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Coronary artery disease

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Abstract

Ischemic heart disease (IHD) is the commonest cause of death worldwide. The primary pathological process that leads to IHD is atherosclerosis, an inflammatory disease of the arteries associated with lipid deposition and metabolic alterations due to multiple risk factors. More than 70% of at-risk individuals have multiple risk factors for IHD, and only 2-7% of the general population has no risk factors. Coronary risk factors include diabetes, hypertension, socioeconomic factors, lifestyle factors and family history. Emotional stress or acute physical exertion may also trigger coronary events. Acute coronary syndrome is often the first clinical manifestation of IHD. Mortality due to IHD increases with advancing age, and death rates are higher among males compared to females. There is a significant regional variation in IHD related mortality both within and between countries.

Key words: ischemic heart disease, acute coronary syndrome, chronic stable angina

Introduction

Coronary artery disease (CAD) is a pathological process characterized by obstructive or non-obstructive atherosclerotic plaque formation in the epicardial coronary arteries. The disease can have a long, stable squeal; however, can also become unstable at any time, typically due to an acute atherothrombotic event caused by plaque rupture or erosion. Broad clinical entities of CAD include chronic stable angina (chronic coronary syndrome) and acute coronary syndromes (ACS) including non-ST elevation myocardial infarction (NSTEMI) and ST elevation myocardial infarction (STEMI).[1]

The major aspects of the management of patients with ACS and chronic coronary syndrome (CCS) are described in this article. ACS consists of a spectrum of conditions presenting with varying clinical symptoms or signs, with or without ECG changes and with or without acute rise in cardiac troponin. Patients presenting with ACS eventually be categorized as having myocardial infarction (MI) or unstable angina (UA). MI is associated cardiomyocyte necrosis hence with elevated cardiac troponin and diagnosis is based on the fourth universal definition of myocardial infarction. UA is defined as ischemia at rest or on exertion without cardiomyocyte necrosis.

Chronic coronary syndrome

Frequently encountered clinical presentations include patients with stable angina or angina equivalent such as dyspnoea, patients with left heart failure due to ischaemic cardiomyopathy, asymptomatic and symptomatic patients with stabilized symptoms after an ACS or patients with recent revascularization, asymptomatic and symptomatic patients >1 year after initial diagnosis or revascularization, patients with angina and suspected vasospastic or microvascular disease and asymptomatic individuals in whom CAD is detected based on the results of screening tests such as exercise electrocardiography or coronary computed tomography angiography.[1]

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Resting electrocardiography should be performed in all patients with suspected angina, although findings may be normal in approximately half of patients with stable angina, including those with severe CAD, particularly in the setting of preserved LV functions. During an episode of angina pectoris, 50% of patients with normal findings on resting electrocardiography develop electrocardiographic abnormalities, with the most common finding being ST-segment depression. ST-segment elevation and normalization of previous resting ST-T wave depression or inversion (pseudo normalization) may also develop. Even in the absence of repolarization abnormalities, an ECG can demonstrate indirect signs of CAD, such as signs of previous MI (pathological Q waves) or conduction abnormalities (mainly left bundle branch block (LBBB) and impairment of atrioventricular conduction). Initial non-invasive functional imaging is recommended to assess myocardial ischemia including stress cardiac MRI (CMR), stress echocardiography or perfusion changes by single-photon emission CT (SPECT), positron emission tomography (PET), myocardial contrast echocardiography, or contrast CMR. Stress can be provoked by exercise of pharmacological agents. Exercise ECG has limited diagnostic value compared with diagnostic imaging tests.[2] The diagnostic accuracy of exercise ECG is lower in women; the sensitivity and specificity were 61% and 70%, respectively in women; compared to 68% and 77%, respectively, in men.[3] SPECT and CT coronary angiogram are recommended for symptomatic patients in whom obstructive coronary artery disease cannot be excluded by clinical assessment. If CT coronary angiogram revealed coronary artery disease of uncertain significance, functional imaging is recommended for myocardial ischemia assessment. Invasive coronary angiography is recommended for patients with a high clinical likelihood and severe symptoms refractory to medical therapy or typical angina at a low level of exercises.

Management of CCS

Management of CCS involves a holistic approach where addressing revascularization, pharmacotherapy, behavioral and lifestyle modification. Revascularization in patients with angina and significant stenosis was often a second-line therapy after medical therapy had been unsuccessful.[4] Angina is associated with impaired quality of life, reduced physical endurance, mental depression, and recurrent hospitalizations and office visits to doctors, with impaired clinical outcomes. Revascularization by PCI or CABG may effectively relieve angina, reduce the use of antianginal drugs, and improve exercise capacity and quality of life compared with a strategy of medical therapy alone. Revascularization aims to effectively eliminate myocardial ischemia and its adverse clinical manifestations among patients with significant coronary stenosis, and to reduce the risk of major acute cardiovascular events including MI and cardiovascular death.

The aims of pharmacological management of CCS patients are to reduce angina symptoms and exercise-induced ischaemia, and to prevent cardiovascular events. Antianginal drugs have proven benefits in symptom relief associated with myocardial ischaemia but do not prevent cardiovascular events in most patients with CCS. The initial choice of antianginal drug(s) depends on the expected tolerance related to the individual patient's profile and comorbidities, potential drug interactions with co-administered therapies, the patient's preferences after being informed of potential adverse effects, and drug availability. Beta-adrenergic blockers or calcium channel blockers (CCBs) are recommended as the first line antianginal treatment.[5] Non-dihydropyridine CCBs including verapamil and diltiazem have a wide range of benefits including all varieties of angina (vasospastic, effort, unstable), supraventricular tachycardias and hypertension. Amlodipine, a dihydropyridine CCB, is a well-tolerated long-acting antianginal that can be used as a once-a-day therapy. The second line antianginal therapy includes short acting or long-acting nitrates. Sublingual or spray nitroglycerin formulations immediately relieve the effort angina. Long-acting nitrate preparations include nitroglycerin, isosorbide dinitrate and isosorbide mononitrates. Prolonged use of long-acting nitrates leads to tolerance with loss of efficacy which requires nitrates low prescription or nitrates free interval.[6] In recent studies, ivabradine is proven to be a non-inferior therapy to control the angina in CCS patients specially when the beta-blockers are not tolerated or contraindicated and when added to maximum tolerable or recommended doses of beta-blockers, if the heart rate still permits to do so.[7] Nicorandil is another nitrate derivative that can be used as an antianginal medication with a low side effect profile. Ranolazine is a selective inhibitor of late inward sodium current and effectively relieves effort angina; however, has a tendency for QT prolongation. Trimetazidine improves effort angina especially when combined with a beta blocker and carries a very low side effect profile.

Platelet activation and aggregation is the driving factor for chronic coronary thrombosis forming the basis for using antiplatelet agents in CCS. There must be a favourable balance between ischemic and bleeding risk when considering antiplatelets. After PCI for stable angina, dual antiplatelet therapy (DAPT) is

recommended for 6 months followed by a single antiplatelet therapy. DAPT includes low dose aspirin and a P_2Y_{12} inhibitor.[8] Aspirin acts via irreversible inhibition of platelet cyclooxygenase-1 and thus thromboxanase production. Current evidence recommends aspirin 75-100 mg daily for prevention of ischemic events in coronary artery disease patients with or without a history of MI. Clopidogrel (P_2Y_{12} inhibitor) 75 mg daily should be considered for patients who cannot tolerate or contraindicated to have aspirin.

In addition to anti-platelet agents current evidence suggests use of low dose anticoagulants to improve the cardiovascular outcome in patients with CCS even in patients with sinus rhythm. Low dose rivaroxaban (2.5 mg bd) was compared with placebo, reduced the composite of MI, stroke or cardiovascular death in stabilized patients treated predominantly with aspirin and clopidogrel following ACS, at the expense of increased bleeding risk, but with evidence of a reduction in cardiovascular death.[9] Statins should be considered in all CCS patients targeting LDL cholesterol level of <55 mg/dL or even lower target level <40 mg/dL in those who experience second vascular event within 2 years. Add on therapy with ezetimibe has achieved cholesterol targets effectively in post ACS patients and those with diabetes.[10] Angiotensin converting enzyme inhibitors and beta-blockers have been shown to improve survival of these patients. Angiotensin converting inhibitors causes reduction in vascular endothelial information and thus leads to reduction in cardiac event rate while beta-blockers, in addition to their antianginal effect, have shown to reduce fatal ventricular arrhythmia in these patients. Low-Dose Colchicine 2 (LoDoCo-2) trial has proven that 0.5 mg of daily colchicine dose significantly lowered the cardiovascular event risk in patients compared to the placebo. Hence the use of colchicine in CCS is encouraged considering individual factors.[11]

Sodium-glucose co-transporter-2 (SGLT2) inhibitors (e.g. empagliflozin, dapagliflozin) are effective in prevention of primary and secondary cardiovascular outcomes in both diabetic and non-diabetic patients with or without heart failure.[12] Glucagon-like peptide-1 (GLP-1) receptor agonists (e.g. liraglutide, semaglutide) have shown to reduce cardiovascular events in patients with type 2 diabetes mellitus. The most convincing evidence was obtained in patients with established CAD.[13]

Lifestyle modifications and risk factor control has a major role in the management of CCS. Implementing healthy life style and behaviors including smoking cessation, undertaking recommended physical activity, adopting to a healthy diet, and maintaining a healthy weight has been shown to decrease the cardiovascular event rate and mortality.[14] Exercise based cardiac rehabilitation has consistently demonstrated its effectiveness in reducing cardiovascular mortality and hospitalization. Also having a less stressful stable psychological mind helps to reduce cardiac mortality in CCS patients. Administrating annual influenza vaccine is important in preventing acute MI in CCS patients, change heart failure prognosis and decrease cardiovascular mortality in patients age >65 years.[15]

Acute coronary syndrome

ACS is a spectrum of conditions consisting of unstable angina (UA), non-ST elevation myocardial infarction (NSTEMI) and ST elevation myocardial infarction (STEMI). The more dangerous extreme of the spectrum is cardiac arrest and death due to malignant arrhythmia following NSTEMI or STEMI (Figure 1).

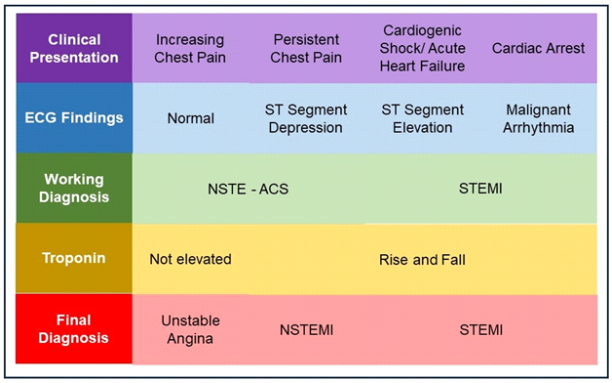

Figure 1. The spectrum of clinical presentations, electrocardiographic findings, and high-sensitivity cardiac troponin levels in patients with acute coronary syndrome.

The focus of this article is on the diagnosis and management of patients who are diagnosed to have type 1 MI. However, other potential causes of myocardial ischemia and myocyte necrosis (type 2-5 MI) also should be carefully considered. Acute onset chest discomfort is the common presentation of all ACS, which can be described as pain, pressure, tightness, burning sensation etc. At the first medical encounter, prompt assessment of vital and the acquisition of initial ECG within 10 minutes is recommended.

Based on the initial ECG, patients with suspected ACS can be categorized into two working diagnoses.

1. Patients with acute chest pain and persistent ST-segment elevation (or ST-segment elevation equivalents) on ECG (working diagnosis: ST-segment elevation MI: STEMI)
2. Patients with acute chest pain but without persistent ST-segment elevation (or ST-segment elevation equivalents) on ECG (working diagnosis: non-ST-elevation [NSTE]-ACS.) Some patients in this category subsequently display a rise in troponin level and will receive the diagnosis of NSTEMI. In other patients, whose troponin level will remain negative, will receive the diagnosis of UA.

ECG criteria for diagnosis of STEMI

- ≥2.5 mm in men <40 years, ≥2 mm in men ≥40 years, or ≥1.5 mm in women regardless of age in leads V_2-V_3.
- and/or ≥1 mm in the other leads (in the absence of left ventricular hypertrophy or left bundle branch block [LBBB]).
- In patients with suspected inferior STEMI, it is recommended to record right precordial leads as well (V_3R, V_4R) and posterior leads(V_7-V_9) can be obtained.
- In the presence of LBBB, right bundle branch block (RBBB) or paced rhythm where accurate diagnosis of STEMI is difficult, patient should be managed similarly to those with STEMI regardless of the BBB previously known.[16]

Management of STEMI

Acute pharmacotherapy includes oxygen supplementation if the SPO_2 is <90% and pain management with nitrates and intravenous opioids. Initial loading dose of aspirin 300 mg and P_2Y_{12} inhibitor should be given to all patients who undergo specific therapy for reperfusion including coronary intervention and fibrinolytic therapy. P_2Y_{12} inhibitors block the platelet P_2Y_{12} receptor, which plays a key role in platelet activation and the amplification of arterial thrombus formation. Conventional P_2Y_{12} has been the clopidogrel and newer agents include prasugrel and ticagrelor. Prasugrel and ticagrelor have more rapid, predictable and on average, greater antiplatelet effect compared to clopidogrel. Prasugrel has greater efficacy than clopidogrel in aspirin-treated patients with ACS undergoing PCI, but not in medically-managed patients with ACS.[17] Novel P_2Y_{12} inhibitors have higher bleeding risks compared to clopidogrel. The use of prasugrel in previous ischemic stroke patients is harmful and lack in benefits in those aged >75 years or bodyweight <60 kg. In addition to loading antiplatelet medications, loading a statin (e.g. atorvastatin 40-80 mg) is also important to stabilize the ruptured plaque.

Primary percutaneous intervention (PPCI) should be done within 120 minutes of the diagnosis of STEMI. In a center where PCI cannot be offered or not possible, to transfer within 120 minutes to a center where PCI available, or administration of a bolus of fibrinolytics within 10 minutes is recommended.[18] Fibrinolytic agents include tenecteplase, alteplase or reteplase and pre hospital administration of thrombolytics by a trained medical or allied health staff has shown to reduce mortality by 17%.[19] The main disadvantage of thrombolysis includes slight increase of intracranial bleeding risk. This risk can be mitigated by halving the tenecteplase dose and without giving pre fibrinolysis intravenous enoxaparin bolus in those age >75 years. Markers of successful fibrinolysis include significant improvement of ischemic symptoms, >50% ST segment resolution and hemodynamic stability. Even after successful fibrinolysis it is recommended that patients should be transferred to a PCI center immediately and should have an angiography within 2-24 hours.

If patients with STEMI are present after 12 hours of onset of pain, fibrinolytic therapy is not indicated. PPCI should be considered if they have ongoing chest pain or haemodynamic instability. Stable patients with late presentation STEMI should be managed as NSTE-ACS with subcutaneous enoxaparin.

Management of NSTE-ACS

Suspected NSTE-ACS should be managed as either NSTEMI or UA. Cardiac biomarkers play a major role in diagnosis, risk stratification and management in this setting. Rise in cardiac troponin (cTn) of a healthy individual points to the diagnosis of MI according to the criteria of fourth universal definition of MI.

Initial management of NSTE-ACS including oxygen therapy, pain relief, loading anti-platelet medications and statins is like that of STEMI. The specific management of NSTE-ACS is subcutaneous enoxaparin 1mg/kg twice daily for at least 3 days. This therapy should be restricted to once-a-day injections if the patient has a glomerular filtration rate of <30 mL/min.

Once the diagnosis of NSTEMI is made, it is advised to risk categorize the patients into very high-risk, high-risk, and non-high-risk categories for adverse

cardiovascular outcomes. Following are features of very high-risk category.

- Hemodynamic instability or cardiogenic shock
- Recurrent or ongoing chest pain refractory to medical management
- Acute heart failure presumed secondary to ongoing myocardial ischaemia
- Life threatening arrhythmia or cardiac arrest after presentation
- Presence of mechanical complications
- Recurrent dynamic ECG changes suggestive of ischemia

If above high-risk features are observed patient should immediately be referred for invasive revascularization treatment.[20]

High-risk features include,

- Confirmed diagnosis of NSTEMI
- GRACE (Global Registry of Acute Coronary Events) risk score >140
- Transient ST segment elevation
- Dynamic ST segment or T wave changes

If the above high-risk features are identified, the patient should be referred for invasive treatment strategy within 24 hours of diagnosis. In the absence of the above features selective invasive treatment can be arranged.

The proven medications that give a survival benefit (e.g. antiplatelet medications, statins, angiotensin converting enzyme inhibitors, beta-blockers, SGLT 2 inhibitors, GLP 1 receptor agonists etc.) should be continued long-term following successful initial management of ACS. Addition of anti-anginal therapy should be considered if the patient still experiences residual angina.

References

1. Lüscher TF. Chronic coronary syndromes: expanding the spectrum and natural history of ischaemic heart disease *Eur Heart J*. 2020; **41**(3): 333-6. DOI: 10.1093/eurheartj/ehaa001
2. Knuuti J, Ballo H, Juarez-Orozco LE, et al. The performance of non-invasive tests to rule-in and rule-out significant coronary artery stenosis in patients with stable angina: a meta-analysis focused on post-test disease probability. *Eur Heart J*. 2018; **39**: 3322-30. DOI: 10.1093/eurheartj/ehy267
3. Bourque JM, Beller GA. Value of Exercise ECG for Risk Stratification in Suspected or Known CAD in the Era of Advanced Imaging Technologies. *JACC Cardiovasc Imaging*. 2015; **8**: 1309-1321. DOI: 10.1016/j.jcmg.2015.09.006
4. Spertus JA, Salisbury AC, Jones PG, Conawa DG, Thompson RC. Predictors of quality-of-life benefit after percutaneous coronary intervention. *Circulation* 2004; **110**: 3789-94. DOI: 10.1161/01.cir.0000150392.70749.c7
5. Thadani U. Management of stable angina - current guidelines: a critical appraisal. *Cardiovasc Drugs Ther*. 2016; **30**: 419-26. DOI: 10.1007/s10557-016-6681-2
6. Wei J, Wu T, Yang Q, Chen M, NiJ, Huang D. Nitrates for stable angina: a systematic review and meta-analysis of randomized clinical trials. *Int J Cardiol*. 2011; **146**: 4-12. DOI: 10.1016/j.ijcard.2010.05.019.
7. Tardif JC, Ponikowski P, Kahan T; ASSOCIATE Study Investigators. Efficacy of the I(f) current inhibitor ivabradine in patients with chronic stable angina receiving beta-blocker therapy: a 4-month, randomized, placebo-controlled trial. *Eur Heart J*. 2009; **30**: 540-8. DOI: 10.1093/eurheartj/ehn571
8. Valgimigli M, Bueno H, Byrne RA, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: The Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J*. 2018; **39**: 213-60. DOI: 10.1093/eurheartj/ehx419.
9. Meg JL, Braunwald E, Wiviott SD, et al; for the ATLAS ACS 2-TIMI 51 Investigators. Rivaroxaban in patients with a recent acute coronary syndrome. *N Engl J Med*. 2012; **366**: 9. DOI: 10.1056/NEJMoa1112277
10. Giugliano RP, Cannon CP, Blazing MA, Nicolau JC, Corbalán R, Špinar J, Park J, White JA, Bohula EA, Braunwald E. IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) Investigators. Benefit of adding ezetimibe to statin therapy on cardiovascular outcomes and safety in patients with versus without diabetes mellitus: results from IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial). *Circulation* 2018; **137**: 1571-82. DOI: 10.1161/CIRCULATIONAHA.117.030950
11. Nidorf SM, Fiolet ATL, Mosterd A, et al. Colchicine in Patients with Chronic Coronary Disease. *N Engl J Med*. 2020; **383**(19): 1838-47. doi:10.1056/NEJMoa2021372. DOI: 10.1056/NEJMoa2021372
12. He G, Yang G, Huang X, Luo D, Tanh C, Zhang Z. SGLT2 inhibitors for prevention of primary and secondary cardiovascular outcomes: A meta-analysis of randomized controlled trials. *Heart and Lung*. 2023; **59**: 109-16. DOI: 10.1016/ j.hrtlng.2023.02.009
13. Piccini S, Favacchio G, Panico C, Morenghi E, Follo F, Mazziotti G, Lania AG, Mirani M. Time-dependent effect of GLP-1 receptor agonists on cardiovascular benefits: a real-world study. *Cardiovascular Diabetology*. 2023; **22**: 69. DOI:10.1186/s12933-023-01800-z
14. Chow CK, Jolly S, Rao-Melacini P, Fox KA, Anand SS, Yusuf S. Association of diet, exercise, and smoking modification

with risk of early cardiovascular events after acute coronary syndromes. *Circulation* 2010; **121**: 750-8. DOI: 10.1161/CIRCULATIONAHA.109.891523

15. Clar C, Oseni Z, Flowers N, Keshtkar-Jahromi M, Rees K. Influenza vaccines for preventing cardiovascular disease. *Cochrane Database Syst Rev* 2015; **5**: CD005050.
16. Ibanez B, James S, Agewall S, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J*. 2018; **39**: 119-77. DOI: 10.1093/eurheartj/ehx393
17. Wiviott SD, Braunwald E, McCabe CH, et al; TRITON-TIMI 38 Investigators. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2007; **357**: 2001-15. DOI: 10.1056/NEJMoa0706482
18. Nallamothu BK, Bates ER. Percutaneous coronary intervention versus fibrinolytic therapy in acute myocardial infarction: is timing (almost) everything? *Am J Cardiol*. 2003; **92**: 824-6. DOI: 10.1016/s0002-9149(03)00891-9
19. Boersma E, Maas AC, Deckers JW, Simoons ML. Early thrombolytic treatment in acute myocardial infarction: reappraisal of the golden hour. *Lancet* 1996; **348**: 771-5. DOI: 10.1016/S0140-6736(96)02514-7
20. Timmis A, Vardas P, Townsend N, et al. European Society of Cardiology: cardiovascular disease statistics 2021. *Eur Heart J*. 2022; **43**: 716-99. DOI: 10.1093/eurheartj/ehab892