognosis but the clinical evaluation (e.g. age, ability to exercise, exercise duration, co-morbidity such as
I, C diabetes, CKD etc) and LV function should also be considered when assessing CV risk.

I, C

Small imaging sub studies have shown mixed results when looking at CV outcomes in individuals with moderate to severe ischemia treated with
IIa, C revascularization as compared to OMT.[149–152] Two large clinical trials have not shown any advantage of revascularization as compared to OMT in these patients.[76,153] In individuals with depressed LV function (LVEF ≤35%) CABG did not reduce all-cause mortality but resulted in a reduction in CV mortality and hospitalizations.[154] The ISCHEMIA trial is a large randomized clinical trial

that is currently underway specifically addressing the role of revascularisation versus OMT in patients with moderate to severe myocardial ischemia.[155]

In patients with unprotected Left Main stem stenosis of > 50%, revascularisation by CABG has been shown to improve survival in the pivotal Coronary Artery Surgery Study (CASS) Registry.[156] In view of this "the benefit of surgery over medical treatment in patients with significant LMS stenosis (greater than 50%) is little argued." [157]

7.5. Risk Stratification of Stable CAD by Anatomic testing

7.5.1 Coronary Calcium (CAC) Score

IIa, B CAC scores help with CV risk stratification.[158-163] (Table 8, pg 57) It guides risk reduction strategy, OMT and the need for further evaluation.

CAC score alone was able to predict CHD risk independently of the Framingham Risk Score.[156,157] When used together with the traditional CV risk factors, it had incremental value in CV risk prediction.[164,165] There is a significant correlation between CAC score and overall coronary artery atherosclerotic plaque, with a high sensitivity >95% and a high negative predictive value of >95%.[109,166,167] The CAC score was found to be highly predictive of CV risk in 4 ethnic groups - white, black, Hispanic, and Chinese.[168]

Persons both asymptomatic and symptomatic, with a calcium score =0 have a low CV event rate and an excellent long-term survival.[167,169] However the PTP of disease and the clinical setting should be considered when interpreting the test result. In interpreting a CAC =0:[170]

- if the PTP of CAD is low (e.g. asymptomatic individuals), there is low risk of CAD and a low risk of near-term coronary events.
- in older asymptomatic patients with risk factors, there is a moderate increased risk of CV events.
- in persons with clinical signs and symptoms associated with an intermediate to high risk of CAD, there is often associated myocardial ischemia on provocative testing and a high risk of near-term coronary events.[171]

Table 8: Coronary Calcium score and CV risk*#

Calcium score	HR for incident MI and CHD mortality	CV Risk (Risk of death at 10 years)
0-100	1.0	Mild
101-400	2.4	Moderate
401-1000	5.1	High
>1000	7.6	Very High

**Based on a prospective study of subjects ≥55 years of age that began in 1990, mean age 71 years and adjusted for age, sex, body mass index, hypertension, total cholesterol, HDL-Cholesterol, smoking, diabetes and a family history of MI.*

#Vliegenthart R, Oudkerk M, Hofman A, Oei HH, van Dijck W, van Rooij FJ, Witteman JC. Coronary calcification improves cardiovascular risk prediction in the elderly. Circulation. 2005:112:572-7.

7.5.2 Computed Tomography Angiography (CTA)

IIa, A CTA may also be used for prognostication. There is a strong predictive value for mortality and major CV events independent of traditional risk factors.[7-9,172-174]

In assessing prognosis, in patients with:

- absence of any plaque the CV event rate is low - 0.24% for CV death/non-fatal MI and an annual mortality of 0.28%.[7,8]
- coronary plaque but without stenosis, the mortality rate is higher but remains below 0.5%.[9]
- left main stenosis or proximal triple vessel disease - the hazard ratio for all-cause mortality is 3.70.[7]

Despite its' excellent predictive value, in a randomized controlled trial comparing functional testing with MPI using SPECT and CTA as initial diagnostic strategies in patients with suspected CAD, there were no differences in clinical outcomes.[59]

I, A Due to the potential overestimation of obstructive coronary disease by CTA, it may be advisable to perform additional testing for the presence of ischemia prior to revascularization in the asymptomatic individual.[175,176]

7.5.3 Risk Stratification by Invasive Coronary Angiography (ICA)

ICA continues to be the "gold standard" in assessing coronary anatomy although it has its limitations. It cannot detect vulnerable plaques which are in most cases not severe (<50% stenosis) but have a rich lipid core.

Despite these limitations, the extent and site of coronary lesions provide good prognostic indicators. The prognosis is worse if: [46,146,147]

- the greater the number of vessels involved.
- there is left main stem stenosis of >50%.
- the proximal LAD is involved.

Recent large clinical trials did not however, show any improvement in clinical outcomes in patients with significant stable CAD when an initial strategy of coronary revascularization was compared to intensive OMT.[76,153,154]

In patients who have unprotected left main stem stenosis, CABG has been shown to improve survival when compared to medical therapy in the large CASS registry.[156] Although this trial was performed before the era of current intensive OMT, it is considered unethical to repeat it.

III, C

Coronary arteriography should **NOT** be performed in patients:

- with angina who refuse invasive diagnostic procedures.
- who prefer to avoid coronary revascularization either by PCI or CABG.
- who are not candidates for PCI or CABG.
- in whom PCI/CABG will not improve quality-of-life.

7.5.4 Risk assessment by Physiological Assessment of the functional severity of coronary lesions

Coronary angiography is of limited value in defining the functional significance of coronary stenosis. Yet the most important factor related to outcome is the presence and extent of inducible ischemia.[177] If a stenosis is not flow-limiting, it will not cause angina and the prognosis without coronary intervention is excellent, with a 'hard' event rate (cardiac death or non-fatal MI) of <1% per year.[175] This event rate was not reduced with PCI and stenting.[175]

7.5.4.1 Fractional Flow Reserve (FFR)

The functional severity of coronary lesions visualized angiographically may be assessed invasively, by measuring the intracoronary artery pressure or Fractional Flow Reserve (FFR). FFR is more accurate than visual assessment of the significance and severity of coronary lesions.[176] Even in the presence of angiographically insignificant stenosis, lesions with low FFR showed significantly higher event rates than those with high FFR.[178]

FFR is presently considered as the **'gold standard'** for invasive assessment of the significance of coronary stenosis and is useful in decision making in the need for coronary revascularization. This: [84]

- takes into consideration collateral blood flow.
- takes into consideration the amount of viable myocardial mass.
- is independent of haemodynamic variations.
- has a high reproducibility.

FFR is indicated for all coronary artery stenosis of 50-90%, including left main stenosis, side branch stenosis, tandem lesions and even in the setting of non-culprit lesions in ACS.[84,179-181] In patients with multivessel CAD, PCI guided by FFR results in an improved outcome irrespective of available non-invasive functional test results.[182-184]

FFR is calculated as the ratio of distal coronary pressure to aortic pressure measured during maximal hyperaemia with either intracoronary or intravenous infusion of adenosine. A normal value for FFR is 1.0 regardless of the status of the microcirculation. In individuals on OMT with:[84,179-184]

- FFR >0.80 - have no improved outcomes with revascularisation.
- FFR between >0.75 but <0.8 - have intermediate benefit with revascularisation and management should be based on clinical judgement.
- FFR <0.75 - benefit from revascularisation.

Use of FFR accurately identifies which coronary lesions should be revascularized and improves outcome.

I, A It is recommended that in individuals with stable CAD, FFR be used to guide revascularization of lesions of intermediate severity.[182-185]

At present, there are ongoing studies on the use of instantaneous wave-free ratio (iFR), a pressure-derived index of stenosis severity that is not obtained

with the administration of a vasodilator such as adenosine.[186-188] The cut-off point is 0.89 when compared to 0.80 for FFR.[186] The initial clinical trials indicate that an iFR-guided revascularization strategy was non-inferior to an FFR-guided revascularization strategy.[187,188]

FFR may also be assessed using CT. A recent meta-analysis showed that FFR_{CT} achieves a moderate diagnostic performance for non-invasive identification of ischemic lesions in stable patients with suspected or known CAD in comparison to invasive FFR measurement.[189] This tool is not yet widely available.

7.5.4.2 Intravascular Ultrasound / Optical Coherence Tomography

FFR provides physiological assessment of the severity of a coronary lesion, while intravascular ultrasound (IVUS) and optical coherence tomography (OCT) allow visual assessment of the lesion. IVUS makes use of the minimum lumen area (MLA) as the marker for significance of coronary stenosis. Overall, IVUS studies showed a relatively high negative predictive value but a low positive predictive value for ischemia.[190]

IIa,B Both IVUS and OCT should not be performed to determine the functional significance of a coronary lesion before intervention.[191] These are useful in optimizing stent deployment and determining the size of the vessel undergoing stent implantation.

7.6 Guidelines for referral to a tertiary cardiac center

Following risk stratification:

Low risk individuals should be managed with risk factor reduction and/or anti anginal medications as necessary. No further intervention is required.

Intermediate risk individuals may be managed with risk reduction strategies +/- anti anginal therapy or considered for invasive coronary angiogram and revascularization depending on the clinical condition and patient preferences.

High risk individuals in addition to risk reduction strategies, should be considered for invasive coronary angiography with view to revascularization.

Low risk individuals can be managed in the general outpatient clinics with Family Medicine Specialists. Intermediate and high risk individuals should be referred to tertiary cardiac centers for further evaluation and revascularisation as indicated.

Key messages:

- Risk may be defined as:
  - high risk - annual mortality of >3%
  - intermediate risk - annual mortality of 1-3%
  - low risk - annual mortality of <1%

Recommendation 4:

- All patients with suspected or known CAD should be risk stratified.
- This is done by:
  - Clinical evaluation
  - Resting ECG
  - Non-invasive assessment of myocardial ischaemia
  - Assessment of Left ventricular function
  - Where indicated, evaluation of coronary anatomy (non-invasively by CT or by invasively) and physiological assessment of the significance of the coronary lesion by Fractional Flow Reserve (FFR)
- Low risk individuals (annual mortality <1%) should be managed with risk factor reduction and/or anti anginal medications as necessary. No further intervention is required.
- Intermediate risk individuals (annual mortality 1-3%) may be managed with risk reduction strategies +/- anti anginal therapy or considered for invasive coronary angiogram and revascularization depending on the clinical condition and patient preferences.
- High risk individuals, (annual mortality >3%) in addition to risk reduction strategies, should be considered for invasive coronary angiography with view to revascularization.

Recommendation 5

- Low risk individuals can be managed in the general outpatient clinics with Family Medicine Specialists.
- Intermediate and high risk individuals should be referred to tertiary cardiac centers for further evaluation and revascularisation as indicated.

8. MANAGEMENT (Fig 2, pg 25)

The treatment goals in stable CAD are to:

- alleviate symptoms and improve quality of life,
- reduce risk of adverse CV outcomes and improve survival and
- prevent progression of atherosclerotic disease.

Optimal Medical Therapy (OMT) is the cornerstone of management of patients with both obstructive and non-obstructive CAD.[72,76,153,154] It has been shown to improve prognosis, reduce symptoms and myocardial ischemia.[72,76,153,154]

I, A

OMT involves:

- intensive lifestyle changes (healthy diet, regular physical activity, smoking cessation and optimal management of risk factors and weight) *and*
- pharmacotherapy which includes:
  - anti-platelet agents *and*
  - statins to achieve target LDL-C.

In addition, ACEi, β-blockers and anti-anginal medications may be necessary to treat co-existing hypertension, LV dysfunction and/or angina.

The management of these patients with Stable CAD should be multifaceted and include:

- behavioural modification therapy (BMT) - patient education and lifestyle modification *and*
- pharmacological therapy *and*
- myocardial revascularization when indicated.

All patients should be educated on behavioural modification therapy and receive OMT for survival benefit. Treatment of CV risk factors to target and adherence to treatment recommendations should also be addressed.

8.1 Behavioural modification therapy (BMT)

8.1.1. Patient education

This should include:

- cause of angina and factors that can provoke symptoms.
- circumstances in which urgent medical attention should be sought, especially if there is a sudden worsening in symptom frequency or severity.
- role and importance of behavioural modification.
- risk-benefit profile of pharmacological treatments.
- importance of adherence to treatment recommendations and OMT.

8.1.2 Diet

Dietary habits influence a variety of cardio-metabolic risk factors such as body weight, cholesterol, blood pressure, glucose metabolism, oxidative stress and inflammation.[192,193] It is being increasingly recognized that instead of focussing on specific nutrients, it is more important to look at specific foods and overall dietary patterns.[192,193] A Mediterranean diet significantly reduces CV events.[194–200] The Dietary Approaches to Stop Hypertension (DASH) diet is associated with a significant reduction in hypertension.[201] A 'high-fat/low-fibre' and 'high-sugar' diet showed a trend for an increased risk of CV events in older men aged 60-79 years.[202]

General recommendations should fit in with the local culture. Energy intake should be adjusted to avoid overweight/obesity. (Table 9, pg 65) Refer to CPG Prevention of Cardiovascular Disease 2017.[22]

8.1.3 Physical activity

Any amount of physical activity (PA) is better than none, as it can offer health benefits.[203] As secondary prevention in patients with stable CAD and post ACS, regular PA confers significant mortality and morbidity benefits.[204-208] Thus it should be incorporated into daily activities.

PA is any bodily movement that substantially increases energy expenditure. This includes: (Table 10, pg 66)

- leisure-time physical activities
- occupational activities
- commuting activities
- exercise: a subset of PA that is planned and structured, involving repetitive bodily movement done with a goal to improve or maintain physical fitness.

Aerobic exercise should be offered to patients with stable CAD, usually as part of a structured cardiac rehabilitation program. This is a medically supervised program consisting of exercise training, education on heart healthy living and counselling to reduce stress. It helps patients return to an active lifestyle and recover more quickly.

In addition, a cardiac rehabilitation program:

- helps the identification and management of comorbid conditions and psychosocial disorder (anxiety and depression).[209,210]
- ensures patient adherence to medical and lifestyle therapies to achieve cardiovascular (CVD) prevention goals.[211]

I, B The recommended duration of PA in healthy adults regardless of age is:[22,212,213]

- at least 150 minutes a week of moderate intensity or
- 75 minutes a week of vigorous intensity PA or an equivalent combination

I, B Sedentary patients should be strongly encouraged to start light-intensity exercise programmes after an adequate exercise-related risk stratification.[214]

In patients with significant CAD who are not candidates for revascularization, exercise training may offer an alternative means of symptom alleviation and improved prognosis.

I, B All individuals should be encouraged to exercise. Any amount of PA is better than none.[203–208]

Wherever possible, individuals should be referred to physiotherapists/ exercise physiologists for exercise prescription.

Table 9: Nutritional Recommendations

A	Recommended Nutrient Intake; Dietary Patterns	Grade of Recommendation and Level of Evidence
	Fat requirements • 20-25 % with an upper safe limit of 30% of energy from fat ➢ 7-10% saturated fatty acid (SFA) ➢ Substitute SFA with monounsaturated fatty acid (MUFA) / polyunsaturated fatty acid (PUFA) ➢ PUFA/MUFA should represent the rest of the calorie intake from fat	I,B I,B
	• <1 % trans fatty Acid (TFA) ➢ Minimise consumption of high fat processed meat (sausages, corned meat, nuggets, salami, burger, pepperoni, ham, serunding etc) and bakery products including cakes, biscuits, frozen pizza, cookies, crackers, and hard margarines and other spreads ➢ Reduce consumption of partially hydrogenated fats	I,A
	Cholesterol rich foods/eggs • No evidence for restriction.* However, it must be cautioned that dietary cholesterol-rich foods such as beef and pork also carry significant content of SFA which are known to increase TC and LDL-C levels.	IIa,B
	Protein • 10-20 % of energy intake	I,B
	Carbohydrate (CHO) • 50-60 % of energy intake ➢ Encourage high fibre, complex CHO, wholegrains, fruits, vegetables ➢ Limit intake of sugar to 5-10% of energy intake. This includes sugar sweetened beverages, kuihs etc	I,B I,A
	# Malaysian Healthy Plate and Current Healthy Eating Recommendation • Increase plant-based foods such as nuts, legumes, beans, fruits and vegetables. (taufu, tempe, 'ulam') • Consume whole grain foods (oats, barley, bran, brown rice) • Eat fish more often (oily/marine fishes - e.g. oily 'kembong/ pelaling', patin, keli, terubuk) • Consume low-fat dairy products • Consume less sweet foods (no added sugar, limit canned and carbonated drinks, fruit juices and 3in1 beverages) • Healthy oils (use blended oils, peanut oil, sunflower oil, olive oil, canola oil and corn oil) • Reduce intake of processed/salty foods.	I,B
B	**Individual Dietary Pattern**	
	• Dietary fibre of 20-30 g fibre per day (vegetables, fruits, legumes and whole grain cereals are encouraged)	I,B
	• Whole grain should form 50% of the total grain intake	I,B
	• 5 servings of fruits and vegetables per day	I,B
	• 30 gram unsalted nuts per day	IIa,B
	• <10% of total energy intake from added sugar. This is equivalent to 50 g (or around 12 level teaspoons) for an adult of healthy body weight consuming approximately 2000 calories per day	I,A
	• <5 g salt or 1 level teaspoon per day or (2000 mg sodium per day)	I,A
	• Abstinence or not more than 1-2 standard servings of alcohol intake per day.	IIa,B

**In individuals with Very High and High CV risk advise < 200mg cholesterol a day*

Table 10: Classification of Physical Activity*

Pa Intensity	Leisure Time & Sports	Occupational	Commuting	Exercises
Low	• Walk with pet • Push stroller with child • Bowling, recreational • Golf, recreational • Slow ballroom dancing	• Sweeping floor, mopping, vacuuming • Washing car • Doing laundry, washing dishes, cooking • Childcare & elderly care • General plumbing & light gardening • Commercial driving, moderate machinery operation • Typing, desk job, light office work	• Driving automobile/ light trucks • Pushing wheelchair on flat surface • Walking from house to car/bus to places/ worksite	**Aerobic Exercise:** • Walking (4.0-4.8 kmh) • Yoga • Stretching • Pilates • Rowing machine, moderate pace Resistance training (moderate effort): • Circuit training
Moderate	• Vigorously playing with children • Non-competitive sports: ➢ Cricket ➢ Ping-pong ➢ Badminton ➢ Basketball ➢ Kayaking/ paddle boat ➢ Snorkelling ➢ Backpacking	• Scrubbing bathroom • Carrying/ moving boxes • Using a hoe & spade, mowing lawn, shovelling 10-15 minutes vigorously • Moderate yard work, using power tools,	• Cycling • Walking and carrying approx. 7kg load • Walking uphill • Using crutches	**Aerobic Exercise:** • Fast walking (5-8kmh) • Combination of jog & walk (< 10 minutes jogging) • Stationary bicycle • Elliptical machine • Slow-moderate swimming • Water-based aerobics Resistance training, (vigorous effort) • Weight training
High	• Rope skipping • Marathon, mountain biking • Football, hockey, martial arts, rugby, rollerblading, volleyball • Track & field	• Carrying load up stairs • Heavy carpentry/ farming • Farming vigorously • Fire fighting • Commercial fishing • Factory work	• Fast stair climbing • Hiking cross country	**Aerobic Exercise:** • Jog/ run > 8km/hr • Vigorous swimming or calisthenics • Stair-treadmill

**Adapted from Ainsworth BE, Haskell WL, Hermann SD et al. The Compendium Of Physical Activities Tracking Guide. Healthy Lifestyles Research Centre, College of Nursing & Health Innovation, Arizona State University.*

8.1.4 Smoking Cessation

Smoking is an independent risk factor for CVD.[215]

It also interacts with other CV risk factors, such as glucose intolerance and low serum levels of HDL-C in a multiplicative manner[215–217] Examples:

- the presence of smoking alone is reported to double the level of risk, but the simultaneous presence of another major risk factor is estimated to quadruple the risk (2 × 2).[215]
- the presence of two other risk factors with smoking may result in approx imately eight times the risk (2 × 2 × 2) of persons with no risk factors.[215]

I, B Smoking is an important cause of plaque rupture leading to ACS.[218] Data from the NCVD-ACS Registry 2014-2015 showed that 37% of patients were smokers.[30] In the INTERHEART study, a dose response relationship was demonstrated between the number of cigarettes smoked and MI, where smokers who smoked >40 cig/day were found to have a 9-fold relative risk of MI compared with non-smokers.[219]

Changing cigarette designs such as filtered, low-tar, and "light" variations, have not reduced overall disease risk among smokers.[215]

Stopping smoking after an MI is the most effective prevention measure.[215] There is significant reduction on morbidity within the first 6 months of quitting and the risks of CVD almost equals the risk of never smokers after 10-15 years of cessation.[215]

Patients may be referred to the mQuit Services. Currently this smoking cessation service is being implemented both in government and private facilities including general practice clinics, private hospital and community pharmacies. More information is available at www.jomquit.moh.gov.my

Non-smokers exposed to second-hand smoke increase their risk of developing:[220]

- CHD by 25-30%.
- stroke by 20-30%.
- lung cancer by 20-30%.

There is no safe level of exposure to second-hand tobacco smoke.[220]

III, B E-cigarette aerosol (vaping) is harmful.[221,222]
- The use of products containing nicotine poses dangers to youth, pregnant women, and foetuses.
- Nicotine exposure during adolescence can cause addiction and can harm the developing adolescent brain.

The use of e-cigarettes and shisha are not recommended.[221,222]

8.1.5. Weight management

Both overweight and obesity are associated with an increased risk of death in CAD.

Obesity increases the risk of:[223–225]
- all-cause mortality by about 20%.
- overall CV mortality by 50%.
- CHD mortality by about 50% in women and about 60% in men.

Every 5 kg/m² higher BMI, was associated, on the average, with a 30% higher overall mortality and 40% increase for vascular mortality. [225] In morbid obesity (BMI ≥40 kg/m²) CV mortality is increased by 200% to 300%.[226] The presence of sleep apnoea symptoms should be carefully assessed, especially in obese patients. Sleep apnoea has been associated with an increase in CV mortality and morbidity.[227,228]

Weight loss is a challenge and preventing weight regain after weight loss may be even more difficult. Modest weight loss of between 5 to 10%, can reduce blood pressure (BP), improve glycaemic control, lipid profile, and quality of life.[229]

I, B The goals of weight management are to achieve 5 to 10% weight loss [229-234] and to maintain this over a period of 1-2 years before attempting further weight loss.

Methods of weight loss include dietary intervention, increased physical activity, behavioural modifications (e.g. self-monitoring of eating habits), pharmacological agents and bariatric surgery.

Anti-obesity drugs that are available locally are:

- Sympathomimetic (Phentermine) - this drug should not be used continuously for longer than 6 months at any one time.[235,236]
- Lipase Inhibitor - Orlistat.[237-239]
- Glucagon-like peptide 1 Receptor Agonist - Liraglutide.[240]

IIa, B These drugs may be considered for overweight and obese people with: [22]

- BMI >25.0 kg/m^2 plus 2 CV risk factors or
- BMI ≥27.0 kg/m^2 after failing to lose weight despite 6 months of lifestyle modification

IIa, B In patients with morbid obesity, bariatric surgery may be considered.[22,241, 245]

8.2. Pharmacological therapy

The aims of pharmacological therapy in patients with both obstructive and non-obstructive CAD are to:

- prevent future CV events and
- relieve symptoms of angina and improve quality of life.

8.2.1. Prevention of future CV events

This is achieved by:

- reducing the progression and possibly causing regression of the coronary atherosclerotic plaque,
- stabilizing the plaque and
- preventing thrombosis in the event of plaque rupture.

8.2.1.1. Antiplatelet agents and anticoagulants

A) Antiplatelet agents

In patients with stable CAD, aspirin reduces the risk of non-fatal MI, non-fatal stroke and vascular death by 22%.[246-248]

I, A Aspirin monotherapy at a dosing of 75-150 mg daily remains the initial antiplatelet agent of choice.[246-248]

In patients who cannot tolerate aspirin, alternatives include:

I, A • Clopidogrel[249]

IIb, B • Ticlopidine - its use is limited by the scarcity of evidence on cardiac outcomes and the associated risk of blood dyscrasias.[250]

IIb, B • Triflusal - Triflusal is an antiaggregant related to the salicylate group. A review did not find any difference between trifusal and aspirin in secondary prevention of stroke or MI.[251]

Ticagrelor and prasugrel as monotherapy have not been studied in patients with stable CAD.

Dual antiplatelet therapy (DAPT) has been shown to reduce all-cause mortality, MI and stroke post ACS whether this is managed medically, by PCI or surgically. The current recommendation is for DAPT for 12 months post ACS.[22,252,253]

Following an ACS, the risk of a recurrent cardiac event remains high.[17-19,254] This may be due to stent thrombosis (late, very late), in-stent restenosis and/or de novo lesions.

The use of DAPT (aspirin + thienopyridine) beyond one year has been shown to reduce additional ischemic events but the risk of bleeding is also increased.[255–257] Similarly, in an extended >one year study of patients post ACS, the use of aspirin in combination with ticagrelor was also associated with a reduction in ischemic events but at the cost of an increased risk of bleeding.[258]

IIa, A The use of DAPT beyond one year, in patients with stable CAD who have undergone PCI and stenting, has to be individualized weighing the risk of a recurrent ischemic event versus bleeding risks.[22,253]

IIa, B In patients with high bleeding risk, the duration of DAPT post stenting can be shortened.[259,260]

B) Newer Oral Anticoagulant (NOACs) / Anticoagulant therapy (Table 11, pg 72)

I, A — In patients with Stable CAD, **NOACs** are indicated for:

- Non-valvular AF both paroxysmal and persistent depending on the CHA2DS2-VASc score.[22,261,262]

IIa, A
- Valvular AF (excluding mechanical heart valves and rheumatic mitral stenosis)[263]

IIa, B — In these patients, concomitant antiplatelet agents is not warranted.[264]

In patients with AF who have undergone PCI and stenting with drug eluting stents, the use of NOACs with antiplatelet therapy is associated with a lower risk of bleeding than the standard triple therapy (DAPT + warfarin).[265] The following regimens are recommended: [266,267]

IIa, B
- ➢ Rivaroxaban 15mg daily (10mg if Creatinine clearance: 30 to 50ml per minute) + clopidogrel 75mg daily (or ticagrelor at a dose of 90mg twice daily or prasugrel at a dose of 10mg once daily)

IIa, B
- ➢ Rivaroxaban 2.5mg BD and DAPT - aspirin 75 to 100 mg per day + clopidogrel 75mg once daily (or ticagrelor at a dose of 90mg twice daily or prasugrel at a dose of 10mg once daily) - The duration of DAPT will depend on the risk of stent thrombosis versus bleeding risk. This dose of rivaroxaban is yet to be registered in Malaysia.

or,

IIa, B
- ➢ Dabigatran 110 or 150mg bid and clopidogrel 75mg daily or ticagrelor 90mg bid

In patients with CAD and non-valvular AF who have undergone PCI and stenting, antiplatelet therapy may be discontinued after a year in stable patients (and only maintained on NOAC as per guidelines).[264,265]

IIa, B
- Reduction of CV events
  - ➢ The use of rivaroxaban 2.5mg twice daily in combination with aspirin 100mg daily in high risk stable CAD patients, significantly reduced the risk of major CV events (the composite of CV death, stroke, or MI) compared to aspirin alone but the risk of major bleeding was also significantly higher.[268]

Warfarin is indicated in patients with Stable CAD for:

I, A • Valvular and non-valvular AF both paroxysmal and persistent.[22,261,262]

IIa, C • LV thrombus - In patients with stable CAD and depressed LV function and a LV thrombus demonstrated for the first time by echocardiography, warfarin for at least 6 months may be considered.

Table 11: Indications for Warfarin and NOACs in patients with Stable CAD

	Warfarin	NOAC
Valvular AF, paroxysmal and persistent	Maintain target INR.	Not indicated at the present time for rheumatic mitral stenosis and mechanical heart valves
LV thrombus	At least for 6 months	Not indicated at the present time
Non-valvular AF depending on the CHA2DS2-VASc score	Maintain target INR Concomitant anti platelet therapy not warranted.	Indicated Concomitant anti platelet therapy not warranted.
Non-valvular AF + PCI and stenting with DES Antiplatelet therapy may be discontinued after a year in stable patients and maintained on warfarin or NOAC alone	Warfarin + DAPT **	Rivaroxaban 15mg daily (10mg if Creatinine clearance: 30 to 50ml per minute) + • clopidogrel 75mg daily or • ticagrelor 90mg bid or • prasugrel 10mg daily OR Rivaroxaban 2.5mg BD + DAPT - aspirin 75-100mg per day + • clopidogrel 75mg daily or • ticagrelor 90mg bid or • prasugrel 10mg daily OR Dabigatran 110 or 150mg bid + clopidogrel 75mg daily or ticagrelor 90mg bid
Reduction of CV events	Not indicated	Rivaroxaban 2.5mg bid + aspirin 100mg daily in high risk stable CAD patients

*** Higher risk of bleeding with warfarin + DAPT*

8.2.1.2. Lipid modifying agents

I, A — Lipid modifying agents have been shown to improve prognosis in patients with stable CAD, the lower the Low-Density Lipoprotein Cholesterol (LDL-C) achieved, the better the CV outcome.[269-277]

I, A — In addition to behavioural modification therapy, statins should be initiated to achieve LDL-C targets, the lower the level of LDL-C achieved, the better the outcome.[278,279]

There appears to be a dose-dependent reduction in CVD with LDL-C lowering; the greater the LDL-C reduction, the greater the CV risk reduction.[269,270] Levels of LDL-C <1.8 mmol/L has been associated with less progression of atherosclerotic plaques.[280] At levels of LDL-C <1.6 mmol/L, regression of atherosclerotic plaques has been demonstrated.[281-283]

IIa, B — A meta-analyses showed that more intensive compared with less intensive LDL-C lowering was associated with a greater reduction in total and CV mortality in individuals with higher baseline LDL-C levels of > 2.6 mmol/l.[284] If LDL-C levels cannot be achieved, the additional use of other non-statin therapy (e.g. ezetimibe, PCSK-9 inhibitors) may be considered.[276-278]

IIa, B — Reloading with high intensity statin before PCI may be considered in patients with stable CAD. This has been shown to reduce peri-procedural MI in both statin-naive and patients receiving chronic statin therapy.[285-290]

8.2.1.3. Renin-angiotensin-aldosterone system blockers

Renin-angiotensin-aldosterone system blockers consist of angiotensin converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARBs) and mineralocorticoid receptor antagonists.

Early trials indicated improved CV outcomes with ACEi in patients with stable CAD and preserved LV function.[291,292] Recent data however show that ACEi/ARB do not have any additional benefits in reducing CV events and death in this group of patients.[293-296]

IIb, B — The routine use of ACEi/ARB in patients with Stable CAD without hypertension and normal LV function is not recommended. [293-296]

8.2.1.4. Depressed LV function (LVEF <40%)

In patient with stable CAD and reduced LV function, the following drugs should be given to improve survival and other CV outcomes:[297]

I, A	• ACEi/ARB
I, A	• β-blockers
I, A	• mineralocorticoid receptor antagonists - spironolactone and eplerenone [298–300]
I, B	• angiotensin receptor neprilysin inhibitor - Sacubitril/Valsartan (Entresto) [301]

8.2.2. Management of symptoms - Anti-ischemic therapy (Fig 2, pg 25)

Anti-ischemic therapy is used to treat the symptoms of angina. While these medications have been shown to reduce symptoms, none have been shown to prevent MI or death in patients with stable CAD.

These medications prevent attacks of angina by:
- decreasing myocardial oxygen consumption (lowering heart rate, blood pressure, myocardial loading, or myocardial contractility) and/or
- increasing myocardial oxygen supply (increasing coronary blood flow).

The available anti-ischemic therapy includes:
- β-blockers
- Nitrates
- Calcium channel blockers (CCB)
- Trimetazidine
- Ivabradine
- Ranolazine
- Nicorandil

The choice of anti-ischemic therapy should be individualised depending upon:
- presence of co-morbidities (such as asthma) and/or
- physiological parameters such as resting heart rate, blood pressure, LV function and/or
- Cost and availability

Combination of anti-ischemic therapy may be necessary to control symptoms.

8.2.2.1. β-blockers

β-blockers are suitable first-line agents to reduce the symptoms of angina. They act by competitively inhibiting catecholamines from binding to β1, β2 and β3 receptors, thus reducing heart rate, myocardial contractility and blood pressure. This results in a decrease in myocardial oxygen demand.[302] The prolongation of diastole also results in improved coronary arterial filling.[302] All these result in an improvement in symptoms and exercise tolerance.

β-blockers have not been shown to reduce the rate of CV events or mortality in patients with stable CAD. A meta-analysis of trials done in post MI patients in the pre-primary PCI era, showed that β-blockers reduced all-cause mortality and nonfatal MI.[303] Current data however, have not shown β-blockers to reduce long term mortality if continued beyond 1-year post MI.[304,305]

β-blockers reduce all-cause mortality in individuals with reduced LV function, both ischemic and non-ischemic heart failure.[306] In these patients however, only carvedilol, bisoprolol, long acting metoprolol and nebivolol have been shown to improve prognosis and CV outcomes.[307-314]

All β-blockers appear to be equally effective in treating stable CAD. However, nebivolol has not been studied in patients with angina or who have had a recent MI. In diabetes, vasodilating β-blockers seem to have better metabolic profile since they cause less insulin resistance.[315] Nebivolol, a β1 selective blocker, has a favourable metabolic profile, improves insulin sensitivity and does not cause deleterious effects on lipid profile.[316,317] Likewise, carvedilol, a non-selective β- and α1-blocker, maintains glycaemic control, while improving insulin sensitivity.[318]

Side-effects of β-blockers include hypotension, fatigue, bradycardia, heart block, bronchospasm, peripheral vasoconstriction, impotence, hypoglycaemia and depression. β-blockers are contraindicated in patients with known conduction disorders, cardiogenic shock and should be used with caution in patients with asthma.[319]

β-blockers can worsen symptoms in patients with vasospastic (Prinzmetal) angina and should therefore be avoided in these patients.

8.2.2.2. Calcium Channel Blockers (CCBs)

CCBs dilate systemic arterioles and coronary arteries, resulting in reduced afterload and peripheral vascular resistance.320 Selective, non-competitive inhibition of voltage-dependent L-type calcium channels lead to reduced myocardium contractility, smooth muscle relaxation and nodal inhibition leading to a slowing down of conduction.[320]

CCBs can be classified as:

- dihydropyridines (DHPs) - amlodipine, felodipine, long-acting nifedipine. These have greater binding affinity to the calcium channels in vascular smooth muscle
- non-DHPs - verapamil and diltiazem. These agents act mainly on the sinus node resulting in a reduction in the heart rate.

DHPs do not lower heart rate or reduce myocardial contractility. In addition to their anti-anginal effects, they are also effective in controlling co-existing hypertension. The CCB-β-blocker combination is beneficial because the DHPs induced reflex tachycardia is blunted with the co-existing use of a β-blocker.[25,321]

The short-acting formulations of DHPs (short acting nifedipine) should be avoided in patients with CAD. Studies have shown that they increase the risk of MI while, at higher doses, they increased mortality rates.[322,323]

Non-DHPs such as verapamil and diltiazem are as efficacious as β-blockers as anti-anginal therapy and cause less symptoms of depression.[25,324,325] However, the multiple daily dosing of the immediate release formulations of the non-DHPs can result in reduced adherence. Concurrent use of a non-DHP and a β-blocker, should be used with caution because of the risk of bradycardia and heart block.[326] They may also be used cautiously in patients with LV dysfunction.

CCBs are effective anti-anginal therapy but have not been shown to have any effect on long term CV outcomes.[327,328]

8.2.2.3. Nitrates

Nitrates are effective in the management of angina due to their coronary arteriolar and venous vasodilatation properties that result in a reduction in preload and afterload.[329]

8.2.2.3.1. Nitrates for acute angina

Sublingual glyceryl trinitrate (GTN) can be given for immediate relief of angina. The aerosol formulation has a faster onset of action. GTN improves exercise tolerance when given prophylactically, thus preventing anticipated angina caused by exertion. Besides its anti-anginal properties, GTN also has shown antithrombotic and antiplatelet activity.[330,331]

GTN tablets should be kept in an amber coloured bottle and protected from sunlight. Once the bottle has been opened, the life-span is reduced to 8 weeks. The aerosol formulation can be used until the expiry date.

8.2.2.3.2. Nitrates for angina treatment and prophylaxis

Nitrates are often used with β-blockers or CCBs to prevent or reduce angina and increase exercise tolerance in symptomatic patients. Isosorbide mononitrate (ISMN) has similar efficacy as isosorbide dinitrate (ISDN) but with a longer duration of action and a better side effect profile.

Long-term regular use of nitrates without a nitrate-free or nitrate-low interval of about 8-10 hours can lead to nitrate tolerance. This could offset the beneficial short-term ischemic preconditioning effects and potentially worsen endothelial dysfunction.[332,332] Twice daily dosing of ISDN that provides a 10-12-hour nitrate-free interval each day is preferred.

The most common side effect of nitrates is headache. It may also cause hypotension. Concurrent use with a phosphodiesterase type-5 (PDE5) inhibitor like sildenafil is contraindicated because of severe hypotension.

8.2.2.4. Ivabradine (I_f inhibitor)

An elevated heart rate is associated with an increase in both all-cause as well as CV mortality.[334–337] This relationship is independent of other risk markers. Decreasing heart rate can lead to an improvement in angina by reducing myocardial oxygen consumption and by increasing diastolic perfusion time.[302]

Ivabradine is a selective inhibitor of the sinus node I_f ion current ('funny current'). It is negatively chronotropic (slows heart rate), thereby decreasing myocardial oxygen demand with no effect on myocardial contractility or systemic blood pressure.[338,339]

Ivabradine has been shown to improve symptoms and reduce CV hospitalization, fatal and non-fatal MI and the need for coronary revascularization in patients with stable CAD, moderate LV dysfunction and HR >70 bpm.[340-344]

Ivabradine may be considered for symptomatic treatment of stable CAD in patients with normal sinus rhythm, especially in those who have a contraindication to or intolerance to β-blockers. It may also be used in combination with β-blockers in patients with high resting heart rates.[344-347] The dose should be decreased or discontinued if HR remains below 50bpm.

Ivabradine is not suitable for patients who are in atrial fibrillation. Its use with rate-limiting non-DHPs should be avoided because of the QT prolonging effect.[348] Side-effects include bradycardia and reversible visual disturbances.[338] There is no significant interaction with most other cardiac drugs e.g. ACEis, ARBs, warfarin, amiodarone, anti-platelet agents, cholesterol lowing agents, digoxin and diuretics.

8.2.2.5. Trimetazidine (3-Ketoacyl CoA thiolase [KAT] inhibitor)

Trimetazidine inhibits 3-KAT (3-ketoacyl CoA thiolase) enzyme in myocardial cells-resulting in a switch of the energy substrate from fatty acid to glucose oxidation. This is a more efficient pathway for adenosine triphosphate (ATP) production.

In small clinical studies, trimetazidine has been shown to be effective in providing angina symptom relief, reduction in the need for nitrates, time to onset of ST depression and improving functional capacity.[349-353] It is useful as monotherapy and in combination with other anti-ischaemic agents.[349-353] Trimetazidine has not been evaluated in large outcome studies in patients with stable CAD.

In patients with erectile dysfunction and using PDE5 inhibitor, the concomitant use of trimetazidine is safe.[354] Trimetazidine should be used with caution in the presence of CKD.[355] There have been reports of association between trimetazidine and symptoms of parkinsonism.[356]

8.2.2.6. Ranolazine (Late Na current inhibitor)

Ranolazine selectively inhibits the late inward sodium current in the myocardium, leading to a reduction in intracellular calcium levels and diastolic LV wall tension, thereby reducing myocardial oxygen demand. Doses of 500-2000 mg daily reduced angina and increased exercise capacity without changes in heart rate or BP.[357]

Compared to placebo, or as additional to current anti-anginal therapy, ranolazine improved angina symptoms, exercise tolerance, and decreased angina attacks and GTN consumption.[357-361] It was equally effective in diabetic patients.[362] Ranolazine has been shown to have a beneficial effect on glycaemic control with significant reduction of HbA1c in patients with and without diabetes.[357,362-367]

Ranolazine was found not to be beneficial in the management of angina following incomplete revascularization by PCI and in the setting of an ACS.[366] Studies on the use of ranolazine for the treatment of microvascular angina has produced conflicting results.[369-371]

Commonly reported side-effects include dizziness, constipation and nausea. Ranolazine prolongs the QTc interval in a dose-related manner although clinical experience has not shown an increased risk of proarrhythmia or sudden death.[372] It should be used with caution in patients with a prolonged QTc interval, liver cirrhosis and stage IV CKD.

8.2.2.7. Nicorandil (K channel activator)

Nicorandil is a nitrate derivative of nicotinamide. It has dual pharmacological mechanism of action with adenosine triphosphate sensitive potassium (KATP) channel agonist and nitrate-like properties.[373]

The antianginal efficacy of nicorandil is similar to β-blockers, CCBs and nitrates.[374–377] It can be used as add-on therapy to other anti-ischemic medications. Tolerance however, develops with long-term use.[378]

Nicorandil can cause serious skin, mucosal, and eye ulceration which persists unless treatment is discontinued.[379] The concurrent use of nicorandil with aspirin increases the risk of gastrointestinal ulcers, perforations, and haemorrhages.[380]

Key Messages:

Optimal medical therapy is the cornerstone of management of patients with obstructive and non-obstructive CAD.

Pharmacological management of stable CAD aims at:

- prevention of cardiovascular events
  - All patients should receive aspirin and a statin (+/- non- statin therapy) with the aim of achieving LDL-C targets - the lower the better.
  - All CV risk factors should be treated to target.
  - Patients with depressed LV function (LVEF <40%) should receive ACEi/ARB, β-blockers and mineralocorticoid antagonists. Angiotensin-receptor-neprilysin inhibitors may also be considered.
- relieving symptoms
  - β-blockers and/or CCBs should be prescribed as first-line treatment to reduce angina because it is widely available.
  - Ivabradine, trimetazidine, long-acting nitrates and ranolazine are recom mended as add-on therapy in patients who remain symptomatic.

- Optimal medical therapy should be instituted prior to revascularization procedures.

Recommendation 6:

- All patients with suspected or known CAD should be on Optimal Medical Therapy (Behavioural modification therapy and appropriate pharmacotherapy).
- Appropriate pharmacotherapy includes:
  - aspirin (or ticlopdine/clopidogrel if aspirin intolerant) and
  - statin (+/- non- statin therapy) with the aim of achieving LDL-C targets and
  - at least 2 anti anginal agents.
- In addition:
  - All CV risk factors should be treated to target.
  - Patients with depressed LV function (LVEF <40%) should receive ACEi/ARB, β-blockers and mineralocorticoid antagonists. Angiotensin-receptor-neprilysin inhibitors may also be considered.
- Optimal medical therapy should be instituted prior to revascularization procedures.

8.3 Myocardial revascularization

Recent clinical trials have not shown that an initial strategy of PCI in combination with OMT to be superior to OMT alone in reducing death, MI or repeat revascularization during short term and long term follow up.[72-76,153,154,381] In a small randomised controlled trial, PCI did not improve exercise time or angina frequency at 6 weeks when compared to a sham procedure.[382]

CABG however, has been shown to improve survival when compared to OMT in patients with LM or three-vessel stable CAD, particularly when the proximal LAD is involved.383 Benefits are greater in those with severe symptoms, early positive exercise tests, and impaired LV function.[383]

The decision to revascularize patients with stable CAD on OMT will depend on:

I, C
- Symptoms - presence of angina affecting quality of life

IIa, B
- Extent of ischemia as determined by non-invasive testing - mild vs moderate to severe myocardial ischemia[151,384,385] Individuals with moderate to severe ischemia benefit from revascularization while those with no or mild ischemia do better with OMT.[151,384–387] (Table 2, pg 24)

I, A
- Extent and severity of coronary disease and where applicable physiological functional testing using FFR:[84]
  - FFR <0.75 - benefit from revascularisation as compared to OMT.
  - FFR between >0.75 but <0.8 - have intermediate benefit with revascularisation and management should be based on clinical judgement.
  - FFR >0.8 - no benefit from revascularisation.

Revascularization has generally been shown to be more effective than OMT in relieving angina and myocardial ischemia.[388,389]

Choice of revascularization strategies is guided by several factors such as number of coronary vessels involved, anatomic complexity of the target lesions, likelihood of complete revascularization, patient comorbidities as well as preference (see Table 12, pg 82).

Table 12: Factors influencing decision on revascularization strategies

Anatomical Factors	Single versus multivessel disease, left main involvement, proximal LAD, chronic total occlusion, number of patent coronaries and SYNTAX score
Technical Factors	Lesion length, calcification, tortuosity, aneurysms, previous PCI or CABG, complete versus incomplete revascularization
Patient Factors	Age, gender, presence of comorbidities such as diabetes, chronic kidney disease, fragility, previous stroke, peripheral artery disease, bleeding risk and life expectancy
Other Factors	Cost, availability of expertise, experience of the operator, patient's preference, volume of the centre and waiting list

There is an inherent difference between the 2 modes of myocardial revascularisation - PCI treats only the coronary lesion and leaves the other segments alone while CABG treats the entire vessel proximal to the site of implantation of the graft.

Wherever possible, a discussion with the patient and Heart Team should be encouraged prior to revascularization.[44,390-391]

In general, in patients with a low burden of CAD - single vessel disease not involving proximal left anterior descending artery (LAD) or dominant circumflex artery, low-risk findings on non-invasive testing and absence of LV systolic dysfunction and diabetes, OMT should be the initial step. In the presence of continuing symptoms and impaired quality of life, PCI may be an option if the coronary stenosis is significant (FFR <0.8).

In patients with complex CAD, evaluation by a Heart Team is recommended. For patients with multivessel CAD, preserved LV systolic function, low complexity coronary anatomy, and absence of diabetes, PCI may be considered. In patients with multivessel disease, complex anatomy, diabetes and low surgical risk, CABG has a better survival benefit.[383,392] Please refer to Malaysian Appropriate Use Criteria for Investigations and Revascularizations in CAD, 1st Ed, 2015.[68]

Key Messages:

The decision to revascularize patients with stable CAD on OMT will depend on:

- Symptoms - presence of angina affecting quality of life.
- Extent of ischemia as determined by non-invasive testing - mild vs moderate to severe myocardial ischemia. Individuals with moderate to severe ischemia benefit from revascularization while those with no or mild ischemia do better with OMT. (Table 2, pg 24)
- Extent of coronary disease and where applicable physiological functional testing using FFR. In individuals with:
  - FFR <0.75 - benefit from revascularisation as compared to OMT.
  - FFR between >0.75 but <0.8 - have intermediate benefit with revascularisation and management should be based on clinical judgement.
  - FFR >0.8 - no benefit from revascularisation

Wherever possible, a discussion with the patient and Heart Team should be encouraged prior to revascularization to determine the best strategy - PCI or CABG.

Recommendation 7:

- The decision to revascularize patients with stable CAD on OMT will depend on:
  - Symptoms
  - Extent of ischemia
  - Extent of coronary disease and where applicable physiological functional testing using FFR.
- Wherever possible, a discussion with the patient and Heart Team should be encouraged prior to revascularization to determine the best strategy.

9. CHRONIC REFRACTORY ANGINA

Chronic refractory angina is a clinical diagnosis based on the symptoms of ischaemic chest pain of >3 months duration which is not controlled by a combination of maximal medical therapy and/or revascularization.

Most common reasons why revascularisation (or repeat revascularization) is not undertaken:

- unsuitable anatomy - e.g. diffuse small vessels disease, calcified aorta
- one or several previous CABG and/or PCI have been performed
- severely depressed LV function
- lack of available graft conduits
- extra-cardiac diseases with increased perioperative morbidity and mortality
- advanced age, in combination with the above factors

Medical management of these patients requires optimisation of risk factors and the use of combination antianginal drugs in maximal tolerated doses.

Options available to these symptomatic patients who are not amenable to conventional therapy include:

- cardiac rehabilitation - This has not been validated in an independent study nor has it been tested in a trial appropriately powered to assess its effect on symptom improvement.
- enhanced external counter pulsation (EECP)[393-396]
- extracorporeal shockwave myocardial revascularisation (ESMR) [397-400]
- acupuncture[401]
- cell therapy and angiogenesis[402-409]
- chelation therapy[410]

Other investigational therapies include:

- neuromodulation techniques (transcutaneous electric nerve stimulation and spinal cord stimulation)[411-413]
- trans myocardial (TMR) or percutaneous laser revascularization[414-424]
- thoracic epidural anaesthesia
- endoscopic thoracic sympathectomy
- stellate ganglion blockade
- heart transplantation
- drugs that modulate metabolism
- coronary Sinus Reducer[425]
- oral morphine therapy

In small clinical trials, these alternative therapies have been shown to relieve angina and improve quality of life to a variable degree in some patients with refractory angina.[393-425]

IIb, B These therapies should only be considered in patients who continue to have troubling angina despite conventional therapy or when conventional therapy is not feasible. [393-425]

Key messages:

- Chronic refractory angina is a clinical diagnosis based on the symptoms of ischaemic chest pain of >3 months duration which is not controlled by a combination of maximal medical therapy and/or revascularization.
- Alternative and investigational therapies have been shown to relieve angina and improve quality of life to a variable degree in some of these patients.
- They should only be considered in patients who continue to have troubling angina despite adequate conventional treatments.

10. SPECIAL GROUPS

10.1 Diabetes

Diabetes is associated with an increased risk of CVD. CAD mortality is increased by 3-fold in diabetic men and 2-5 fold in diabetic women.[426-429] Diabetics have a higher prevalence of asymptomatic myocardial ischemia.[430] Symptoms occur at an earlier age. Diabetics may also have subclinical ventricular dysfunction which may reduce their exercise capacity.[431]

In patients with diabetes, the poorer the glycaemic control the greater the incidence of CVD.[432,433] Diabetics tend to have extensive CAD with high rates of multi-vessel disease and restenosis, post-PCI. This is due to the chronic metabolic disturbances.[434,435]

Conventional therapies for CAD and indications for coronary revascularisation are similar in diabetic and non-diabetic patients.[436]

DM management should include:

I, B
- Lifestyle and pharmacotherapy (OMT) measures to achieve a near-normal HbA1c[437]

I, B
- Long-term maintenance of near-normal blood glucose levels substantially reduces complications and mortality.[438-441] However, this should be individualized based on the patient's age and comorbidities.
- In the pharmacotherapy of diabetic patients with CAD:
  - both the SGLT2i and the GLP-1 agonists have been shown to be associated with a reduction in the risk of CV composite end-points.[442-445]
  - the SGLT2i have been shown to reduce the risk of heart failure.[442]
  - In a meta-analysis, the SGLT2i and GLP-1 agonists have been associated with a reduction in all cause mortality.[446]
  - thiazolidinediones are associated with an increase in the incidence of heart failure and should be avoided in those in NYHA Functional class 3 & 4.[447,448]
  - Saxagliptin, a DPP-4i, was also shown to be associated with an increase in hospitalization for heart failure.[449] However this is not seen with the other agents of the same class.[450]

In general, in diabetic patients with multivessel disease, CABG is the preferred revascularization strategy.[153,381]

10.2. Women

CVD is the main cause of death among women both worldwide and in Malaysia.[451] It is 2½ times more common as a cause of death than all cancers combined.[10]

There are numerous gender differences in the epidemiology of CAD. There is a significantly lower age-specific risk of CAD in women, the risk of death being similar to that of men 10 years younger.[451-454] Despite this, the greater likelihood of survival of women to advanced age, produces nearly equal numbers of actual deaths due to CAD in both gender.[451-454]

Women with angina may have:[455]
- atherosclerotic obstructive Coronary Artery Disease (CAD)
- non-obstructive CAD (≥20% and <50% luminal narrowing)
- normal coronary arteries (Cardiac Syndrome X) - (<20% luminal narrowing)

Other unique gender specific cardiac issues include:[455]
- Takotsubo Cardiomyopathy
- spontaneous coronary artery dissections

Other diseases that are associated with increased CV risk in women include:[455]
- connective tissue diseases (especially rheumatoid arthritis, systemic lupus erythematosus (SLE) and systemic vasculitis) and the drugs that are used to treat these diseases
- chemotherapy and radiation induced cardio toxicity
- infections such as influenza, periodontal disease and human immunodeficiency virus (HIV)
- obstructive sleep apnoea (OSA)

Angina is a more common presentation in women as compared to ACS and sudden death in men. Women often have atypical presentations.[456] In addition to chest pain or discomfort, women also have a lot of non-chest related pain symptoms. Compared to men, women's symptoms are more often precipitated by mental or emotional stress and less frequently by exertion. [456]

Following an MI, women have worse outcomes irrespective of age.[457,458] More women had sudden cardiac death (SCD) before their arrival in hospital and almost two thirds of women who died suddenly, had no previous symptoms.[459,460]

Non-obstructive CAD is more common in women.[461,462] Patients with non-obstructive CAD may present as stable angina, ACS and sudden death.[461] The prognosis of this condition is not benign. Compared to persons with no apparent coronary lesions (<20% luminal narrowing), non-obstructive CHD (≥20% and <50% luminal narrowing) was associated with significantly higher risk of MI and all-cause mortality in both gender.[461,463]

The WISE study showed that the 5-year cardiac event rate for MI and CVD death were significantly different (P ≤0.002) in the 3 subgroups:[464]
- 16% for women with angina and non-obstructive CAD (stenosis <50%)
- 7.9% for women with angina and normal coronary arteries (Cardiac Syndrome X)
- 2.4% for the asymptomatic control group

Women with non-obstructive CAD and documented myocardial ischemia have a poorer prognosis.[34,465] Women with Syndrome X and severe endothelial dysfunction have a 30% increased risk of developing CAD at 10 years.[464,466-468]

Paradoxically, women tend to have lower prevalence of obstructive coronary disease but more symptoms, ischemia and adverse outcomes.[459,469] It has been

postulated that this could be due to abnormal coronary vasomotor reactivity, microvascular dysfunction, distal coronary erosion/embolization and non-obstructive coronary disease. [459,470]

Data seems to suggest that the adverse outcomes seen in women could be due to their baseline risk and clinical characteristics rather than to gender dependent factors or to bias in therapies.[471]

10.2.1. Diagnosis of CAD in women

The diagnosis of angina in women is more difficult for the following reasons:

- Atypical chest pain and angina-equivalent symptoms such as dyspnoea are more common in women.
- Correlation between symptoms and 'significant' luminal obstruction at coronary angiography is weaker in women.
- Angina with demonstrable myocardial ischaemia may be present in the presence of normal coronaries or minor atherosclerotic disease.

In the non-invasive evaluation of women with chest pain, exercise stress ECG is the first test of choice in women with good exercise capacity and a normal resting ECG. Exercise stress ECG have higher false positive rates in women than in men. The sensitivity is 31-71% and specificity is about 66 to 78% in women and about 80% for both in men.[66,472,473]

Despite these limitations, a normal exercise stress ECG at adequate workloads in women with intermediate probability of CAD is a good indication that there is no significant obstructive lesion.[66,471] An exercise ECG stress test, however, does not detect myocardial ischemia in women with non-obstructive coronary lesions.

Due to the limitations of exercise ECG stress testing, stress echocardiography (exercise or dobutamine) and stress SPECT have been recommended in women. Both these tests can detect myocardial ischemia in the presence of obstructive and non-obstructive coronary lesions.[66] These tests also have higher specificity.[473] The diagnostic accuracy of SPECT however, can be reduced in women by both breast tissue and obesity, especially in the anterior myocardial segments, resulting in false-positives.

Cardiac Magnetic Resonance (CMR) is a newer imaging tool to investigate CAD in women. A negative stress CMR study is associated with very low risk of CV death and MI.[474]

10.2.2. Management

Management should be similar in both gender. Women tend to present at an older age and therefore have higher morbidity and mortality after an MI, PCI and CABG.[455] For more details please refer to CPG Prevention of Cardiovascular Disease in Women, 2nd Ed.[455]

10.3. Elderly

In the elderly, often defined as >75 years of age, there is equal prevalence of CAD in both gender.[475]

In this age group, complaints of chest discomfort, weakness and dyspnoea are common, and evaluation of chest pain can be difficult. This may be further compounded when some of the elderly have difficulties expressing their symptoms due to dysphasia or cognition issues. Comorbidities that can mimic stable CAD are common (e.g. gastroesophageal reflux disease, musculoskeletal pain). The elderly are usually undertreated and under-represented in clinical trials and most of the available knowledge is derived from sub analyses of main trials or retrospective studies.

10.3.1. Diagnostic testing in the elderly

Diagnostic testing in the elderly may be problematic. Exercise stress testing is often difficult due to muscle weakness and deconditioning and osteoarthritis of the knees. Less challenging exercise stress protocols or pharmacological stress imaging such as DSE may be appropriate.[476]

The specificity of test results is often reduced because of a higher rate of false positive results due to abnormal resting ECG and a higher prevalence of confounders including prior MI, conduction disturbances, hypertension and left ventricular hypertrophy. At the same time a negative test may be a false negative in a population with high prevalence of disease. Arrhythmias are also more common at higher exercise workloads.[477]

CTA may not be suitable in the elderly because of the presence of coronary calcification making visualization of the lumen difficult.

Elderly patients with objective evidence of moderate to severe ischemia on non-invasive testing or with troubling angina despite OMT, should have similar

access to ICA as younger patients. Elective coronary angiography is safe in this age group.[478-480] Age > 75 years is an important predictor of contrast-induced nephropathy.[481]

The elderly are more likely to have extensive disease and impaired LV function.

10.3.2. Management

Elderly patients have the same benefit from OMT and coronary revascularization as younger patients.[482-487] Management should be individualised taking into consideration comorbidities and should not be based on age alone.

Important considerations in drug therapy in the elderly are dose modification, drug interactions, polypharmacy and compliance.[488,489]

Meta-analysis have shown that patients >65 years of age with multivessel disease had better outcomes when they underwent CABG compared with PCI, while younger patients tended to have more favourable outcomes with PCI.[490-492] An all comers registry demonstrated that patients in the age group ≥74 years and triple vessel CAD had significantly higher all-cause mortality when they underwent PCI as compared to CABG (even after adjustment of confounders).[493] PCI was also associated with a significantly higher risk for cardiac death, MI, heart failure hospitalization, and new coronary interventions, but with a similar risk for sudden death, and significantly lower risk for stroke.[493]

Frailty is an important confounding factor when one looks at CV outcomes following PCI. It often results in poorer outcomes.[494,495] However, the difficulty lies in the diagnosis of frailty as there are numerous scales with little agreement on the best assessment tool.

The choice of revascularization in the elderly should be discussed by the Heart Team considering local expertise and patient preferences.

10.4. Chronic Kidney Disease

Chronic Kidney Disease (CKD) is strongly associated with CAD and has a major impact on outcomes and therapeutic decisions. The incidence and severity of obstructive CAD increases as glomerular filtration rate (GFR) declines. [496,497] Patients with CKD have diffuse multi-vessel disease with coronary calcification.[497,498] Cardiovascular morbidity and mortality are inversely and independently associated

with kidney function, particularly in patients with advanced CKD (GFR<15 ml/min per 1.73 m^2).[139,499-502]

Emerging evidence indicates that the pathology and manifestation of CVD differs in the presence of CKD. It is being increasingly recognized that mineralocorticoid excess, mineral and bone metabolism abnormalities play a role in the pathogenesis of CAD and its complications in CKD patients.[503-505]

10.4.1. Diagnostic testing in CKD

The increased prevalence of CAD among CKD patients reduces the negative predictive value of diagnostic studies.

Exercise ECG stress testing is limited by an abnormal baseline resting ECG, lack of specificity of the ST-segment response and by the inability of many CKD patients to exercise to a diagnostic workload.[506,507]

Stress echocardiography may be compromised by small LV cavity size in patients with elevated LV mass index.[508,509] Sensitivity and specificity for pharmacological stress echocardiography in CKD patients is 69-95% and 76-94%, respectively.[510,511] Nephrotoxicity of contrast agents limit the use of CMR and CTA. Further, the high prevalence of coronary calcification makes interpretation of CTA very difficult.

MPI is more sensitive but less specific than stress echocardiography. The accuracy of exercise and of pharmacological MPI is reduced in CKD patients, and the sensitivities and specificities are <80%.[512]

10.4.2. Management

The role of lifestyle modification, good glycaemic and blood pressure control to reduce CV events in patients with advanced CKD remains unclear. Strict glycaemic control may not benefit patients with advanced CKD.[513] Randomized data on the efficacy of specific BP goals in advanced CKD patients are lacking.[514,515] Lifestyle modification has not been widely studied in CKD patients.

Data regarding the efficacy of prophylactic aspirin is also limited. Subgroup analyses of randomized trials have demonstrated CV risk reduction with aspirin in individuals with eGFR <45 mL/min per 1.73 m^2, despite a higher incidence of bleeding.[246,516] Several antiplatelet and anticoagulant agents are metabolized through the kidneys and require dose adjustment in CKD patients.

Subgroup analysis of several randomized clinical trials suggests benefit with the use of statins in patients with moderate CKD.[517] However, two large trials comparing statins with placebo in haemodialysis patients did not demonstrate benefit.[518,519] In the SHARP trial, the combination of simvastatin and ezetimibe in CKD patients (including stage V) reduced major atherosclerotic events by 17%, but did not reduce overall mortality.[520] As no significant harm from statin use was demonstrated in any of the trials, this reduction in non-fatal events provides a rationale for the use of statins in CKD patients despite the apparent lack of efficacy in reducing the risk of death.

There is a paucity of data regarding revascularization in CKD patients with stable CAD. There have been no randomized clinical trials comparing coronary revascularization strategies in advanced CKD patients. A subgroup analysis of the COURAGE trial did not find a benefit from PCI compared with OMT in ~320 patients with CKD Stage III-IV who had predominantly low-risk, multivessel disease.[521] The ARTS-1 trial found no significant difference in the primary end point (death, MI, stroke) between PCI and CABG surgery in 290 patients with creatinine clearance <60 ml/min.[522]

Observational data consistently show increased risk of serious operative complications in CKD patients.[523-525] Incidence of operative death after CABG is 9-12.2% for CKD stage V, and 3- to 7-fold higher in CKD stage IV-V than in non-CKD.[523,524] PCI may be an alternative but may pose the added risk of contrast-induced nephropathy. In a study of CKD stage V patients undergoing first revascularization, in-hospital mortality was lower with PCI (4.1 vs 8.6%), but 2-year survival was better with CABG (56.4 vs 48.4%).[525]

The ISCHEMIA-CKD (International Study of Comparative Health Effectiveness With Medical and Invasive Approaches-Chronic Kidney Disease) trial is a randomized ongoing trial with a target of 1,000 patients with eGFRs <30 mL/min/1.73 m^2 (or on dialysis therapy) and moderate ischemia to determine whether a routine invasive strategy (cardiac catheterization and then revascularization together with OMT) is superior to a conservative strategy (OMT; catheterization and revascularization available as indicated). [526]

Key Messages:

- Diabetes is associated with an increased risk of CVD.
  - Conventional therapies for CAD and indications for coronary revascularisation are similar in diabetic and non-diabetic patients.
  - Long-term maintenance of near-normal blood glucose levels substantially reduces complications and mortality.
  - The SGLT2i and the GLP-1 agonists have been associated with improved CV outcomes.
- There are difficulties in the diagnosis of CAD in women and the elderly.
  - Women should, in general, be managed in a similar manner as men.
  - In the elderly, management should be individualised taking into consideration comorbidities and should not be based on age alone.
- Chronic Kidney Disease (CKD) is strongly associated with CAD and has a major impact on outcomes and therapeutic decisions. However, there is limited data on the efficacy and the role of pharmacotherapy and revascularization in these patients.

11. FOLLOW-UP OF PATIENTS WITH STABLE CAD

All patients with Stable CAD (no change in symptoms and medications over a period of 1-2 years) can be discharged from the speciality cardiology clinics.

There are no randomized trials evaluating the impact on outcome of different strategies for the follow-up of patients with stable CAD. In addition, there are currently no data suggesting that any form of follow up stress testing improves outcome in asymptomatic patients.[527]

The frequency of follow-up and further evaluation of these patients will depend on:
- severity of CAD
- comorbidities and optimization of risk factors
- symptoms - particularly a change in symptoms and functional capacity
- local resources

Clinical judgement is required in determining the need for repeated testing.

IIa, C In general, a repeat exercise stress ECG (or pharmacological stress) may be warranted if there is a change in the patient's:

- symptoms - worsening angina or effort tolerance
- clinical condition eg worsening LV function as detected by echocardiogram and/or heart failure
- development of malignant arrhythmias

When a patient with stable CAD develops an ACS and worsening angina, factors that need to be considered include:

- ensuring that the patient has quit smoking.
- treatment of BP and diabetes have been optimized.
- aiming for LDL-C goals that are lower than when the patient developed the ACS – at least < 1.8 mmol/l - the lower the better.
- adequately addressing psychosocial stressors.

Wherever necessary, these patients should be referred back to tertiary cardiac centres for optimization of management and revascularization as indicated. When stable, they can be transferred back to their primary or general physicians.

Close follow-up and rapport with patients generally leads to improved adherence to OMT.

Key Messages:

- All patients with Stable CAD can be managed both at hospital and at general outpatient clinics.
- In general, a repeat exercise stress ECG (or pharmacological stress) may be warranted if there is a change in the patient's:
  - symptoms - worsening angina or effort tolerance
  - clinical condition eg worsening LV function as detected by echocardiogram and/or heart failure
  - development of malignant arrhythmias
- Whenever indicated, these patients should be referred to tertiary cardiac centres for optimization of management. When stable, they can be transferred back to genaral outpatient clinics with Family Medicine Specialists.

Recommendation 8:

- All patients with Stable CAD with no change in symptoms and medications over a period of 1-2 years, can be discharged from the speciality cardiac clinics.
- When there is a change in the patient's clinical condition, they should be referred to tertiary cardiac centres for optimization of management. When stable, they can be transferred back to general outpatient clinics with Family Medicine Specialists.

12. PRE-OPERATIVE ASSESSMENT FOR ELECTIVE NON-CARDIAC SURGERY

The extent of investigation in the pre-operative assessment of patients with stable CAD going for elective non-cardiac surgery will depend on the risk of the surgery:

- low risk surgery (risk of death or MI <1%[528] e.g. cataract, simple plastic surgery)
- intermediate risk and High-Risk surgery (risk of death or MI > 1%[528] e.g. intra peritoneal, intra thoracic surgery)
- vascular surgery/liver and kidney transplant

In addition, other factors that need to be considered include the presence of:

- diabetes
- CKD
- LV dysfunction

I, C — In general, a resting ECG should be performed in all patients and compared with previous ECGs.

IIa, B — An echocardiogram may be considered in:[528]

- intermediate and high-risk surgery
- >1 other clinical risk factors that include:
  - CAD - previous revascularization/MI
  - heart failure
  - stroke/TIA
  - renal dysfunction (serum creatinine >170umol/l or Cr Cl <60 mL/min)
  - diabetes

I, C — If a previous echocardiogram had been done within the last 12 months and it was normal and the patient has no change in his symptoms, then a repeat examination is not warranted.

IIa, B If the patient is asymptomatic with good effort tolerance (>4 METS*), no further investigations is necessary.[68,528]

IIb, C Non-invasive stress testing may be considered if the patient has:[68]
- poor functional capacity (<4 METS) and
- ≥1 clinical risk factors and
- undergoing intermediate and high-risk surgery or vascular surgery/liver and kidney transplant.

I, C We advocate that these considerations should be done prior to listing the patient for surgery, for proper evaluation, planning of investigations and appropriate ethical informed consent process to be offered.

In patients who have undergone PCI and stenting and are on DAPT, a consultation with the cardiologist is necessary.

**4 METS is equivalent to doing housework, sweeping floors and climbing 1 flight of stairs.*

Key Messages:

- The extent of investigation in the pre-operative assessment of patients with stable CAD going for elective non-cardiac surgery will depend on the risk of the surgery:
  - low risk surgery (risk of death or MI <1% e.g. cataract, simple plastic surgery)
  - intermediate risk and High-Risk surgery (risk of death or MI > 1% e.g. intra peritoneal, intra thoracic surgery)
  - vascular surgery/liver and kidney transplant
- In addition, other factors that need to be considered include the presence of:
  - diabetes
  - CKD
  - LV dysfunction
- In general, a resting ECG should be performed in all patients and compared with previous ECGs.
- An echocardiogram may be considered in selected patients.
- If the patient is asymptomatic with good effort tolerance (>4 METS), no further investigations is necessary.

13. MONITORING AND QUALITY ASSURANCE

Recommended Performance Indicators for Management of Stable CAD - to be audited on hospital discharges and at review at the outpatient clinics on an annual basis.

Percentage of patients with CAD on antiplatelet therapy:

$$= \frac{\text{No. of patients with CAD on aspirin (or clopidogrel or ticlopidine, if aspirin intolerant)}}{\text{No. of patients with CAD seen on that clinic day}} \times 100\%$$

Percentage of patients with CAD on statins:

$$= \frac{\text{No. of patients with CAD on statin}}{\text{No. of patients with CAD seen on that clinic day}} \times 100\%$$

(Target > 70%)

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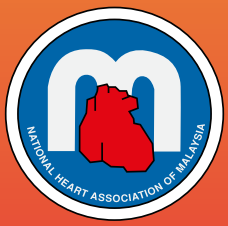

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