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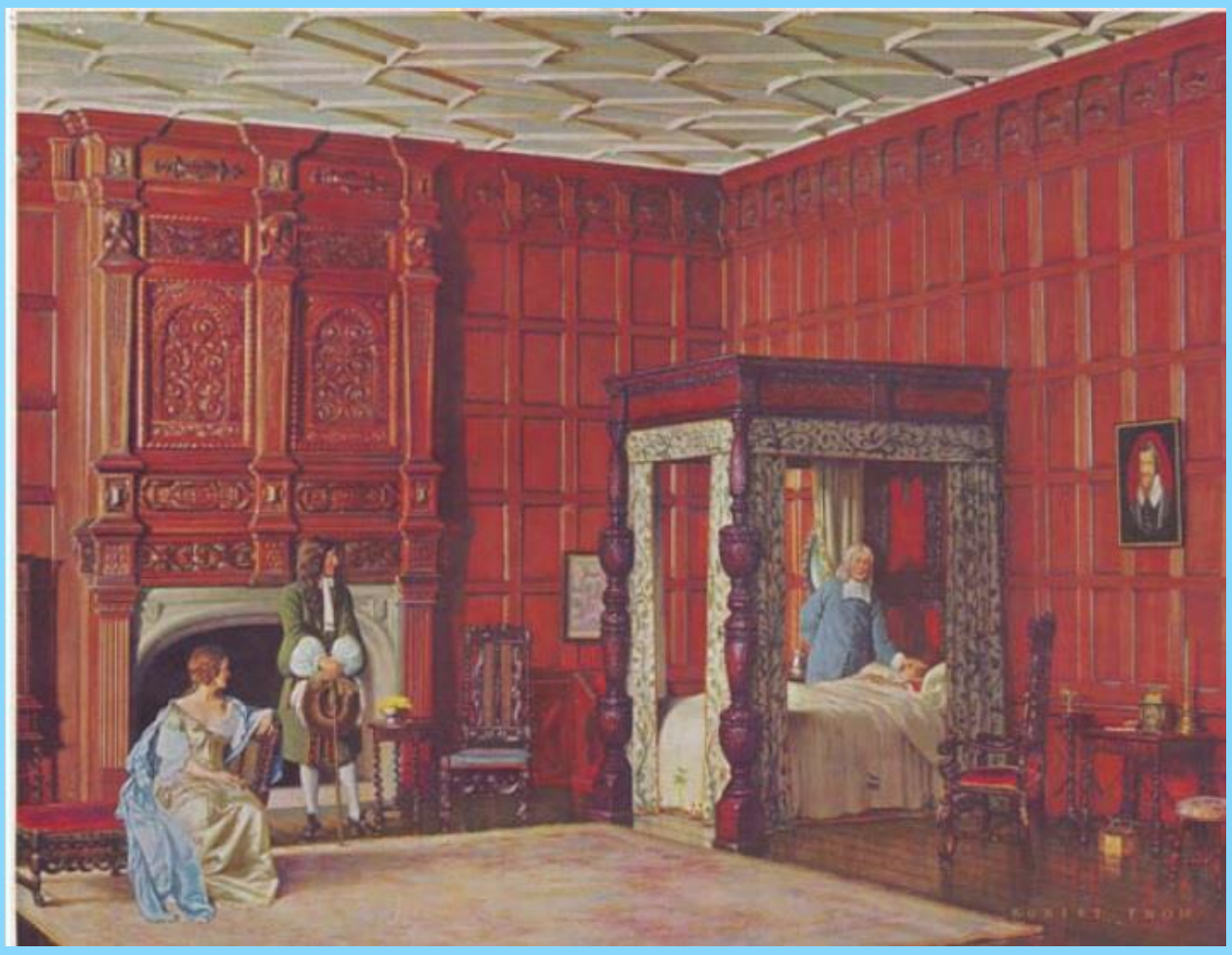

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The Sri Lanka Prescriber

Management of non-ST elevation acute coronary syndromes

Introduction

Coronary plaque rupture with thrombus formation leading to total or subtotal coronary occlusion causes an acute coronary syndrome [ACS].

The current nomenclature used to describe coronary artery disease [CAD] clinical syndromes based on symptoms, ECG ST segment changes and cardiac biomarkers is listed in **Text box 1**.

Text box 1: Nomenclature of CAD

1. Acute coronary syndromes [ACS]
   - 1.1 ST segment elevation myocardial infarction [STEMI]
   - 1.2 Non ST segment elevation acute coronary syndromes [NSTE-ACS]
     - 1.2.1 Non ST elevation myocardial infarction [NSTEMI]
     - 1.2.2 Unstable angina [UA]

2. Chronic coronary syndromes [CCS]

Worldwide approximately three fourth of ACS patients belong to the non-ST elevation ACS [NSTE-ACS] type while one fourth belong to ST elevation myocardial infarction [STEMI] [1]. The annual incidence of STEMI in Sri Lanka is estimated at 20,000 patients based on annual thrombolytic usage and results of an ACS national audit [2]. Extrapolating from this data the estimated annual incidence of NSTE-ACS in Sri Lanka is approximately 60,000 patients out of a total of 80,000 ACS patients.

Pathophysiology and clinical correlation

Myocyte injury causes a rise in cardiac biomarkers such as serum high sensitive cardiac troponin I [HScTn-I]. When clinical, ECG and imaging evidence of myocardial ischemia is present with >95th percentile rise of HScTn-I a myocardial infarction [MI] is diagnosed [3].

According to the 4th Universal Definition of Myocardial Infarction [UDMI] [1], such an MI commonly due to coronary athero-thrombosis and is named a Type 1 MI. Other less common non athero-thrombotic causes of coronary ischaemia such as due to an oxygen supply demand mismatch, spasm or spontaneous coronary dissection are named Type 2 MI. Sudden cardiac death [SCD] from CAD is also an ACS (Type 3 MI). Pathology related to a coronary stenting causing an MI is named Type 4 MI and an MI related to coronary artery bypass grafting [CABG] is named a Type 5 MI.

If these pathological MI types especially 1, 2, 4, and 5 causes complete coronary occlusion it results in a full-thickness infarction. If occlusion is subtotal then a subendocardial infarction occurs. Full thickness and sub endocardial infarcted areas are seen in late gadolinium enhancement cardiac magnetic resonance imaging [MRI]. A full thickness

infarction shows ECG ST elevation or Q waves, while subendocardial infarction shows no ECG ST elevation and only ST depression or T wave inversion.

Diagnosis and management of NSTE- ACS based on current evidence based guidelines [4] will be discussed in this article. Therapeutic management of acute STEMI and chronic coronary syndromes [CCS] are discussed in separate SL Prescriber articles [5].

Diagnosis

Anginal or cardiac type severe prolonged chest pain at rest or with minimal exertion is the typical clinical presentations of an ACS. Additionally dyspnea and autonomic features such as sweating, palpitation, light headedness and hemodynamic instability due to cardiac arrhythmias or cardiogenic shock may occur. Patients with unstable angina [UA] may also present as prolonged episodes of angina at rest, new onset angina or worsening in severity and intensity of previous angina over a short period of time [crescendo angina].

Patients with clinical features of an ACS need an ECG and if ST segment elevation is present an acute ST segment elevation myocardial infarction [STEMI] is diagnosed. When persistent ST segment elevation is absent in the ECG and typical ST segment depression, T wave inversion or pseudo normalization are present then a diagnosis of NSTE-ACS is made.

NSTE-ACS consists of non-ST elevation myocardial infarction [NSTEMI] and unstable angina [UA] which are a continuum with varying severity of myocardial ischemia. NSTEMI and UA are differentiated based on raised cardiac biomarkers in NSTEMI indicative of myocyte necrosis.

Rule-in and rule-out protocols to diagnose NSTEMI

The preferred cardiac biomarker to diagnose NSTEMI is serum high sensitive cardiac troponin I [HScTn-I] which is detected earlier than standard assays of Troponin I thus reducing the cardiac biomarker blind period. HScTn-I has a high negative predictive value. Normal HScTn-I values are useful in patients without ongoing chest pain and a normal ECG to rule-out ACS.

HScTn-I is a quantitative biomarker of myocyte damage and a higher level denotes a larger area of myocyte damage and a higher likelihood of myocardial infarction and greater risk of death. NSTEMI can be ruled-in or ruled-out as early as 1 hour from presentation to hospital if 1st sample value is high or 1-3 hours from chest pain onset using a rise in HScTnI values between 1st and 2nd samples. Significance values are given for the type of commercial assay used to decide on ruling-in or ruling-out [4].

HScTn-I assay has resulted in about a 20% relative increase in diagnosis of myocardial infarction and a similar reduction in the diagnosis of UA. With the advent of these high sensitive cardiac troponin assays, creatine kinase myocardial isoenzyme (CK-MB) and

myoglobin are no longer recommended for diagnosing NSTEMI.

Management

In patients with NSTE-ACS, those diagnosed as NSTEMI benefit from intensified management with an invasive strategy and anti-thrombotic therapy.

Acute NSTEMI is a medical emergency with high in-hospital mortality and mortality at 6 months that can equal or exceed STEMI [4]. At 1 year the risk of MI and recurrent ACS is >10% [4].

All patients with acute NSTEMI need ICU care and rhythm monitoring in the first 24 hours.

All NSTEMI patients are recommended an invasive strategy [4] where an invasive coronary angiogram is performed with a view to revascularization by percutaneous coronary intervention [PCI] or coronary artery bypass graft [CABG] surgery.

Evidence based guideline directed medical therapy for NSTEMI includes dual anti-platelet therapy [DAPT], anticoagulation, statins, beta blockers [BB], angiotensin converting enzyme inhibitors [ACEI] or angiotensin receptor blockers [ARB], and mineralocorticoid receptor antagonists [MRA] all of which are proven to improve survival [4].

A comparison of diagnosis and management of STEMI [6] and NSTEMI is given in **Text box 2.**

Patients with NSTE-ACS and negative troponin diagnosed as unstable angina are considered low risk and may be considered for a selective invasive strategy and benefit less from such interventions and anti-thrombotics than NSTEMI patients [4].

Text box 2: Comparison of diagnosis and management of STEMI and NSTEMI

	STEMI	NSTEMI
ECG	ST elevation, Q waves or New LBBB	No ST elevation. ST depression or T wave inversion.
HScTnI	Not needed for diagnosis	Essential for diagnosis
Invasive strategy	Invasive angiogram and Primary PCI<120 minutes of ECG diagnosis. Invasive angiogram 3-24 hours after fibrinolytic therapy	Invasive angiogram and revascularization <120 minutes if very high risk. Invasive angiogram < 24 hours for all NSTEMI
Fibrinolytic strategy	<10 minutes of ECG diagnosis if timely PCI not possible and <12 hours from symptom onset	Fibrinolytics are contraindicated. Only anti-thrombotics (LMWH, aspirin, P2Y12 inhibitors) given.

Coronary revascularization in NSTEMI

Patients with hemodynamic instability, cardiogenic shock, life threatening arrhythmias, acute LVF, mechanical complications of MI, refractory chest pain, ECG ST depression > 6 leads or ST elevation in aVR or v1 are categorized as very high risk and are recommended an immediate invasive strategy with revascularization within 2 hours.

All other NSTEMI patients are categorized as high risk and are recommended an early invasive approach with revascularization within 24 hours [4]. A radial approach and newer drug eluting stents are the standard of care during PCI.

Those selected for an immediate coronary intervention strategy are best given the loading dose of platelet P2Y12 inhibitor after seeing the coronary anatomy as they may require CABG [4].

Major bleeding events increase mortality in NSTE-ACS and bleeding risk assessment using a validated score is indicated especially in patients selected for invasive strategy [4]. Fibrinolytics are contraindicated in NSTEMI or UA.

Evidence based drug therapy in NSTEMI

The following guideline directed medical therapy [GDMT] improve symptoms or survival in ACS.

1. Nitrates

Sublingual or IV nitrates may be used for symptom relief, especially with uncontrolled hypertension or left heart failure [LVF].

2. Anti-thrombotic drugs

Antithrombotic drugs are prescribed after considering the thrombotic risk and bleeding risks to an individual.

In the acute stage UA/NSTEMI patients are treated with anti-thrombotic drugs such as parenteral anticoagulation with low molecular weight heparin [LMWH] enoxaparin subcutaneously and oral dual anti-platelet therapy [DAPT] with aspirin and a platelet P2Y12 inhibitor such as clopidogrel, prasugrel or ticagrelor.

Enoxaparin 30 mg and 60 mg vials are available to be given subcutaneously [SC] at a dose of 1 mg / kg body weight SC twice daily [BD] usually for 6-8 doses or until PCI if done sooner. Dose adjustment In those over 75 years is 0.75 mg/kg body weight SC BD and in renal failure patients 1mg/kg body weight SC once daily. Fondaparinux SC is no longer used in Sri Lanka for ACS management.

C**lopidogrel** 75 mg is the P2y12 inhibitor available in the Sri Lankan government hospital setting.

Soluble aspirin is available as 300 mg tablets for the loading dose and slow release aspirin as 75 mg, 100 mg or 150 mg tablets and 100 mg capsules for maintenance dose.

Loading doses of DAPT [soluble aspirin 150-300 mg, clopidogrel 300-600 mg] are given in NSTEMI except when early

invasive strategy is planned when the platelet P2Y12 inhibitor may be withheld till coronary anatomy is known. DAPT maintenance doses [aspirin 75-100 mg, clopidogrel 75 mg] are continued up to 1 year as the default strategy and a single antiplatelet drug usually aspirin 75-100 mg is continued thereafter for life.

Extended DAPT beyond one year may be considered in high thrombotic risk patients such as those with diabetes mellitus, history of recurrent MI, multi vessel CAD, poly-vascular disease [CAD] and peripheral vascular disease [PVD], premature [<45 years] or accelerated [new lesion within 2 years] CAD, chronic kidney disease [CKD] and systemic inflammatory disease such as HIV infection, systemic lupus erythomatosis [SLE] or chronic arthritis [9].

Technical aspects of PCI such as 3 or more stents implanted, total stent length >60 mm, past stent thrombosis or complex PCI such as left main, bifurcation stenting, chronic total occlusion stenting and stenting of last patent vessel also carry a high thrombotic risk and extended DAPT is recommended in such instances [4].

When an oral anticoagulation drug such as a Vitamin K antagonist [VKA] warfarin or a newer direct oral anticoagulant [DOAC] needs to be added as triple therapy to the DAPT in condition such as atrial fibrillation, then DAPT duration is reduced to 1 week considering bleeding risk of triple therapy [4]. Dual therapy with 1 antiplatelet drug and DOAC or VKA is continued 3-6 months depending on the bleeding risk and the DOAC or VKA only is continued thereafter.

The DOACs in current use are direct factor Xa inhibitors such as rivaroxaban 20 mg once daily [15 mg daily if added to single or DAPT], apixaban 5 mg twice daily, edoxaban 60 mg once daily or direct thrombin inhibitor Dabigatran 150 mg twice daily.

3. Statins

High dose statins such as atorvastatin 40-80 mg or rosuvastatin 20-40. mg to achieve a target LDL of <55 mg/dl and a 50% LDL reduction is recommended. In-patient LDL measurement is not recommended for statin prescribing or dosing in ACS patients [4].

4. Beta blockers [BB] such as carvedilol, bisoprolol, metoprolol or nebivolol is especially useful if LV dysfunction present but not in overt heart failure.

5. Angiotensin converting enzyme inhibitors [ACEI] or angiotensin receptor blockers [ARB] are indicated but not both together**.**

6. Mineralocorticoid receptor antagonists [MRA] are additionally recommended in left ventricular dysfunction.

7. Calcium channel blockers [CCB] are useful to treat co morbidities such as hypertension. Careful dose titration is required with BB, ACEI, ARB, MRA and

CCB giving consideration to hemodynamic stability.

8. Proton pump inhibitors [PPI] such as pantoprazole 40 mg once daily or s-omeprazole 40 mg once daily are indicated in those with a high gastro-intestinal bleeding risk.

Management of complications - NSTEMI

Acute left ventricular failure, cardiogenic shock, arrhythmias such as atrial fibrillation or ventricular tachycardia need specialized guideline directed evidence based management. Mechanical complications such as severe mitral regurgitation due to ischemic chordal rupture may need early surgical correction. Left ventricular thrombus formation needs anticoagulation.

CAD risk factor control targets

- LDL - 50% reduction and LDL<50 mg/dl is currently recommended [4, 7].
- Office BP target <130/80 [4, 8].
- HBA1C target of < 7% for either type 1 or 2 diabetes mellitus to prevent microvascular complications [4, 9].
- Smoking cessation [4].

Follow up

All ACS patients after one year of the ACS whether symptomatic or not and even before one year if asymptomatic or stable symptoms are now categorized as chronic coronary syndromes [CCS][10].

Lifestyle changes in ACS

Lifestyle changes are similar to those described for CCS and include a healthy diet, physical exercise, smoking cessation and weight management.

Enrolment in a cardiac rehabilitation program is proven beneficial.

Lifestyle changes for CCS patients are-

- Smoking cessation
- Healthy diet recommended is a low carb, low lipid, low salt, high fiber, high fruit and vegetable diet. The 'Mediterranean type diet' is recommended for CVD event reduction [10].
- Physical exercise- 150-300 minutes of moderate intensity or 75-150 minutes of strenuous aerobic exercises per week is recommended [10].
- Stress management

Performance and quality measures for management of ACS

Audit standards suggested for management of NSTE-ACS in Sri Lankan setting are listed in **Table 1**. The Acute Coronary Care Sri Lanka Audit Project [ACSSLAP] [2] was the first national clinical audit done in Sri Lanka involving the entire country using local and international audit standards for ACS management. Some notable observations from ACSSLAP are;

- Of STEMI patients 66.9% received reperfusion therapy where 63.2% STEMI patients received fibrinolytics and only 3.8% underwent primary PCI.
- In patients with STEMI, 69.1% received secondary prevention medications, while in NSTAMI/ UA such usage was 76.1%.
- Aspirin, clopidogrel and statins were given to over 90% patients in acute setting and on discharge.

- On discharge, BB and ACE inhibitors/angiotensin II receptor blockers were given to only 50.7% and 69.2%, respectively.
- Cardiac catheterization was performed only in 14% patients and only 17.6% had coronary interventions planned.

In comparison;

- Over 90% of acute STEMI patients undergo primary PCI in the UK [11].
- Approximately 70% of patients with a diagnosis of NSTEMI undergo PCI within 24 hours in Europe [4].

While there are many areas for improvement of ACS care in Sri Lanka, the in-hospital overall mortality was 2.1% [4.0% in the STEMI group] which was similar to or even lower than in registries from high income countries [12].

It is envisaged that in the future more patients may receive guideline recommended coronary interventions for ACS in Sri Lanka due to-

- The 'Suwasariya' 1990 free ambulance services extending to most parts of the country is planned to be equipped with ECG machines and telemedicine systems enabling trained paramedics to take an out of hospital ECG, get it interpreted by on call cardiology intervention team, and transport ACS patients to PCI capable hospitals directly reducing time delays.
- Availability of free coronary stents and consumables in government hospital cath labs at preset.

Conclusions

Recent improvements in CAD detection and treatment has made significant impact on management and outcome of ACS. In NSTE-ACS, introduction of high sensitive cardiac troponin [HScTn-I] assays results in an earlier diagnosis of NSTEMI within 1 to 3 hours of presentation with chest pain. Coronary angiogram and revascularization is recommended now for all NSTEMI patients within 24 hours. For unstable and very high risk NSTEMI patients with complications, such coronary interventions are recommended within 2 hours similar to acute STEMI primary PCI.

Newer antiplatelet drugs and high dose statin therapy are further recommendations in ACS. Thrombolytics are contraindicated in NSTEMI. When a DOAC is needed long term added to DAPT as triple therapy, aspirin is given for one week only. After 6 months only the DOAC is continued. New nomenclature of stable CAD patients as chronic coronary syndromes [CCS] highlights the dynamic and evolving nature of atherosclerotic process in individuals. All ACS patients after one year and earlier if asymptomatic or their symptoms are stable are thereby diagnosed as CCS. An emphasis is made on regular follow up, lifelong interventions such as CAD risk factor control, lifestyle changes such as quitting smoking, exercise and diet], and giving evidence based medications and doing appropriate revascularizations to reduce the progression of disease process and to confer event and mortality reduction in CCS patients.

Table 1. Audit standards recommended for management of NSTE-ACS in Sri Lankan setting.

1	ECG within 10 min of arrival with ACS symptoms	Y/N
2	Blood drawn for HScTnI measurement at arrival	Y/N
3	HScTnI repeat measurement if indicated for diagnosis	Y/N
4	Bleeding risk assessment	Y/N
5	Aspirin loading dose on arrival	Y/N
6	Aspirin maintenance dose at discharge	Y/N
7	Platelet P2Y12 inhibitor loading dose at arrival	Y/N
8	Platelet P2Y12 inhibitor maintenance dose at discharge	Y/N
9	Enoxaparin SC treatment for eligible patients	Y/N
10	Very early [within 2 h] invasive strategy in very high risk NSTEMI	Y/N
11	Early [within 24 hours] invasive strategy in high risk NSTEMI	Y/N
12	Ischemia guided invasive strategy in low risk NSTEMI/UA	Y/N
13	Evaluation of LVEF with echocardiogram	Y/N
14	High intensity statins at discharge	Y/N
15	Beta blockers for eligible patients	Y/N
16	ACEI or ARB for eligible patients with LV systolic dysfunction	Y/N
17	MRA for eligible patients with LV dysfunction	Y/N
18	PPI for patients on DAPT	Y/N
19	Smoking cessation advice for eligible patients	Y/N
20	Cardiac rehabilitation enrolment	Y/N
21	Inappropriate prescriptions-[NSAID, Prasugrel in patients with past stroke or TIA, Aspirin more than 100 mg daily along with Ticagrelor]	Y/N

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Management of Chronic Coronary Syndromes

Introduction

More people die every year from cardiovascular diseases [CVD] than from any other cause. Approximately 18 million CVD deaths occur annually representing 31% of all deaths globally. 85% of these CVD deaths are from heart attacks and strokes [1].

Most heart disease and stroke can be prevented by addressing a common set of risk factors at individual and population level. These include hypertension, diabetes, hyperlipidemia, and obesity attributable largely to lifestyle and behavioral risk factors such as unhealthy diet, physical inactivity, tobacco smoking, and harmful use of alcohol. The underlying 'causes of the causes' are a combination of poverty, urbanization, stress, socio cultural practices and hereditary factors [1].

Atherosclerotic coronary artery disease [ASCAD] is increasingly diagnosed in young adults especially in Asian countries including Sri Lanka. Those with established CVD and those identified as very high or high risk and are recommended aggressive lipid management with lifestyle counselling, evidence based medical therapy and appropriate vascular interventions [2, 3]. For primary prevention, the 10 year CVD risk can be assessed from validated risk estimation charts such as the 'SCORE2'charts for Europe [2, 3], 'pooled cohort risk equations' for America [4], or World Health Organization CVD risk estimation charts for South East Asia Region [SEAR] B for Sri Lanka [5].

Clinical and pathophysiological correlation

The clinical presentation of CAD can be acute or chronic and are thus named as-

A. Acute coronary syndromes
B. Chronic coronary syndromes.

The current nomenclature to describe CAD clinical syndromes has been described previously.

Underlying pathophysiology in ASCAD is the development of an atherosclerotic plaque in the intimal layer of the coronary artery wall. Coronary atherosclerosis is a dynamic lifelong process affected by the ongoing status of atherosclerosis risk factors [6]. The clinical presentation will largely depend on the pathophysiology of CAD [7].

Acute coronary plaque rupture with thrombus formation leading to total or subtotal coronary occlusion causes an acute coronary syndrome [ACS]. If such ischemia leads to significant myocyte injury then a rise in a cardiac biomarker such as High sensitive Cardiac Troponin I [HScTnI] occurs. A rise in HScTnI with supportive clinical, ECG and imaging evidence of myocardial ischemia is diagnosed as a myocardial infarction [MI] according to the 4th Universal Definition of MI [7]. Such an MI is named as ST elevation MI [STEMI] or non-ST elevation MI [NSTEMI] depending on the presence or absence of electrocardiogram [ECG] ST segment elevation respectively. A patient with clinical features of an ACS but no ST segment elevation and no rise in HScTnI is diagnosed as unstable angina [UA] within the category of non ST elevation acute coronary syndromes [NSTE-ACS].

Rarely a troponin rise indicating myocyte injury may occur without coronary ischemia but due to other pathologies

such as myocarditis, uncontrolled hypertension or fast cardiac arrhythmias.

During physical exertion coronary flow insufficiency by an obstructive atheromatous plaque causes exertional or stable angina. Exertional angina can also occur from myocardial oxygen supply demand mismatch (anemia, aortic stenosis or coronary spasm).

Management of STEMI [8], and NSTE-ACS are discussed in separate SL Prescriber articles. This article will discuss the therapeutic management of chronic coronary syndromes according to current evidence based guidelines [6].

Chronic coronary syndromes [CCS]

CAD patients other than those with ACS were previously labelled as having 'stable CAD' or 'stable angina'. Such patients are now classified as having chronic coronary syndromes [CCS] [6].

This is to focus on the dynamic nature of coronary atherosclerosis while emphasizing on the role of risk factor control, healthy diet, exercise and guideline directed medical therapy in preventing progression of coronary atherosclerosis and reducing morbidity and mortality.

Clinical types of CCS

Presentation of CCS includes the following 6 clinical scenarios [6].

1. Suspected CAD with 'stable' angina like exertional chest pain or dyspnoea.
2. Suspected CAD causing new onset heart failure [HF] or LVF.
3. Within one year of an ACS or revascularization if symptoms are absent or stable.
4. After one year of an ACS or revascularization whether symptomatic or not.
5. Angina due to microvascular disease or vasospastic angina.
6. CAD detected at screening with no symptoms.

Diagnosis and management of CCS

1. Diagnosis of CCS

In patients with suggestive anginal symptoms the best path of investigations to rule in or rule out CAD is decided based on 'pretest probability of angina' and 'clinical likelihood of CAD', two new terms introduced recently [6].

Pretest probability [PTP] of angina depends on age, gender and the characteristics of the anginal symptoms, whether typical, atypical or unlikely. It can be calculated from a given chart [6].

Clinical likelihood of CAD is determined by the degree of PTP whether high or low combined with the presence or absence of CAD risk factors and risk modifiers such as exercise ECG test or CT coronary artery calcium score [6].

Diagnostic approach to a patient with chest pain and or dyspnoea due to suspected CAD is based on six steps emphasizing on management [6]

- Step 1 - Exclude an acute coronary syndrome [ACS] by assessing symptoms, electrocardiogram [ECG] and cardiac biomarkers. If it is an ACS then manage according to STEMI or NSTE-ACS guidelines.
- Step 2 - If co-morbidities and quality of life make revascularization futile then medical therapy is chosen.
- Step 3 - In CCS assess left ventricular [LV] function with an echocardiogram. If LV ejection fraction [LVEF] is < 50% with

suggestive LV regional wall motion abnormality then consider management of heart failure and additionally where appropriate coronary angiogram and revascularization.

- Step 4 - Assess pretest probability [PTP] and clinical likelihood of CAD.
  PTP is calculated from a given chart using clinical symptoms of chest pain whether typical, atypical or unlikely to be angina, age and gender.
  Clinical likelihood of CAD is increased with a high PTP and presence of CVD risk factors [diabetes, hypertension, smoking, dyslipidemia, family history of CVD], resting ECG changes [Q waves, ST/T wave changes], LV dysfunction suggestive of CAD, abnormal exercise ECG, or coronary calcium by CT.
  Clinical likelihood of CAD is reduced with a low PTP and normal exercise ECG or no coronary calcium by CT [Agatston score=0].
  If other cause of chest pain is considered likely based on PTP and clinical likely of CAD assessment then appropriate tests for such non CAD causes need to be done.
- Step 5 - Perform further diagnostic testing based on the clinical likelihood of obstructive CAD.
  If clinical likelihood of obstructive CAD is low no further tests are needed or a CT coronary angiogram is done.
  If clinical likelihood of obstructive CAD is high an invasive coronary angiogram with a view to revascularization is recommended.
  Noninvasive testing for ischemia such as stress echocardiography or thallium perfusion scan may be done prior to invasive angiography in high clinical likelihood patients to assess viability or if revascularization is likely to help in decision making.
- Step 6- Chose appropriate coronary revascularization therapy based on symptoms and event risk determined from coronary angiogram findings, stress imaging or invasive tests.

This stepwise approach to diagnosing and managing patients with suspected CCD is summarized in **Table 1.**

2. Management of CCS

Risk of death and myocardial infarction in CCS patients can be reduced with

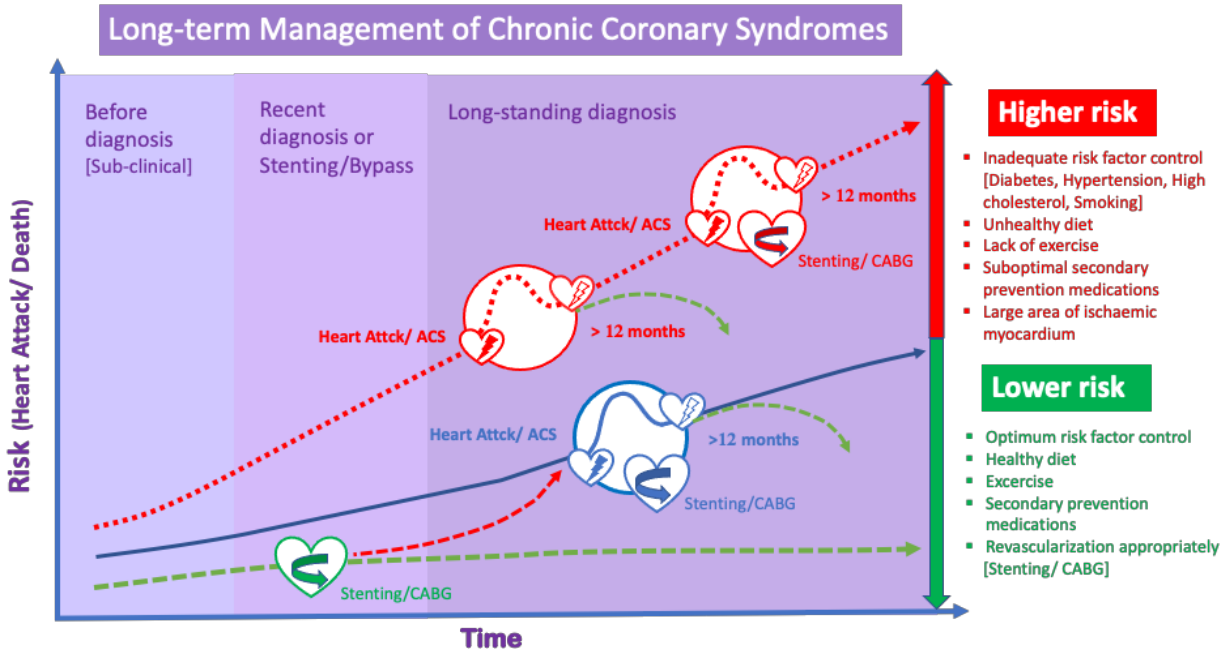
1. CAD risk factor control
2. Healthy lifestyle and diet
3. Evidence based drug treatment and
4. Regular follow up and appropriate coronary revascularization.

Following the initial diagnosis and management, special attention should be made by physicians to these 4 management aspects at each regular follow-up visit.

Table 1: Stepwise approach to diagnosing and managing patients with suspected CCD.

STEP 1	**ASSESS SYMPTOMS AND INVESTIGATIONS**	→	**ACS?**	→ **FOLLOW ACS GUIDELINES**
STEP 2	Comorbidities and quality of life	→	Revascularization futile?	→ Medical therapy
STEP 3	ECG, biochemistry, echo for LVEF	→	LVE F<50%	→ HF management
STEP 4	Pretest probability and clinical likelihood of CAD	→	Non cardiac chest pain?	→ Investigate other causes of chest pain
STEP 5	Invasive angiogram if high clinical likelihood of CAD	←	Clinical likelihood of CAD	→ No testing or Coronary CTA If low clinical likelihood of CAD
STEP 6	Choose therapy based on event risk and symptoms			

Figure 1 depicts that risk of heart attacks and death for an individual with CCS can change dynamically over time depending on the higher or lower modification and prevailing status of these CVD risk determinants. [Modified from the ESC 2020 NSEMI Guidelines]



2.1 CAD risk factor control targets-

Diabetes, hypertension, hyper LDL and adiposity are considered major risk factors for CAD.

- LDL: 50% reduction and LDL< 50 mg% is the current recommendation [2, 3].
- Office BP target <130/80 [9].
- HBA1C target of < 7% for either type 1 or 2 diabetes mellitus to prevent microvascular complications [3, 10].
- Adiposity correction

2.2 Lifestyle changes for CCS patients-

- Smoking cessation advice for smokers.
- Healthy diet recommended is a low carb, low sugar, low lipid, low salt, high fiber, high fruit and vegetable diet. The 'Mediterranean type diet' is recommended for CVD event reduction [3, 6]. Fatty fish is

recommended but restrict alcohol, salt, sugar and meat.

- Physical exercise- 150-300 minutes of moderate intensity or 75-150 minutes of strenuous aerobic exercises per week is recommended [3]. If unable to do physical activities sedentary time should be reduced.
- Stress management

2.3 Evidence based drug treatment

2.3.1 Drugs for event prevention in CCS

- **Anti-thrombotic drugs**

o Antiplatelet drugs- low dose aspirin 75-100 mg or a platelet P2Y12 inhibitor such as clopidogrel 75 mg daily is recommended for all CCS patients.

o In CCS patients who had drug eluting stent implantation [DES] in sinus rhythm, dual anti platelet therapy [DAPT] with low dose aspirin and a platelet P2Y12 inhibitor is indicated up to 6 months and aspirin alone thereafter.

o In CCS patients who had DES and having atrial fibrillation, triple anti thrombotic therapy is recommended, initially for one week but up to 1 month.

o DAPT with a direct oral anticoagulant drug [DOAC] is preferred over DAPT with a vitamin K antagonist such as warfarin for such triple therapy. DOACs that may be used are factor Xa inhibitors such as rivaroxaban 20 mg once daily, apixaban 5 mg twice daily, edoxaban 60 mg once daily or factor IIa inhibitor dabigatran 150 mg twice daily. Notably, prasugrel or ticagrelor are not given as part of such a triple regimen.

o Duration of oral antithrombotic therapy is determined by calculating the risk of stent thrombosis and bleeding risks of an individual patient. Usually, after the initial triple anti thrombotic therapy, dual anti thrombotic therapy with clopidogrel and a DOAC is recommended for six months in CCS patients with AF and DES, followed by long term treatment only with a DOAC [11].

- Statins in high doses- atorvastatin 40-80 mg or rosuvastatin 20 mg daily. If target LDL level is not achieved with high dose statin alone, add ezetimibe or PCSK9 inhibitors [not available in Sri Lanka presently] as appropriate.
- ACEI or if not tolerated an ARB [but not simultaneously] is recommended.
- If HF or LV dysfunction, appropriate beta blockers and HF therapy needs to be given.
- In those with type 2 diabetes mellitus and ASCVD the use of a glucagon peroxidase receptor agonist GLP-1RA or SGLT2 inhibitor is recommended to reduce cardiovascular and renal outcomes [3].

2.3.2 Anti-anginal drugs in CCS

Anti-anginal drugs are chosen depending on baseline heart rate, blood pressure, LV dysfunction and co morbidities and are added in a step wise manner. **Table 2** shows the recommended stepwise selection of anti-anginal medications.

o 1st line drugs are- BB or CCB or both.

o 2nd line drugs are- Long acting nitrates [LAN] such as

o long acting or slow releasing isosorbide mononitrate tablet [ISMN-SR] 30-60 mg daily, ranolazine 500mg twice daily, ivabradine 2.5- 5 mg twice daily, nicorandil 10 mg twice or thrice daily, and trimetazidine 35 mg twice daily.

o 3rd line drugs are combinations of 1st and 2nd line treatments.

Table 2. Recommended steps in choosing anti-anginal medications based on heart rate, blood pressure, heart failure [HF]/ LV dysfunction.

	Standard treatment	High HR>80	Low HR<50	HF/ LV dysfunction	Low BP
1ST STEP	BB or CCB	BB or NON-DHP-CCB	DHP-CCB	BB	LOW DOSE BB OR LOW DOSE NON-DHP-CCB
2ND STEP	BB+DHP-CCB	BB+CCB	Switch to LAN	BB+LAN OR BB+ IVABRADINE	IVABRADINE RANOLAZINE OR TRIMETAZIDINE
3RD STEP	ADD 2ND LINE DRUG	BB + IVABRADINE	DHP-CCB + LAN	ADD ANOTHER 2ND LINE DRUG	COMBINE TWO 2ND LINE DRUGS
4TH STEP	ADD NICORANDIL, RANOLAZINE OR TRIMETAZIDINE				

BB=beta blocker, CCB, any class of calcium channel blocker, DHP-CCB=dihydropyridine CCB, HF=heart failure, LAN=long acting nitrate

- Nitrates- Sublingual glyceryl trinitrate 0.3-0.6 mg tablets or 0.4 mg spray can be used prophylactically or for immediate relief of angina. A nitrate free interval of 10-14 hours is needed to prevent nitrate tolerance.
- Nicorandil which is a K channel opener or nitrates are contraindicated with phosphodiesterase inhibitors such as sildenafil which may lead to hypotension and death.
- Ivabradine is an 'iF' channel blocker in the sinus node which can be combined with a BB carefully monitoring for bradycardia but should not be combined with a non-DHP CCB. Ivabradine should not be used if heart rate is <70.
- Ranolazine is a late sodium channel blocker which may cause QT interval prolongation.

2.4 Coronary revascularization in CCS and regular follow up

Coronary revascularization

In CCS patients revascularization by PCI has not proven superior to CABG in long term follow up of 5- 10 years in several trials comparing these two methods of coronary revascularization [12].

In patients with CCS the following CAD disease patterns in suitable locations seen in the invasive coronary angiogram are considered suitable for revascularization by PCI or CABG on top of optimum medical therapy [6]

- >90% stenosis - Revascularization with PCI or CABG is indicated. The best mode of revascularization, either PCI or CABG, can be decided according to the ESC [13] or ACC Revascularization Guidelines [14] considering also the patient's preference and local expertise. In complex lesions the

SYNTAX score is useful to decide on CABG or PCI[15] where CABG is preferred when SYNTAX score is >22.

- Lesions with established correlation to ischemia-
  - 70-90% stenosis- Assess fractional flow reserve [FFR] using a coronary pressure wire. If FFR is > 0.8, PCI is considered beneficial to that particular coronary artery stenosis based on results from the FAME trial [16].
  - If LV function is <35% and it is s likely to be due to ischemia then revascularization is recommended.
  - If ischemia is proven by perfusion scan attributed to a vessel, then revascularization of that vessel is recommended.
- <70% stenosis - Medical management is recommended except in special instances.

Detailed decision making on coronary revascularization is an evolving subject with emerging novel functional testing and is beyond the scope of this article.

In CCS patients who have a drug eluting stent implanted, DAPT can be stopped after 6 months usually and thereafter only one antiplatelet drug is continued for life [3].

Regular follow up

After PCI, regular clinic visits are recommended every 1-3 months initially and every 1-2 years later on evaluating clinical symptoms, risk factor control, resting ECG, echocardiography and stress testing for inducible ischemia performed where indicated. At these visits if clinically indicated appropriate coronary angiogram and revascularization needs to be done.

Conclusions

New nomenclature of stable CAD patients as chronic coronary syndromes [CCS] highlights the dynamic and evolving nature of atherosclerotic process in individuals. An emphasis is made on lifelong interventions such as CAD risk factor control, lifestyle changes, evidence based medications and appropriate revascularization when indicated detected at regular follow up to reduce the progression of disease process and to confer event and mortality reduction.

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