Ischaemic heart disease: pathophysiology, diagnosis, and therapeutic strategies

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Abstract

Ischaemic heart disease is the most prevalent cardiovascular disease, accounting for high global mortality. Ischaemic heart disease is a pathological condition characterised by a mismatch between myocardial oxygen supply and demand, caused by reduced cardiac blood flow due to atherosclerotic obstruction or microvascular dysfunction. Atherosclerotic plaques in the arterial lumen form blockages in the arteries. Risk factors include hypertension and hyperlipidaemia, exacerbated by modifiable risks such as smoking, diet and stress.

Ischaemic heart disease can be classified as stable ischaemic heart disease (chronic coronary syndrome) and acute coronary syndrome, which is further divided as unstable angina, ST- elevation myocardial infarction and non-ST elevation myocardial infarction.

Ischaemic heart disease is a preventable disease that can potentially be eradicated through effective management of risk factors. The dynamic process can be influenced by lifestyle modifications (smoking cessation, diet and stress management), pharmacological interventions (antiplatelet therapy and cholesterol-lowering agents) and revascularisation procedures (percutaneous coronary intervention and coronary artery bypass grafting).

Pharmacological interventions aim at preventing clot formation and prevention and stabilisation of plaques in the arterial lumen. Comorbidities such as hypertension must be optimally managed to reduce the workload and oxygen demand of the myocardium. Medicine such as statins, ACE-I and β-blockers are essential for the management of ischaemic heart disease.

The aim of this paper is to provide an update on the management of ischaemic heart disease, and to describe the role of the pharmacist in prevention of modifiable risk factors and management of established ischaemic heart disease.

Keywords: ischaemic heart disease, angina, STEMI, NSTEMI, risk factors, pharmacist

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Introduction

Cardiovascular diseases account for approximately one-third of all deaths globally, ischaemic heart disease (IHD) being the most prevalent.[1] Ischaemic heart disease is a pathological condition characterised by a mismatch between myocardial oxygen supply and demand, caused by reduced cardiac blood flow.[2] Coronary artery disease (CAD), usually due to atherosclerotic obstruction or microvascular dysfunction, is most frequently the underlying pathological process.[1] Although IHD is a progressive disease, it can become an unstable condition due to an acute plague rupture or erosion of an atherosclerotic plaque. It can result in different clinical presentations, categorised as chronic coronary syndrome (CCS) or acute coronary syndrome (ACS).[2]

There are still major differences between countries in the burden of cardiovascular disease.[2] A global increase of 1.3 million incident cases and 5 million disability-adjusted life years (DALYs) were observed during 2021, when compared to 2019.[3] The burden of IHD in low-to-middle income countries is severe, with around 80% of deaths in these countries, including South Africa where over half of the adult population presented with hyperlipidaemia.[3,4] In developed countries, whilst still a major cause of mortality, the burden in developed areas in Europe and United States of America, is decreasing.[2] This heightened burden in developing countries is primarily linked to rapid economic transitions, industrialisation, urbanisation, globalisation, and population ageing, which have significantly altered lifestyles and consequently increased the prevalence of IHD.[5] A household survey in South Africa indicated that the prevalence of IHD rises with age, mirroring the trend observed with hypertension.[4] Risk factors associated with the pathophysiology of IHD include hypertension, diabetes and dyslipidaemia, exacerbated by modifiable risks such as smoking, unhealthy diet (including obesity), harmful use of alcohol and physical inactivity.[4,6]

Ischaemic heart disease is a preventable disease and can potentially be eradicated through effective management of risk factors.[5] The dynamic process, characterised by atherosclerosis of the coronary arteries, or functional changes in coronary circulation, can be influenced by lifestyle modifications, pharmacological interventions and revascularisation procedures.[2] Even though the risk associated with these diseases remains elevated, the progression of CAD and IHD can be effectively managed through optimal medication management, including antiplatelet agents, statins, ACE-inhibitors, and β-blockers.[7]

The aim of this review paper is to provide an update on the management of IHD including the effective diagnosis, revascularisation and pharmacotherapeutic management thereof.

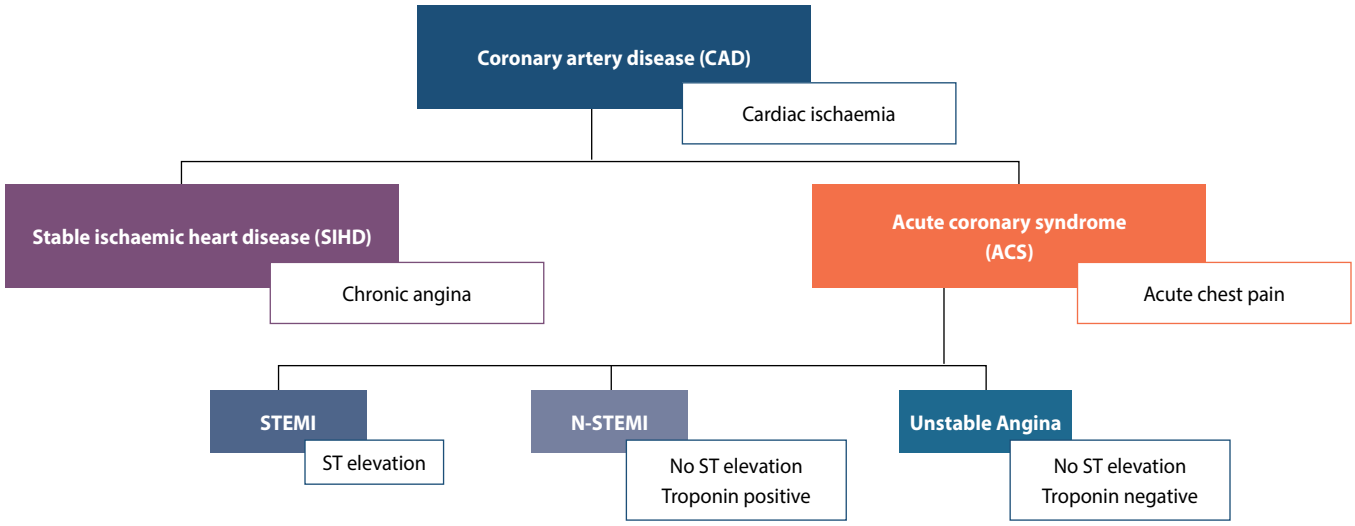

Figure 1: Classification of coronary artery disease (adapted from Shahjehan, Bhutta and Sharma, 2024).[8]

Classification of IHD

Ischaemic heart disease or CAD is mainly classified into two categories namely, stable ischaemic heart disease and acute coronary syndrome, based on the clinical manifestations of the disease.[8]

1. Stable Ischaemic Heart Disease (chronic coronary syndrome)
   - Stable angina pectoris
   - Microvascular angina (syndrome X)
   - Vasospastic angina (Prinzmetal variant angina)
2. Acute coronary syndrome
   - Unstable angina
   - Non-ST segment elevation myocardial infarction (NSTEMI)
   - ST-segment elevation myocardial infarction (STEMI)

Pathophysiology

Atherosclerosis, coronary microvascular dysfunction, inflammation, and vasospasm collectively contribute to the intricate and multifaceted pathophysiology of ischaemic heart disease.[2]

The formation of atherosclerotic plaques, which is a key characteristic of the pathophysiology of IHD, results in the accumulation of plaque within the arterial lumen, resulting in obstruction of blood flow.[9] A "fatty streak" is created by lipid-laden macrophages, commonly known as "foam cells", depositing themselves in the subendothelial space as the initial stage of the process. Following a vascular insult, monocytes migrate into the subendothelial region, where they transform into macrophages, and the intima layer ruptures. Foam cells are created when these macrophages absorb oxidised low-density-lipoprotein (LDL) particles. Cytokines are released to support the inflammatory process when T cells are activated. Growth factors cause smooth muscles to contract, absorbing collagen and oxidised LDL particles, depositing them with activated macrophages and boosting the number of foam cells, forming subendothelial plaques.[8,9]

The plaque may either expand or stabilise over time, provided that no additional endothelial damage occurs. A fibrous cap develops when the plaque achieves stability and undergoes calcification over time; the lesion can attain haemodynamic significance, a form of arterial stenosis. If 70% of the lumen is obstructed, the proximal resistance significantly increases, while the distal coronary perfusion pressure decreases, leading to inadequate myocardial tissue perfusion, leading to angina symptoms during periods of increased demand. Angina can further manifest at rest when the coronary artery experiences 90% stenosis.[8,9,10]

Certain plaques have the potential to rupture, exposing tissue factors, which can lead to thrombosis and result in either subtotal or total occlusion of the lumen. Severe acute obstruction generally leads to acute coronary syndrome (ACS), presenting as unstable angina, non-ST elevation myocardial infarction, or ST elevation myocardial infarction, contingent upon the severity of the injury.[8,9,10]

Symptoms

Ischaemic cardiomyopathy and myocardial infarction are two clinical manifestations of IHD.[11] Angina pectoris, characterised by chest pain that arises behind the sternum during physical exertion, exposure to cold weather, or emotional stress, is the most prevalent symptom of ischaemic heart disease.[12] Chest pains are described as pressure, or a feeling of squeezing of fullness in the centre of left side of the chest. In female patients, IHD is frequently characterised by angina or discomfort that radiates to the neck, abdomen, shoulders, teeth or jaw and head. Additionally, patients may exhibit symptoms such as breathlessness, fatigue, sweating, palpitations, anxiety, nausea, and vomiting.[10,12]

Silent angina is particularly common in patients with diabetes and can only be detected with angiogram or cardiac echogram. This type of IHD does not present any noticeable symptoms.[10]

Refractory angina can be defined as the presence of angina symptoms for three months or more, which does not respond to pharmacological therapy.[13]

Diagnosis of ischaemic heart disease

Final diagnosis of IHD involves a combination of medical history and assessment of risk factors, physical examination and the appropriate diagnostic tests to assess heart function and blood flow. The initial diagnostic management of suspected CCS is based on selecting the most suitable noninvasive functional or anatomical test to qualify the risk of obstructive CAD and indication for revascularisation.[2]

The diagnostic work-up can be summarised in five steps:[2]

1. Assessment of the symptoms, excluding ACS
2. Resting electrocardiogram (ECG) and echocardiography to examine clinical cardiac symptoms
3. Evaluation of comorbidities that may influence symptoms, or need for further testing or potential treatment
4. Evaluation of likelihood of CCS
5. Decision whether computed tomography angiography (CTA) or further noninvasive testing like stress ECG or positron emission tomography (PET) is needed

Table I provides an overview of the diagnostic process followed when tests are available to diagnose IHD.

Table I: Diagnostic tests

Test	Description and Aim
Physical Exam and History	Assess symptom severity and risk factors
Electrocardiogram	Records electrical activity in the heart and identify blood flow restrictions
Blood tests (e.g. blood urea nitrogen, creatinine-kinase, d-dimer and troponin)	Proteins released during a myocardial infarct can be detected in the blood Further blood tests include cholesterol panel, glucose levels and haemoglobin levels
Catheterisation	A catheter is inserted to examine the blood flow in coronary arteries directly
Imaging tests	Chest X-rays and echocardiogram can visualise the structure and function of the heart

Nonpharmacological management of ischaemic heart disease

Lifestyle modifications, when implemented consistently, are the mainstay of non-pharmacological intervention for IHD. Reduction in modifiable risk factors can improve angina symptoms and reduce myocardial infarction risks.[14] Smoking cessation, healthy nutrition, stress management and regular mild exercise can reduce the progression of IHD and the risk of infarctions.[4]

Cognitive behavioural therapy and cardiac rehabilitation form part of the therapy due to the psychological effect these diseases have on patients.[14] Cognitive behavioural therapy involves educating the patient about the disease, its risk factors, misconceptions and how to recognise symptoms and when to seek urgent medical attention. Cardiac rehabilitation aims to reduce the psychological toll such as anxiety and depression that patients experience as it may have an impact on the effectiveness of therapy.[14]

Invasive and non-invasive non-pharmacological techniques are used to treat refractory angina. These methods include surgical techniques, e.g.:[13]

1. Coronary sinus reducer: a stainless steel, hourglass-shaped, balloon-expandable device, placed on the coronary sinus through the jugular vein. It redistributes blood and increases myocardial perfusion through the coronary sinus.
2. Revascularisation of chronic total occlusion: technique to restore blood flow through occluded coronary arteries either by percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG).[15] Coronary artery bypass graft surgery is more common and has better long-term outcomes than PCI.
3. Enhanced external counter pulsation (EECP): a non-invasive technique which aims to decrease the intensity and frequency of angina episodes. It works by applying three pairs of inflatable cuffs around the lower legs, upper legs and buttocks, which continuously inflate and deflate increasing blood flow back to the heart.[16] Increased blood flow and oxygenation enable the heart to function more efficiently, reducing chest pain.
4. Extracorporeal shockwave myocardial revascularisation: improves myocardial perfusion in ischaemic areas by applying low intensity acoustic shockwaves.[14] It involves inserting a device which contains and emits low intensity shockwaves into the ischaemic section of the heart.[17] The mechanical stress from the shockwaves triggers a biological response producing nitric oxide synthase and vascular endothelial growth factor resulting in angiogenesis – the formation of blood vessels, improving blood flow and reducing chest pain.[17]
5. Spinal cord stimulation and transcutaneous electrical nerve stimulation (TENS): involves surgical implant of an epidural lead with multiple electrodes delivering low-output electrical impulses, modulating pain stimuli.[18]

Pharmacological therapy

Different classes of medication are used to prevent and treat angina. These medications can be used as monotherapy or in combination depending on factors such as the comorbidities of the patient and cardiac function of the patient. The classes of these medications are antiplatelets, statins, angiotensin converting enzyme-inhibitors (ACE-I) or angiotensin receptor blockers, beta-blockers, calcium-channel blockers, nitrates and other vasodilators, and analgesics.

Table II provides an overview of different medicine classes, their specific indications and mechanism of action, with examples.

Role of the pharmacist

Pharmacists, as front-line healthcare workers, can play an important role in the prevention and management of ischaemic

Table II: Overview of medicines in the management of IHD

Class	Indication/Mechanism	Examples
Antiplatelets	Prevent and treat angina by inhibiting platelet aggregation, preventing clot formation. Aspirin blocks the cyclooxygenase-1 (COX-1) enzyme, preventing the production of thromboxane A_2. Clopidogrel blocks P_2Y_2 receptors on platelets, preventing aggregation in response to ADP.[14]	Aspirin Clopidogrel
Statins	Lower low-density-lipoprotein (LDL) through blockade of the HMG-CoA reductase enzyme, which catalyses the first step in cholesterol synthesis. Further decrease triglyceride levels by inhibition of synthesis in the liver, enhancing activity of lipoprotein lipase in adipocytes. Increase high-density lipoprotein (HDL) levels by inducing apolipoprotein A1 (Apo-A1). HDL inhibits the progression of the atherosclerotic process by facilitating reverse transport of cholesterol from the monocytes in vascular walls, modulating inflammatory response	Simvastatin Atorvastatin Rosuvastatin
ACE-I/ARB	Recommended for patients with comorbidities e.g. cardiac failure. Blocks the formation of angiotensin-II hormone responsible vasoconstriction and increase blood pressure, which will reduce pressure and workload of the heart. Vasodilation will result in improved blood flow to the heart.[14]	Enalapril Perindopril Losartan Valsartan
Beta-blockers	Competitive blockers of catecholamines e.g. noradrenaline on cell-membrane β-receptors. Reduce heart rate, increase myocardial contractility, reduce force of contractility on decrease oxygen demand. Beneficial to angina patients and prevents exercise-induced angina.[19]	Atenolol Carvedilol
Calcium-channel blockers	Blocks inward movement of calcium by binding to L-type "long-acting" voltage-gated calcium channels in the heart and vascular smooth muscle Antianginal effects derived from vasodilator and cardio-depressant actions. Systemic vasodilation reduces arterial pressure, reduces ventricular afterload, and decreases oxygen demand. Dilate coronary arteries and prevent or reverse coronary vasospasm (Printzmetal's variant angina).[20]	*Cardio selective CCB:* Verapamil Diltiazem
Nitrates	Exogenous source of nitric oxide (organic nitrates) which is a potent coronary vasodilator.[21] Relief angina symptoms by facilitating flow of blood from epicardial to endocardial vessels. Improve myocardial ischaemia by improving regional myocardial blood flow. Reduce the preload and the workload on the heart by increasing venous capacitance and peripheral pooling of blood, reducing myocardial oxygen demand. Reduce afterload by reducing aortic systolic pressure without corresponding drop in peripheral arterial pressure.	Isosorbide mononitrate
Analgesics	Reduce pain. Inhibit the release of pain signalling neurotransmitters by mu-receptor binding in central nervous system. Reducing blood pressure may be beneficial in IHD.[14]	Opioids (specifically morphine)

heart diseases. In collaboration with the patient, they can ensure adherence to the prescribed medication, through educating the patient on when and how to take the medication. They can emphasise the importance of adherence in the long-term outcomes and disease progression of IHD. They can make patients aware of the symptoms and signs they may experience, and when to seek urgent medical attention when experiencing symptoms. Pharmacists help in monitoring side-effects and conduct medication reviews to assess the appropriate medications with the correct dose and frequency. Their expertise allows them to evaluate patients' comorbidities and treatments and enables them to identify clinically significant drug interactions and adverse drug reactions. They provide guidance on lifestyle modifications by ensuring that the patient is consistent and adjusting properly to the lifestyle modifications. They play a vital role in collaboration with other healthcare professionals in medication therapy management through monitoring drug interactions to optimise the medication regimens of the patients.[22]

Conclusion

Ischaemic heart disease is still a major contributor to mortality globally. However, the reduction of risk factors, especially modifiable risk factors, may have a great influence on prevention of IHD, as well as to modify disease progression. The pharmacist can educate patients to reduce risks but also assist with optimising therapy once the disease is treated. Although the incidence of IHD in South Africa is high, and rising, optimal treatment of comorbidities and improvement of lifestyle may reduce the burden of the disease. Pharmacists, as part of the multidisciplinary healthcare team, can assist in the management of this patient population.

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