Review Article

Hacettepe University Journal of the Faculty of Pharmacy
Volume 44 / Number 4 / December 2024 / pp. 373-389

Ischemia Heart Disease: Current Diagnosis, Treatment Methods, and Genetic Research

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Received date : 10.06.2024
Accepted date : 23.10.2024

DOI: 10.52794/hujpharm.1498649

ABSTRACT

Ischemic heart disease (IHD) is a top non-infectious disease that causes more deaths worldwide and it increases progressively over the years. It becomes a burden to low and middle-income countries. The management and treatment of ischemic heart disease have become more challenging due to improper lifestyle, adverse effects of currently available drugs, limited access to various diagnostic methods, genetic variations, and lack of knowledge among healthcare professionals. In this comprehensive survey, the different kinds of diagnostic approaches and modes of therapy, current research, molecular and genetic basis, future directions like integrative therapy and precision medicine, and global health initiatives related to IHD were summarized. This review is based on a literature survey of studies published between 2001 and 2024 using databases such as PubMed, Scopus, Web of Science, and relevant website like the World Health Organisation. The main goal of this literature survey is to create awareness that will help healthcare professionals save patients' lives and aid researchers in developing new molecules to treat IHD.

Keywords: Heart, IHD, Diagnostic methods, Genetic basis.

1. Introduction

Ischemia is characterized by a region receiving insufficient blood flow because of a blockage in the blood arteries supplying that area. Ischemic conditions occur when an organ, like the heart, does not receive enough blood or oxygen. Heart issues brought on by constricted coronary arteries that provide blood to the heart muscle are referred to as ischemic heart disease, also known as coronary heart disease (CHD) or coronary artery disease [1]. Atherosclerosis, a disorder marked by plaque accumulation, is frequently the source of this narrowing, however, blood clots or constricted vessels can also be the reason. Myocardial infarction (MI), sometimes known as a heart attack, is a disorder in which there is total blockage of blood supply to the heart muscle, leading to the death of heart muscle cells. The majority of people with CHD do not exhibit any symptoms or blood flow restrictions while the condition is in its early stages (less than 50% narrowing). However, symptoms may appear as atherosclerosis worsens, especially if left untreated. When there is an increased demand for oxygen due to physical effort or mental stress, these symptoms are more likely to manifest. It is characterized by discomfort in the arms, shoulders, back, chest, and jaw. Usually brought on by stress or physical activity, it is eased by rest or nitroglycerin. Patients with hypertrophic cardiomyopathy, valvular disease, uncontrolled hypertension, and congestive heart failure can all have angina. Angina can occasionally occur in people with normal coronary arteries as a result of endothelial dysfunction or coronary spasm [2].

The World Health Organisation (WHO) reports that ischemic heart disease accounts for 16% of all deaths globally, making it the leading cause of mortality. Of the 8.9 million fatalities in 2019, more than 2 million were due to this condition, which has resulted in the largest increase in mortality since 2000 [3]. It places a heavy financial burden on society due to increased healthcare expenditures and decreased productivity, as well as years of life loss and disability-adjusted living years. Over three-quarters of IHD deaths occur in low- and middle-income countries due to urbanization and limited healthcare access. In addition to non-modifiable risk factors like age and heredity, modifiable risk factors including obesity, smoking, and hypertension are important targets for prevention. To manage and lessen the burden of IHD globally, technological advancements in medicine and global health efforts are critical [4].

Diagnosing and treating ischemic heart disease presents several challenges. Non-invasive tests like stress tests and echocardiography may yield inaccurate results, complicating IHD identification. Limited access to advanced diagnostic tools such as coronary angiography, especially in low- and middle-income countries, due to financial and infrastructure limitations exacerbates diagnostic challenges. Treatment hurdles include ensuring adherence to medications like statins and antiplatelet agents, managing side effects, and addressing disparities in access. Lifestyle modifications such as diet and exercise are crucial in IHD management, but they face barriers like socioeconomic factors and inadequate patient education [5]. Addressing these issues requires strategies to improve diagnostic accuracy, enhance medication adherence through education, expand access to interventions, and promote healthier lifestyles through public health initiatives [6]. In this current review, the various diagnostic approaches, treatments, present research, and future options for IHD treatment were summarized. To conduct this review, we performed a literature search for studies published between 2001 to 2024. Databases including PubMed, Scopus, Web of Science, and relevant website from the World Health Organisation (who. int) were utilized. Keywords used in the search included ischemic heart disease, heart, diagnostic methods, genetic basis, etc. That aids medical professionals in correctly diagnosing, recommending, and treating patients in a way that helps preserve lives. Additionally, by understanding how medications interact with different genetic conditions, researchers can develop new molecules for the better treatment of ischemic heart disease.

2. Diagnostic Approaches of Ischemic Heart Disease

Ischemic Heart Disease is a major source of morbidity and death worldwide, prompt and precise diagnostic methods are required. The basis for diagnosis includes risk assessment, clinical evaluation, and diagnostic testing such as stress testing and invasive coronary angiography based on risk and symptoms. The electrocardiogram (ECG) helps identify ischemia alterations, and cardiac magnetic resonance imaging (MRI) and echocardiography offer fine-grained structural and functional information. Nuclear imaging techniques that measure myocardial

perfusion include single photon emission computed tomography (SPECT) and myocardial perfusion imaging (MPI). Troponins are one type of biomarker that indicates myocardial damage and complements diagnosis. New technologies, such as genetic testing and sophisticated imaging, provide prospective paths toward more precision. Clinicians can effectively identify IHD by utilizing a multifaceted strategy that integrates various approaches, leading to optimum therapy and better patient outcomes [7–9]. The details of the diagnostic methods used for ischemic heart disease are explained in Table No. 1.

3. Methods for Treating Ischemic Heart Disease

3.1. Pharmacological treatments

3.1.1. Standard therapies

Standard therapies for ischemic heart disease involve antiplatelet agents, statins, beta-blockers, ACE inhibitors/ARBs, calcium channel blockers, nitrates, and diuretics, targeting different aspects like platelet aggregation, cholesterol levels, myocardial oxygen demand, blood pressure, and vasodilation to manage symptoms and prevent complications. Antiplatelet agents like aspirin, clopidogrel, ticagrelor, and prasugrel are crucial in preventing thrombus formation. Aspirin is the most commonly used antiplatelet for both primary and secondary prevention of IHD, effectively reducing the risk of myocardial infarction (MI) and stroke. For patients with stable angina or those at high risk of cardiovascular events, low-dose aspirin (75-100 mg daily) is recommended. In cases of acute coronary syndrome (ACS), aspirin is combined with a P2Y12 inhibitor (such as clopidogrel, ticagrelor, or prasugrel) to prevent recurrent ischemic events [20]. The choice of P2Y12 inhibitor depends on the clinical scenario. Clopidogrel is commonly used for patients who are aspirin intolerant or as part of dual antiplatelet therapy (DAPT) following percutaneous coronary intervention (PCI) with stenting. Ticagrelor or prasugrel may be preferred in acute coronary syndrome due to their more potent platelet inhibition and better outcomes in reducing major adverse cardiovascular events; however, they are associated with higher bleeding risk. Antiplatelet therapy must be individualized based on the patient's bleeding risk, comorbidities, and specific clinical condition to optimize benefits and minimize potential complications [21]. Statins are essential in managing ischemic heart disease (IHD) for both primary and secondary prevention. For primary prevention, they are prescribed to individuals at high risk of cardiovascular disease, including those with elevated LDL levels or multiple risk factors. For secondary prevention, statins are crucial for patients with established IHD, such as those who have had a myocardial infarction (MI) or undergone coronary artery bypass grafting (CABG), helping to reduce the risk of subsequent cardiovascular events. High-intensity statins, like atorvastatin or rosuvastatin, are often preferred to achieve significant LDL reduction and maximize cardiovascular benefits. The choice and dosage of statins should be personalized based on the patient's risk profile, tolerance, and monitoring for potential side effects [22].

Beta-blockers are fundamental in managing ischemic heart disease (IHD), particularly for chronic stable angina and post-myocardial infarction (MI). They reduce myocardial oxygen demand by decreasing heart rate, blood pressure, and contractility, effectively alleviating angina symptoms and preventing episodes [23]. In post-MI patients, beta-blockers significantly reduce mortality, decrease the risk of recurrent MI, and prevent the onset of heart failure. Long-acting agents like carvedilol, metoprolol, or bisoprolol are often preferred due to their additional cardioprotective properties. For patients with heart failure with reduced ejection fraction (HFrEF), beta-blockers such as carvedilol, bisoprolol, and metoprolol succinate not only improve symptoms but also enhance survival and reduce hospitalization rates [24]. The choice of beta-blocker should be individualized, taking into account patient-specific factors, comorbidities, and tolerance. While beta-blockers are crucial in acute coronary syndrome (ACS) for their role in stabilizing the myocardium and preventing arrhythmias, they are contraindicated in patients with conditions like severe bradycardia, decompensated heart failure, or certain types of asthma. Careful monitoring and dose adjustment are necessary to maximize therapeutic benefits and minimize potential side effects, ensuring optimal outcomes in the management of IHD [25]. ACE inhibitors in ischemic heart disease (IHD) emphasize their expanded use beyond blood pressure control, particularly in patients with hypertension, diabetes, heart failure, or chronic kidney disease. ACE inhibitors are now recommended early in

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Table 1. Overview of Ischemic Heart Disease Diagnostic Techniques

Diagnostic methods	Description	Application	Benefits	Drawbacks	Required Preparation	References
Clinical Diagnosis						
1. Physical examination and medical history	Evaluation of physical results, risk factors (such as diabetes, smoking), and symptoms (such as chest discomfort).	Preliminary assessment of possible IHD.	Affordable, simple to execute, and non-invasive.	Subjective and might miss some IHD instances.	No specific preparation.	Skinner JS, Smeeth L et al.,(2010) [10]
2. Evaluation of Risk Factors	Examination of factors such as blood pressure, cholesterol, age, gender, and lifestyle.	Estimating the probability of IHD.	Non-invasive, and helpful in risk classification.	Does not validate IHD; it only evaluates risk.	For lipid profiles, fasting can be necessary.	
Electro cardiogram (ECG)						
1. ECG at rest	It records the heart's electrical activity without any added physical stress.	Diagnosis of arrhythmias and conduction abnormalities. Monitoring of ongoing heart conditions.	Non-invasive, straight forward, useful for routine check-ups and diagnosing resting cardiac issues.	It may not detect issues that arise only during physical exertion or stress and is limited in evaluating heart performance under these conditions.	Ensure the patient is calm with clean, dry skin and no special preparations are needed.	Virani SS, Newby LK et al., (2023) [11]
Exercise ECG (Stress Test)	ECG monitors the heart's response to increased workload during physical activity or pharmacological stress.	It detects exercise-induced ischemia or arrhythmias, evaluates exercise tolerance and cardiac function, and assesses heart disease severity and treatment effectiveness.	It reveals how the heart responds to physical stress, crucial for diagnosing conditions not apparent at rest, and helps assess coronary artery disease risk and guide treatment decisions.	It may be uncomfortable for some patients and requires careful monitoring and preparation to avoid complications.	Patients may need to avoid food, and caffeine, wear comfortable clothing and appropriate footwear, and prepare for potential discomfort or fatigue.	
Imaging Techniques						

Diagnostic methods	Description	Application	Benefits	Drawbacks	Required Preparation	References
1. Echo cardiography	A non-invasive imaging technique using ultrasound waves to create images of the heart's structure and function.	Assessing heart structure, function, and evaluating valvular heart disease and ventricular function.	Provides real-time images of heart structures and no radiation involved.	Limited in detecting coronary artery disease directly	Ensure patient is relaxed and no special preparation needed.	Hundley WG, Bluemke DA et al., (2010) & Knuuti J, Wijns W et al., [12,13]
2. Stress Echocardiography	Combines echocardiography with stress testing (exercise or pharmacological) to evaluate heart function under stress.	Identifying exercise-induced ischemia, assessing cardiac function and wall motion abnormalities.	Detects stress-induced changes in heart function; useful for diagnosing ischemia.	May be uncomfortable and require patient to exercise or tolerate the stress-inducing medication.	Patient may need to avoid food before the test and wear comfortable clothing.	
3. Coronary Angiography	Invasive procedure using a catheter and contrast dye to visualize coronary arteries and detect blockages.	Evaluating severity and location of coronary artery blockages.	Provides detailed images of coronary arteries and guides treatment decisions.	Invasive with associated risks such as bleeding, infection and requires contrast dye.	Fasting before the procedure and hydration.	
4. Computed Tomography Angiography (CTA)	Non-invasive imaging using CT scan and contrast dye to create detailed images of coronary arteries.	Diagnosing coronary artery disease, assessing coronary anatomy and stenosis.	Provides detailed 3D images of coronary arteries.	Radiation and contrast dye exposure—not recommended for those with renal impairment.	Fasting and do not consume caffeine and nicotine before diagnosis.	
5. Cardiac Magnetic Resonance Imaging (MRI)	Non-invasive imaging using magnetic fields and radio waves to create detailed images of the heart's structure and function.	Assessing myocardial viability, evaluating heart function, and detecting myocardial infarction or scarring.	Excellent tissue characterization, no radiation, detailed functional and structural data.	High cost and may be challenging for patients with claustrophobia or metal implants.	No special preparation for the MRI itself, avoid metal objects and need to fast depending on protocol.	
Nuclear Imaging						
1.Myocardial Perfusion Imaging (MPI)	Uses a radioactive tracer to show the cardiac muscle's blood flow.	Measuring blood flow and locating hypo-perfused regions.	Functional evaluation of myocardial perfusion that is non-invasive.	Radiation exposure, high cost, and limited availability.	Do not consume caffeine, nicotine, and other medications before diagnosis.	Dilsizian V, Bacharach SL et al., (2016) & American Society of Nuclear Cardiology (2016) [14,15]
2. Single Photon Emission Computed Tomography (SPECT)	3D imaging to assess blood flow and detect ischemia.	Detailed blood flow assessment in heart muscle.	3D functional imaging without invasive methods.			
Biomarkers and Laboratory Tests						

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Diagnostic methods	Description	Application	Benefits	Drawbacks	Required Preparation	References
1. Blood Tests	Evaluate blood glucose, C-reactive protein (CRP), lipid profiles, troponins, and other cardiac biomarkers.	Identifying damage to the cardiac muscle and assessing risk variables.	Non-invasive, helpful for risk assessment, and capable of confirming myocardial infarction.	Only determine the damages to cardiac muscle, not provide anatomical information,	Fasting for lipid and glucose tests	Thygesen K, Alpert JS et al., (2018) [16]
Other Diagnostic Tests						
1. Ankle-Brachial Index (ABI)	uses a blood pressure comparison between the arm and ankle to find peripheral artery disease.	Associated to an increased risk of coronary heart disease.	Non-invasive, simple, inexpensive.	Not exclusive to coronary arteries, may be impacted by several illnesses.	No specific preparation	Aboyans V, Criqui MH et al., (2012) [17]
2. Coronary Calcium Scan	CT scan indicating atherosclerosis by detecting calcium in the coronary arteries.	Evaluating the coronary artery disease condition.	Quick, non-invasive, and helpful for risk assessment.	Functional information is not provided by radiation exposure.	Do not consume caffeine and nicotine before diagnosis.	Naghavi M, Atlas K et al., (2024) [18]
Emerging Diagnostic Techniques						
1. Genetic Testing	Finds genetic susceptibilities to IHD.	Identifying hereditary IHD risk factors.	Non-invasive gives genetic risk information.	Expensive, with limited clinical applicability that might raise ethical concerns.	No specific preparation	de Oliveira, Correia VM et al., (2023) [19]
2. Advanced Imaging techniques	Details of the insides of coronary arteries may be seen with methods like intravascular ultrasound (IVUS) and Optical coherence tomography (OCT).	Comprehensive analysis of coronary artery diseases.	Gives high-resolution pictures of the inside of arteries, which are helpful in directing treatment.	Costly, invasive, and rarely accessible .	Fasting, sedation	

acute coronary syndrome to reduce recurrent events and improve outcomes and for secondary prevention in all patients with a history of myocardial infarction (MI) or coronary artery disease at high cardiovascular risk [26]. A personalized approach is advised, considering age, renal function, and side effects, with gradual dose titration to minimize risks. Regular monitoring for electrolyte imbalances and kidney function is emphasized, particularly in elderly patients or those on diuretics. Tailoring ACE inhibitor therapy helps optimize cardiovascular benefits while reducing potential complications [27].

Calcium channel blockers such as amlodipine, diltiazem, and verapamil are used for angina and hypertension, especially in patients who cannot tolerate beta-blockers. Amlodipine and diltiazem, are now recommended as first-line therapy for stable angina, particularly in patients with Prinzmetal's angina or coronary artery spasm. Amlodipine for patients with concomitant hypertension and diltiazem are recommended for those with heart rate control needs. Newer recommendations stress avoiding short-acting calcium channel blockers due to the risk of reflex tachycardia and emphasize selecting agents

based on patient-specific factors such as comorbidities, side effects, and drug interactions to optimize therapeutic outcomes [28,29]. Nitrates for ischemic heart disease emphasize their role in relieving angina symptoms, especially when beta-blockers or calcium channel blockers are inadequate or not suitable. Long-acting nitrates, such as isosorbide mononitrate, are preferred for managing chronic stable angina, particularly in patients with Prinzmetal's angina or coronary artery spasm. Short-acting nitrates, like nitroglycerin, are used for the immediate relief of acute angina attacks. Current practices highlight the importance of implementing a nitrate-free interval to avoid tolerance [30]. Diuretics such as hydrochlorothiazide and furosemide are used for controlling fluid overload and reducing blood pressure in patients with IHD and heart failure with reduced ejection fraction (HFrEF). In patients with resistant hypertension, mineralocorticoid receptor antagonists like spironolactone are increasingly considered to optimize blood pressure control [31]. The choice of diuretic should consider the patient's renal function, electrolyte balance, and risk of adverse effects such as hypokalemia or dehydration, ensuring effective management of both IHD and its comorbid conditions [32]**.** The details of various drugs used in the treatment of IHD are discussed in Table no 2,

3.2. New pharmacological developments

3.2.1. Proprotein convertase subtilisin/kexin type 9 (pcsk9) inhibitors

A new family of medications known as PCSK9 inhibitors lowers levels of low-density lipoprotein cholesterol (LDL-C) by blocking PCSK9, a protein that controls LDL receptor levels. PCSK9 inhibitors improve the liver's capacity to remove LDL-C from circulation by stopping the degradation of LDL receptors. This lowers the risk of atherosclerotic cardiovascular events, including myocardial infarction (MI) and stroke, by significantly reducing LDL-C levels [40].

3.2.2. Sodium-glucose cotransporter-2 (SGLT2) inhibitors

SGLT-2 inhibitors have been recognized for their expanded role in managing chronic coronary syndromes and heart failure. Medications such as empagliflozin, dapagliflozin, and canagliflozin are acknowledged for their effectiveness in controlling blood glucose and their significant cardiovascular benefits. SGLT-2 inhibitors are recommended for patients with heart failure with reduced ejection fraction (HFrEF) and chronic kidney disease, irrespective of diabetes status. They are noted for their ability to reduce hospitalization for heart failure and lower cardiovascular mortality. SGLT-2 inhibitors work by inhibiting the sodium-glucose co-transporter 2 (SGLT-2) in the kidneys, leading to increased glucose excretion and improved fluid balance. Clinical evidence supports their efficacy in reducing cardiovascular death, heart failure hospitalization, and the progression of kidney disease, highlighting their growing importance in treatment strategies for chronic cardiovascular and renal conditions [41,42] **.**

3.2.3. Novel anticoagulants

Direct oral anticoagulants, or DOACs, are another name for novel oral anticoagulants (NOACs), which are a major development in anticoagulant treatment for patients with IHD. NOACs offer better predictable pharmacokinetics and pharmacodynamics along with a decreased risk of bleeding problems since they preferentially target particular coagulation factors (e.g., factor Xa or thrombin), in contrast to standard anticoagulants like warfarin [43]. NOACs are being investigated more and more for their potential involvement in the secondary prevention of IHD. They have been demonstrated to be either noninferior or even superior to standard treatments in reducing thromboembolic events in patients with atrial fibrillation and venous thromboembolism [44].

3.3. Revascularization techniques

3.3.1. Percutaneous coronary intervention (PCI)

Percutaneous Coronary Intervention (PCI) is a form of minimally-invasive surgery used to treat ischemic heart disease. It is sometimes referred to as coronary angioplasty or stenting [45]. Using X-ray imaging, a catheter is inserted into a blood vessel, usually in the wrist or groin, and guided to the blocked coronary artery. After it is in position, a balloon is inflated to expand the constricted artery and bring blood flow back to the heart muscle. To maintain the artery open, a stent a tiny mesh tube may occasionally be implanted. While PCI has benefits like quicker symptom alleviation and higher survival rates, there is a chance of problems including bleeding and restenosis [46].

ISSN: 2458 - 8806

Table 2. Clinical Significance of Drugs Used in Ischemic Heart Disease

Drug Class	Examples	Mechanism of Action	Adverse Effects	References
Antiplatelet Agents	Aspirin, Clopidogrel	Inhibit platelet aggregation and thrombus formation. Aspirin irreversibly inhibits COX-1 enzyme, reducing thromboxane A2. Clopidogrel inhibits the P2Y12 ADP receptor.	Gastrointestinal bleeding, peptic ulcer, hemorrhagic stroke, dyspepsia.	Clappers N, Brouwer MA et al., (2005) [33]
Statins	Atorvastatin, Rosuvastatin	Inhibit HMG-CoA reductase, the rate-limiting step in cholesterol synthesis. Lower LDL-C levels, stabilize atherosclerotic plaques and reduce inflammation.	Myopathy, rhabdomyolysis, liver enzyme elevation, gastrointestinal disturbances, diabetes risk.	Oikawa T, Sakata Y et al., (2018) [34]
Beta-Blockers	Metoprolol, Atenolol	Block beta-adrenergic receptors, decreasing heart rate and contractility. Reduce myocardial oxygen demand and improve survival after myocardial infarction.	Bradycardia, hypotension, fatigue, depression, sexual dysfunction, bronchospasm in asthma patients.	Khan O, Patel M et al., (2023) [35]
ACE Inhibitors	Enalapril, Lisinopril	Inhibit angiotensin-converting enzyme, reducing the formation of angiotensin II. Lower blood pressure, decrease afterload, and reduce adverse cardiac remodeling.	Cough, hyperkalemia, angioedema, hypotension, renal impairment.	O'Keefe JH, Wetzel M et al., (2001) [36]
Angiotensin II Receptor Blockers (ARBs)	Losartan, Valsartan	Block the angiotensin II type 1 receptor, reducing the effects of angiotensin II. Lower blood pressure and decrease adverse cardiac remodeling similar to ACE inhibitors.	Hyperkalemia, hypotension, renal impairment, dizziness, rare angioedema.	Böhm M, Baumhäkel M et al., (2010) [37]
Calcium Channel Blockers	Amlodipine, Diltiazem	Inhibit L-type calcium channels, leading to vasodilation and reduced myocardial oxygen demand. Used to manage angina and hypertension.	Edema, constipation, bradycardia, dizziness, flushing, headache.	Shemin DG, Dworkin LD (2008) [38]
Nitrates	Nitroglycerin, Isosorbide Mononitrate	Release nitric oxide, causing vasodilation of coronary arteries and veins. Reduce preload and myocardial oxygen demand. Used to relieve angina.	Headache, hypotension, dizziness, flushing, reflex tachycardia, tolerance with long-term use.	Giuseppe C, Paul J Et al., (2015) [39]

3.3.2. Coronary artery bypass grafting (CABG)

With the development of less invasive methods and robotically aided surgery, Coronary Artery Bypass Grafting (CABG), a key therapy for ischemic heart disease, has changed [47]. Comparing minimally invasive CABG to standard methods, smaller chest incisions are made, which leads to less pain after surgery, a faster recovery, and shorter hospital stays. Furthermore, the use of robotic assistance in surgery improves accuracy and dexterity during the process, which may result in better results and faster recovery periods. The continued dedication to improving patient care and results in the therapy of IHD is shown by these developments, which provide patients with less invasive choices that are equally effective as standard CABG [48].

3.4. Innovative therapies

3.4.1. Gene and stem cell therapy

Promising treatments for ischemic heart disease include gene and stem cell therapy. Gene therapy involves implanting therapeutic genes targeting angiogenesis, vasculogenesis, or myocardial function, crucial pathways implicated in IHD. While proven effective in preclinical studies using animal models, clinical trials with human patients have shown promising results. Despite this, obstacles remain before the widespread clinical use of gene therapy. Conversely, stem cell therapy utilizes various stem cell types to regenerate damaged heart tissue and promote blood vessel growth. Both preclinical and clinical studies have demonstrated improvements in cardiac function and symptoms in IHD patients. However, challenges such as immune rejection, engraftment, and cell survival need resolution to maximize therapeutic efficacy. Nonetheless, ongoing research on innovative gene and stem cell-based therapeutics offers promise for more personalized and efficient IHD treatments in the future [49,50].

3.4.2. Immunotherapy

Using the body's immune system, immunotherapy reduces inflammation, stabilizes atherosclerotic plaques, and encourages vascular repair inside artery walls. Preclinical research has demonstrated the efficacy of several strategies in reducing the development of atherosclerosis and enhancing vascular function, including anti-inflammatory biologics, immunizations, cell-based treatments, and methods based on nanoparticles. Immunotherapy for IHD is safe and feasible in clinical trials; certain studies have even shown improvements in cardiovascular risk indicators and clinical outcomes. There are still issues to be resolved, like figuring out the best patient subgroups and improving treatment plans. However, more study in this field has the potential to transform the management of IHD and improve patient outcomes [51,52].

3.4.3. Lifestyle and behavioral interventions

Interventions based on behavior and lifestyle are essential for treating ischemic heart disease. These include following a medication schedule, quitting smoking, controlling weight, managing stress, cutting back on alcohol, and implementing a heart-healthy diet. These therapies improve cardiovascular function, successfully lower risk factors, and stop the progression of atherosclerosis. They lessen the impact of IHD while enabling people to take charge of their health and improve outcomes and quality of life [53].

4. Current Research on Ischemic Heart Disease

Recent research has begun to clarify the role that uncommon genetic variants and gene-environment interactions play in disease susceptibility, in addition to identifying common genetic variations linked to IHD risk. Individualized IHD risk prediction has shown potential with polygenic risk scores (PRS), which are generated from numerous genetic variations. Moreover, research into the genetic makeup of IHD subtypes that show differently in the clinic (such as stable angina or acute coronary syndrome) and coronary artery disease (CAD) has shed light on the heterogeneity of the illness and possible subtype-specific genetic variables [54]. Non-coding RNAs (ncRNAs), long non-coding RNAs (lncRNAs), and chromatin remodeling complexes are now being studied about epigenetic processes. These epigenetic regulators have a role in the onset and progression of IHD by modifying gene expression in response to environmental cues and metabolic alterations. It may be possible to reverse the degenerative processes linked to IHD by targeting particular epigenetic changes, such as DNA methylation or histone acetylation [55].

Advances in high-throughput technologies have enabled the integration of multi-omics data to construct comprehensive molecular networks underlying IHD pathogenesis. Network-based approaches, including protein-protein interaction networks and gene regulatory networks, have facilitated the identification of key hub genes and signaling pathways dysregulated in IHD. Computational models and machine learning algorithms applied to omics data have provided predictive insights into disease progression, treatment response, and patient stratification. The translation of basic research findings into clinical applications has led to the development of novel therapeutic modalities for IHD [56]. These include gene therapy, RNA-based therapeutics (antisense oligonucleotides, mRNA vaccines), and gene editing technologies like clustered regularly interspaced short palindromic repeats (CRISPR-Cas9) to correct disease-causing

ISSN: 2458 - 8806

genetic mutations or modulate gene expression. Additionally, precision medicine initiatives, such as the identification of biomarkers for patient stratification and the repurposing of existing drugs based on molecular subtypes of IHD, hold promise for personalized treatment approaches [57].

5. Molecular and Genetic Basis of Ischemic Heart Disease

An identifiable biological characteristic, or phenotypic trait, has a genetic framework made up of the genes and their variations that influence or are connected to the trait of interest. It's critical to determine the genetic component's relevance before exploring a characteristic's genetic framework of the genetic element before delving into the genetic architecture of a characteristic [58,59]. A greater risk is associated with a family history of IHD, indicating important genetic variables. However, family history also involves attitudes and way of life decisions. For IHD, the range of heritability and the percentage variation of a characteristic associated with genetic diversity is between 35% and 55% [60]. Two major categories of phenotypes or disorders are related to genetic transmission. Diseases can be classified as polygenic or complex, where risk involves multiple genes, numerous variants, and their interaction with environmental factors, as seen in IHD, and monogenic (or oligogenic), where risk is linked to variants in a single or few genes, such as familial hypercholesterolemia, determined by variants in low-density lipoprotein receptor (LDLR), apolipoprotein B (APOB), proprotein convertase subtilisin/kexin type 9 (PCSK9), and low-density lipoprotein receptor adaptor protein 1 (LDLRAP1) [61,62]. Four methods may be used to investigate a phenotypic trait's genetic architecture Linkage analysis, Candidate-gene association studies, Genome-wide association studies (GWAS), and Genome sequencing studies

5.1. Linkage analysis

Linkage Analysis is a valuable tool in investigating oligogenic and monogenic illnesses. It entails examining families in which the proband for at least one member that has the condition over several generations [63]. To find correlations with the illness, family members are evaluated for several hundred genetic markers spread throughout the genome [64]. Their transmission is also examined. The objectives include finding the gene's genomic area and identifying the disease-causing variation. For example, in familial hypercholesterolemia, linkage analysis located the PCSK9 gene on chromosome 1, and sequencing found the variations that cause the condition. Linkage study has found arachidonate 5-lipoxygenase-activating protein (ALOX5AP) and myocyte enhancer factor 2 (MEF2A) gene variations related to IHD, albeit these variants are less effective for complicated disorders [65,66].

5.2. Candidate-gene association studies

A case-control method is frequently used to determine if certain gene variants are more or less common in patients with an illness than healthy controls. This hypothesis-testing technique focuses on frequent genetic variants (allele frequency > 5%) to identify the candidate gene based on the known pathophysiology of the disease. However, our knowledge of the genetic basis of complex characteristics like IHD has not substantially improved as a result of candidate-gene association research. This approach's main problem is limited repeatability, which is usually caused by tiny sample numbers and reduces the statistical power to identify weak relationships [67].

5.3. Genome-wide association studies (GWAS)

Technological developments in genotyping and genome sequencing over the last two decades have improved our knowledge of the genetic underpinnings of complicated disorders. Genome-wide association studies (GWAS) are made possible by kits that can identify 100,000–500,000 sequence variations thanks to these technologies and our understanding of linkage disequilibrium [68]. Without a guiding premise, GWAS analyses a large number of genetic traits; significance is determined by a P value of less than $1 \times 10{-}8$. They have shown that complex features have modest relationships (OR 1.1 to 1.4), which calls for bigger samples and cross-border cooperation. Early GWAS for IHD found polymorphisms on chromosome 9, which linked to lipid metabolism, blood pressure, and inflammation and explained around 15% of heritability [69].

Many variations located near gene promoters indicate an impact on gene expression and epigenetics. Systems biology techniques have identified IHD-associated genes in a variety of metabolic processes. Databases such as database of genotypes and phenotypes (dbGaP), CARDIoGRAMplusC4D collabora-

tion, and European genome-phenome archive catalogue results for IHD. Consistent outcomes, teamwork, and data accessibility are among GWAS's advantages. Limitations, however, include an emphasis on common variations with little effect and discovered variants not causally connected to the condition. Unknown sequence variations or epigenetic modifications influencing gene expression may be among the unidentified heritable components that need to be found [70,71].

5.4. Genome sequencing studies

In the past, monogenic and oligogenic disorders with obvious familial segregation were studied using sequencing methods. The exome—the region of the genome that codes for proteins—may be the subject of sequencing research, as can a single gene, a panel of genes, or the entire genome. The exome only has about 30 million nucleotides and about 23,000 genes, compared to the human genomes about 3100 million nucleotides. Large-scale sequencing investigations of IHD can find uncommon genetic variations that, in theory, should have a greater impact than common variants. In a recent study, approximately 6700 patients and 6700 controls underwent discovery exome sequencing, which was followed by targeted exon sequencing. The analysis revealed rare variants in the LDLR and apolipoprotein A-V (APOA5) sequences that were linked to a higher risk of acute myocardial infarction (OR from 1.5 to 4.5), providing fresh evidence for the significant impact of lipid metabolites (triglycerides and low-density lipoprotein cholesterol [LDL-C]) on cardiovascular risk. In addition to identifying uncommon IHD-associated variations in the lipid metabolism genes apolipoprotein C3 (APOC3), niemann-Pick C1-Like 1 (NPC1L1), scavenger receptor class B, type I (SCARB1), angiopoietin-like (ANGPTL), lipoprotein lipase (LPL), and Sushi, von willebrand factor type A, EGF, and pentraxin domain containing 1 (SVEP1), other investigations have focused on certain genes [72].

5.4.1. Apolipoprotein C3 (APOC3)

APOC3 is an important regulator of triglyceride metabolism. It is primarily produced in the liver and inhibits lipoprotein lipase (LPL), reducing the clearance of triglyceride-rich lipoproteins. Variants in APOC3 are associated with altered triglyceride levels and IHD risk. Loss-of-function mutations in APOC3 are linked to lower plasma triglyceride levels and a reduced risk of coronary heart disease. Conversely, gain-of-function mutations can lead to hypertriglyceridemia and increased IHD risk. Genome sequence studies have identified rare variants, such as the APOC3 R19X mutation, which protects IHD [73].

5.4.2. Niemann-nick C1-like 1 (NPC1L1)

NPC1L1 is critical for the intestinal absorption of cholesterol, facilitating the uptake of dietary and biliary cholesterol into enterocytes. Variants in NPC1L1 affect cholesterol absorption efficiency, influencing plasma cholesterol levels and IHD risk. Genome studies have highlighted the impact of NPC1L1 polymorphisms on cholesterol levels. The therapeutic use of ezetimibe, an NPC1L1 inhibitor, demonstrates reduced LDL cholesterol levels and lowered IHD risk, underscoring the gene's significance in lipid metabolism.

5.4.3. Scavenger receptor class B, type I (SCARB1)

SCARB1 encodes a receptor involved in the selective uptake of HDL cholesterol into hepatocytes and steroidogenic cells, playing a crucial role in reverse cholesterol transport. Variants in SCARB1 can affect HDL function and cholesterol uptake, influencing IHD risk. Certain mutations in SCARB1 are linked to higher HDL cholesterol levels but paradoxically increased IHD risk, indicating a complex role in cardiovascular health. Genome sequence studies have identified key SCARB1 variants that contribute to IHD susceptibility [74,75].

5.4.4. Angiopoietin-like (ANGPTL)

The ANGPTL family, particularly ANGPTL3, ANGPTL4, and ANGPTL8, regulate lipid metabolism by inhibiting lipoprotein lipase, thus controlling triglyceride clearance from the bloodstream. Genetic variants in ANGPTL genes can significantly impact lipid levels and IHD risk. Loss-of-function mutations in ANGPTL3 are associated with reduced levels of triglycerides and LDL cholesterol, leading to a decreased risk of IHD. Genome studies have explored the roles of ANGPTL family members in lipid regulation and cardiovascular disease [76,77].

5.4.5. Lipoprotein lipase (LPL)

LPL is an enzyme crucial for the hydrolysis of triglycerides in lipoproteins, converting them into free fatty acids and glycerol. Mutations in LPL can lead

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to hypertriglyceridemia, increasing the risk of atherosclerosis and IHD. Conversely, some variants can confer protection against IHD by enhancing lipid clearance. Genome sequence studies have identified various LPL mutations that influence lipid metabolism and IHD risk, highlighting the enzyme's pivotal role in cardiovascular health [78].

5.4.6. Sushi, von willebrand factor type A, EGF, and pentraxin domain containing 1 (SVEP1)

SVEP1 is a multifunctional protein involved in cellular adhesion and signaling. Its role in lipid metabolism and cardiovascular health is not fully understood, but variants in SVEP1 have been linked to increased risk of coronary artery disease (CAD) and IHD. It is thought to influence vascular inflammation and plaque stability. Genome sequence studies continue to investigate the specific mechanisms by which SVEP1 variants affect IHD susceptibility, providing insights into its role in cardiovascular disease [79].

6. Future Directions for the Management and Treatment of Ischemic Heart Disease

6.1. Integrative approaches

Diet is of utmost importance in managing ischemic heart disease. Add various fruits, vegetables, seeds, grains, nuts, herbs, fish, and omega-3 fatty acids-containing foods to the diet. Consume less salt, sugar, and saturated fats. Apart from the diet, it is essential to do regular exercise for at least an hour a day [80]. Regular exercise improves cardiac health and reduces the risk of IHD. Incorporate stress-relieving practices like yoga, meditation, or deep breathing exercises in addition to physical activity. IHD can be managed by giving up smoking, drinking less alcohol, controlling body weight, getting frequent checkups, and monitoring [81].

6.2. Precision medicine

The use of genetic profiling, individualized therapies, and clinical and technology integration in precision medicine can completely transform the way that ischemic heart disease is treated in the future. Genetic profiling includes identifying genetic risk factors, predicting drug response, and identifying familial genetic conditions [82]. The risk of IHD is increased by the genetic polymorphisms. Impair in the lipid metabolism and risk of IHD is associated with the variant's genes like LDLR, APOB, and PCSK9. Pharmacogenomic studies help understand how genetic variation affects drug interaction and their responses in patients. Cytochrome P450 2C19 gene polymorphism affects the metabolism, efficacy, and increases the risk of adverse effects of clopidogrel, an antiplatelet drug used in the treatment of IHD. From this genetic and phenotypic information, choosing another appropriate drug to improve efficacy and reduce the adverse effects can be suggested. Adding various fruits, vegetables, seeds, grains, nuts, herbs, fish, and omega-3 fatty acids-containing foods to the diet, consuming less salt, sugar, and saturated fats, incorporating foods like berries, citrus fruits, apples, leafy greens, cruciferous vegetables, tomatoes, chia seeds, flaxseeds, pumpkin seeds, whole grains, almonds, walnuts, pistachios, and fatty fish into the diet must be considered. These foods provide essential nutrients, antioxidants, and omega-3 fatty acids, which support heart health. Reduce salt, sugar, and saturated fats. Medications such as statins (atorvastatin, rosuvastatin), ACE inhibitors (enalapril, lisinopril), beta-blockers (metoprolol, bisoprolol), antiplatelet agents (aspirin, ticagrelor), omega-3 supplements, PCSK9 inhibitors (alirocumab, evolocumab), and SGLT2 inhibitors (empagliflozin, canagliflozin) can improve efficacy and reduce adverse effects in IHD management [83]. Physicians can guide personalized lifestyles based on the genetic data of the individual. Patients with specific genetic predisposition to dyslipidemia or hypertension can receive targeted dietary and exercise advice. Electronic health records, clinical decision support systems, and sophisticated genomic technologies are widely available and affordable for facilitating comprehensive genetic profiling, including targeted gene panels, whole exome sequencing, and genome sequencing [84]

6.3. Global health initiatives

The management of ischemic heart disease is greatly impacted by global health programmes that support treatment equity, early identification, and prevention, especially in low- and middle-income nations. These initiatives are spearheaded by groups like the UN's Sustainable Development Goals (SDGs) and the WHO, the World Heart Federation (WHF), and other NGOs. Programs like the WHO's Global

Hearts Initiative are examples of these initiatives. To lower the prevalence of IHD and enhance cardiovascular outcomes worldwide, these programs make use of tactics including the HEARTS technical package, public-private collaborations, and technological breakthroughs in digital health [85].

7. Conclusion

WHO expresses concern about the continuous increase in ischemia heart disease as a leading cause of death over more than a decade and challenges in the management and treatment of ischemia heart disease due to various hurdles in the currently available diagnostic tools, lifestyle conditions, currently available marketed drugs used for the treatment of IHD have limited efficacy and more side effects due to genetic variations. The main objective of this review is to provide an overview of the clinical consequences of various diagnostic techniques and treatment strategies, including standard drugs, innovative pharmacological findings, and revascularization treatments. Current research, genetic investigations, integrative medicine methods, precision medicine strategies, and initiatives by different organizations raising awareness of IHD. With the use of all this information, physicians are better able to identify problems in their patients, provide suggestions, and provide appropriate care, ultimately saving lives. Additionally, by understanding how medications interact with different genetic conditions, researchers can develop new molecules with less adverse effects and maximum efficacy.

Acknowledgements

I would like to express my sincere gratitude to all those who contributed to this review. I extend my deepest appreciation to our institution “Faculty of Pharmacy-Sri Adichunchanagiri College of Pharmacy” for providing the necessary resources and support. Special thanks to our colleagues for their insightful discussions and valuable feedback that significantly enhanced the quality of this work.

Conflict of Interest

The authors have no conflicts of interest, financial or otherwise, to declare.

Statement of Contribution of Researchers

Concept-M.C. T.Y.P.; Design-G.H., K.B.; Super Vision-D.R., G.K.; Data Collection-G.H., M.C.; Literature Search- G.H., G.K.; Writing- G.H., K.B.; Critical Review-T.Y.P., M.C.;

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ISSN: 2458 - 8806