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CHF: A Disease Capturing Indians

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Abstract **Original Research Article**

At 30% of all fatalities worldwide, cardiovascular diseases (CVDs) are the major cause of mortality. The WHO estimates that 17.9 million people die from CVDs annually and that number will rise to 22.2 million by 2030. As individuals age, the mortality rate rises. In terms of gender, women die from CVD at a greater rate (51%) than do men (42%). The intricate clinical illness known as congestive heart failure (CHF) is marked by an inefficient heartbeat, which compromises the body's blood flow. Any condition affecting blood ejection from the ventricles into the systemic circulation or ventricular filling might lead to CHF. *Daucus carota, Nerium oleander, Amaranthus viridis, Ginkgo biloba, Terminalia arjuna, Picrorhiza kurroa, Salvia miltiorrhiza, Tinospora cordifolia, Mucuna pruriens, Hydrocotyle asiatica, Bombax ceiba,* and *Andrographis paniculate* are a few medicinal plants that are well-known for treating cardiovascular disease. These plants include flavonoids, polyphenols, plant sterol, plant sulphur compounds, and terpenoids, which are active phytochemicals. Given the rising incidence of CVD, a number of physiologically active substances with established biological effects have been identified discovered in a variety of plants; nonetheless, proper CVD preventive and treatment strategies are still needed. To fully comprehend the mechanism and phytochemicals found in particular plants that cure CVD, more study is required.

Keywords: Congestive heart failure, CHF, Flavonoids, Sterols, Cardiovascular diseases, CVD.

INTRODUCTION

Congestive heart failure (CHF) is characterised as "a complex clinical syndrome that results from any structural or functional impairment of ventricular filling or ejection of blood," according to the American College of Cardiology (ACC) and the American Heart Association (AHA). The primary cause of CHF and the main cause of mortality globally is ischemic heart disease [1, 2]. Globally, CHF is a prevalent condition with a high rate of morbidity and death. With a projected 26 million cases globally, CHF lowers functional ability, raises healthcare expenses, and has a major negative impact on quality of life. To reduce morbidity and mortality, avoid repeat hospital stays, and improve patient outcomes, the condition must be identified and treated promptly [3].

ETIOLOGY

Although there are several causes of CHF, the most prevalent one is coronary artery disease (CAD), which results in ischemic heart disease. It is important to make every effort to determine the underlying causes in order to inform treatment plans [4]. The diseases that are infiltrative, congenital, valvular, myocarditisrelated, high-output failure, and secondary to systemic illness can be roughly categorised as aetiologies of intrinsic heart disease. There is a lot of overlap between these classes [5]. About two-thirds of CHF cases are caused by the four most frequent aetiologies: rheumatic heart disease, hypertensive heart disease, ischemic heart disease, and chronic obstructive pulmonary disease (COPD). Lower-income nations have greater incidence of hypertensive heart disease, cardiomyopathy, rheumatic heart disease, and myocarditis; higher-income nations have higher rates of ischemic heart disease and COPD [6].

Ischemic Heart Disease

Globally, ischemic heart disease is the predominant cause of congestive heart failure. Ischemia causes the heart's muscles to get less blood, which lowers the EF. As developing nations embrace a more Western food and way of life, the rate of infections rises there; yet, as medical treatment improves, the infectious load in these nations declines (myocarditis is frequently infection-related) [7].

Valvular Heart Disease

Another prevalent intrinsic cardiac issue that can lead to CHF is valve disease. In children and young adults globally, rheumatic heart disease is the most frequent cause of valvular heart disease. It generally results in mitral and aortic stenosis and is brought on by an immunological reaction to group A streptococcus. Age-related degradation is the most frequent cause of valvular disease overall, with the aortic valve being the most often impacted valve [8]. Men are more prone to suffering from aortic valve disorders such as regurgitation or stenosis, whereas women are more likely to have mitral valve prolapse or rheumatic heart disease. Furthermore more prevalent in males is endocarditis.

Hypertension

Regardless of the absence of ischemic heart disease or CAD, hypertension is the cause of CHF. Because of elevated afterload and neurohormonal alterations that result in an increase in ventricular mass, high blood pressure produces mechanical stress. Aggressively treating hypertension has been demonstrated to reduce the risk of CHF. HTN is also significantly linked to other comorbidities for the development of CHF [9].

Cardiomyopathy

A diverse range of conditions known as cardiomyopathies are typified by enlarged ventricles with compromised function that are unrelated to secondary causes including hypertension, ischemic heart disease, valvular heart disease, or congenital heart disease. Hypertrophic, dilated, restricted, arrhythmogenic right ventricular, and left ventricular noncompaction cardiomyopathies are the most prevalent forms. Apart from congestive heart failure, cardiomyopathy can also manifest as arrhythmia or unexpected cardiac death, which emphasises the need to identify underlying medical conditions. Given the hereditary foundation of many of these disorders, a thorough family history of sudden cardiac death should be obtained, particularly in first-degree relatives who are older than 35 [10, 11]. By it, more than 50 genes have been shown to be involved in the formation of dilated cardiomyopathy.

Inflammatory Cardiomyopathy

Ventricular remodelling, cardiac dysfunction, and myocarditis are the hallmarks of inflammatory cardiomyopathy. The most frequent reason is infection with a virus. Additional causes include immune-mediated illnesses; toxic chemicals or medications; and infections caused by bacteria, fungi, or protozoa. Trypanosoma cruzi, which is prevalent in Latin America and frequently causes myocarditis, cardiomyopathy, and CHF, is the cause of Chagas disease. Herpes virus 6, EpsteinBarr virus, cytomegalovirus, adenoviruses, and enteroviruses are other viruses that can cause myocarditis and inflammatory cardiomyopathy [12]. Viruses such as HIV, hepatitis C virus, influenzas A and B, and coronaviruses (particularly COVID-19) can also trigger autoimmune myocarditis. These disorders typically have a bad prognosis when linked to CHF.

Infiltrative Cardiomyopathies

A restrictive cardiomyopathy pattern, similar to the inheritable restricting cardiomyopathy variety, is brought about by infiltrative cardiomyopathies. This pattern is characterised by normal ventricular systolic function, but also by diastolic dysfunction and restricted filling dynamics of the LV and RV. A high E/A ratio that indicates more early filling and slower late filling is frequently linked to this [13]. Misfolded protein deposits in the heart cause cardiac amyloidosis, which causes cardiomyocyte separation, cellular toxicity, and tissue stiffness. Patients are susceptible to symptomatic hypotension and are dependent on preload. As of right moment, cardiac amyloidosis can only be prevented with tamifidis. It inhibits amyloid buildup but does not stop it. Another constraining issue is its high cost.

Takotsubo or Stress-Induced Cardiomyopathy

Under-recognized as a cause of CHF, takotsubo, also known as stress-induced cardiomyopathy (also known as broken-heart syndrome), involves transitory anomalies of the left ventricle that are not restricted to a particular vascular area. Numerous pathophysiologic explanations have been hypothesised for it, such as enhanced sympathetic nervous system activation, coronary vasospasm, and microcirculatory dysfunction [14]. Treatment for this illness involves standard CHF drugs, with the incorporation of antithrombotic medications for specific clinical scenarios including anomalies in wall motion. The number of confirmed cases during the COVID-19 pandemic sharply rose.

Peripartum Cardiomyopathy

One important factor contributing to maternal death is peripartum cardiomyopathy. Pregnancy causes an increase in heart rate and stroke volume, which causes a 20% to 30% increase in cardiac output. It manifests as CHF in late pregnancy, postpartum, or even months after birth as a result of LV systolic dysfunction. Presumably, there is a genetic component at play, and it is more prevalent in Black women, older mothers, and multifetal pregnancies. Anticoagulation is necessary if motions in the walls abnormalities are evident because pregnancy causes a hypercoagulable condition. The rate of recovery varies by world area and is negatively correlated with reduced EF [15].

Obesity

Similar to the "Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity" (the CHARM trial), obesity is a major risk factor for CHF in people under 40. The "obesity paradox" that has been discussed elsewhere is based on older data and contains serious research problems. It is estimated that obesity alone accounts for up to 10% of CHF cases [16].

Individuals who are obese have an increased risk of having HFpEF, which may be caused by cytokines released by fat cells such TNFα, IL-1b, and IL-8. Natriuretic peptides are also broken down by adipose tissue.

Tachycardia and Arrhythmia

An arrhythmia or tachycardia can cause a low-output CHF condition. All of the heart chambers typically enlarge, while the thickness of the biventricular wall either remains the same or thins. This is accompanied by electrophysiologic alterations in the myocytes, such as prologued duration and reduced amplitude of action potentials. These elements all trigger the normal neurohormonal reaction that results in CHF. Because of myocardial hibernation, these alterations are frequently reversible with rate regulation [17].

Thyrotoxicosis

Although thyrotoxicosis can create a hyperdynamic circulatory condition, it is an uncommon cause of heart failure. This could be partly caused by increased blood volume from erythropoietin-stimulating agent upregulation and salt and water retention brought on by activation of the renin-angiotensin-aldosterone axis. CHF can also result from persistent tachycardia, either with or without atrial fibrillation [18].

High-Output Cardiac Failure

Thiamine deficiency is an uncommon illness that is typically observed in elderly, homeless, or alcohol addiction disorder patients; it has been linked to high-output heart failure. Systemic vasodilation results from reduced ATP synthesis brought on by a buildup of adenosine caused by thiamine deficiency. As a result, cardiac output rises and systemic vascular resistance decreases. This leads to a compromised heart and reduced heart filling flow. Using diuretics might exacerbate the problem by causing thiamine loss in the urine [19]. High-output cardiac failure can also be caused by arteriovenous shunts, obesity, and liver illness. Decreased afterload, or systemic vascular resistance, and enhanced metabolism are the physiologic factors that are causing the modifications. Preserved EF, pulmonary congestion, raised filling pressures, and increased natriuretic peptides are common presentations of these [20].

EPIDEMIOLOGY

Due to the wide variations in the disease's geographical spread, evaluation techniques, absence of imaging modalities, and disregard for standard disease staging and diagnosis, it is impossible to determine the exact worldwide size of the illness. In 2017, the cause of almost 1.2 million hospital admissions was CHF. According to some statistics, the prevalence is rising as more people undergo therapy, although the incidence rate appears to have peaked. Neither a decrease in the frequency of hospitalisations for CHF patients nor an improvement in their quality of life have resulted from this. 64.34 million instances of CHF are now reported to be prevalent globally, based to the Global Health Data Exchange register. This corresponds to 346.17 billion US dollars spent on healthcare and 9.91 million years wasted because of disability (YLDs) [21, 22].

One important factor affecting HF is age. The prevalence of heart failure (HF) rises sharply with age, regardless of the underlying reason or the criteria used to categorise people with HF. According to the Framingham Heart Study, the prevalence of CHF in males aged 50 to 59 was found to be 8 per 1000, whereas in those aged 80 to 89, it increased to 66 per 1000. After the age of 65, the incidence of heart failure (HF) in males doubles for every ten years of age rise; for the same age cohort, the prevalence triples in women. Worldwide, the incidence of CHF and heart disease are greater in males than in women [23].

A racial preference is also noted by the worldwide registry, with Black patients having a 25% greater frequency of heart failure than White patients. In the senior population, heart failure (HF) remains the leading cause of hospitalisation and causes 8.5% of cardiovascular-related deaths in the US [24].

Comparable global statistics are available for the epidemiology of heart failure. With ageing, metabolic risk factors, and a sedentary lifestyle, the prevalence rises sharply. In underdeveloped nations, ischemic cardiomyopathy and hypertension are major causes of heart failure. A study of small cohort studies from these countries has revealed a noteworthy difference: a greater prevalence of isolated right heart failure (HF) [25].

PATHOPHYSIOLOGY

Heart failure advances with time. The compensatory process, which leads to maladaptation once it is exhausted, can be triggered by any acute shock to the structure of the heart or abrupt modification caused by genetic mutation, cardiac tissue infiltration, ischemia, valvular heart disease, myocarditis, or acute myocardial damage. Several compensatory mechanisms work to sustain cardiac output and fulfil systemic demands during the early stages of CHF. Chronic sympathetic nervous system stimulation lowers adrenaline reserves and beta-receptor sensitivity [26]. Myocyte renewal, cardiac hypertrophy, and myocardial hypercontractility are altered as a result.

The renin-angiotensin-aldosterone system (RAAS) system, systemic vasoconstriction, and salt retention are also brought on by an increase in sympathetic drive. The RAAS is stimulated by a reduction in cardiac output and an increase in sympathetic drive, which results in increased vasoconstriction and salt and water retention [27]. This contributes to the heart's dysfunctional processes and leads to progressive heart failure. Angiotensin II, which

has been demonstrated to enhance myocardial cellular hypertrophy and interstitial fibrosis and so contribute to myocardial remodelling, is also released via the RAAS system.

The neuroendocrine system is stimulated by a drop in cardiac output, which results in the production of vasopressin, endothelin-1 (ET-1), norepinephrine, and adrenaline [28]. Vasoconstriction brought on by these mediators increases afterload. The myocytes' cytosolic calcium rises as a result of an increase in cyclic adenosine monophosphate (cAMP). This further inhibits cardiac relaxation and raises myocardial contractility. Myocardial oxygen demand is raised by increased afterload and myocardial contractility with reduced myocardial relaxation. Myocardial cell loss and apoptosis are ultimately caused by this contradictory requirement for higher cardiac output to fulfil myocardial demand. The process of apoptosis perpetuates a loop of increasing neurohumoral stimulation, maladaptive hemodynamic and myocardial responses, and decreased cardiac output with increased demand [29]. Myocyte loss reduces cardiac contractility, or EF, which results in partial left ventricular emptying.

Pulmonary congestion results from elevated left ventricular volume and pressure. Antidiuretic hormone (ADH) is released as a result of renal hypoperfusion, which exacerbates water and salt retention. Reduced renal blood flow from elevated intraabdominal and central venous pressure lowers GFR even further. Peripheral vasoconstriction and enhanced preload supply to the overworked heart are features of decompensated congestive heart failure. Although produced, the natriuretic peptides BNP and ANP are unable to offset the extra salt and water retention [30].

Neprilysin is an enzyme that targets many innovative treatments and breaks down multiple hormones, such as bradykinin, ANP, and BNP. Because it raises angiotensin II levels and produces substantial angioedema when given with an ACE inhibitor, it is usually taken in conjunction with an angiotensin receptor blocker.

HISTORY AND PHYSICAL EVALUATION

History

The existence and extent of symptoms as well as the results of a physical examination are the main factors used in the diagnosis and categorization of HF. To treat the patient appropriately, a thorough history of symptoms, underlying medical disorders, and functional abilities must be obtained [31].

Congestion is the main symptom of acute CHF, while other symptoms including organ hypoperfusion or cardiogenic shock are also possible. Breathlessness is the symptom that is most frequently reported. This has to be further divided into acute and chronic categories, as well as exertional and positional (orthopnea). Anorexia, exertional tiredness, and chest discomfort are among the other symptoms of CHF that are frequently observed. Reduced blood supply to the splanchnic circulation, intestinal edoema, and hepatic congestion are the causes of anorexia. Due to orthopnea, some individuals may exhibit a reclined cough. Ascites or hepatic congestion can also cause pain in the abdomen in patients. Patients with arrhythmias might appear with palpitations, presyncope, or syncope. Edoema is another symptom, particularly in the lower limbs, that raises morbidity [32]. This can impair balance and movement; weight increases exceeding 20 pounds and complete body water are typical.

Patients with chronic heart failure typically reduce their physical activity, thus symptoms may be hidden. In contrast, patients with acute heart failure typically appear with overt respiratory discomfort, orthopnea, and paroxysmal nocturnal dyspnea. Determine whether factors, such as a recent illness, noncompliance with cardiac medication, use of NSAIDs, or increased salt consumption, are triggers for abrupt decompensation.

Physical Evaluation

The results of the examination change depending on the disease's acuity and stage. Individuals may have left- or right-sided heart failure symptoms alone or in combination.

General Physical Examination

Patients with severely decompensated HF or severe CHF present with diaphoresis, tachycardia, tachypnea, and anxiety. Patients with long-term decompensated heart failure may seem skeletal. Pulmonary rales, a typical chest examination finding, correspond to moderate-to-severe heart failure. In cases of acute decompensated heart failure, wheezing may occur. Sputum that is frothy and has a red tint may be observed when the degree of lung congestion worsens [33]. It is crucial to understand that pulmonary congestion does not always result from the lack of rales. Another characteristic sign that has to be evaluated in all HF patients is jugular venous distention. Hepatojugular reflux, defined as a prolonged rise in JVP of more than 4 cm after pressure over the liver while the patient is laying at a 45° angle, is frequently observed in individuals with increased left-sided filling pressures.

Poor perfusion can manifest in patients with Stage D HF as hypotension, decreased capillary refill, chilly extremities, impaired mentation, and decreased urine production. A strong and weak pulse that alternates may be seen, known as pulsus alternans, which is indicative of significant ventricular dysfunction. Ectopic beats or atrial fibrillation can cause abnormal pulse patterns [34]. In most cases of HF, there is some degree of peripheral edoema. Another way to measure volume retention is by weight increase, and accurate weight measurements every day can be a helpful tracking tool.

Patients with HF may present with precordial symptoms such as an S3 gallop or misplaced apex beat (dilated heart). Aortic stenosis systolic ejection murmur, mitral regurgitation or tricuspid regurgitation pansystolic murmur, or early diastolic murmur of aortic regurgitation are examples of murmurs of related valve lesions that may be present. Individuals suffering from pulmonary hypertension may experience loud or perceptible P2 or parasternal heave. Clubbing, cyanosis, and splitting of the second heart sound are additional symptoms that may be present in patients with congenital heart disease.

The most important and early discovery related to HF is an S3 gallop. Individuals with loud A2 or S4 heart sounds may have hypertensive heart disease. Ventricular noncompliance may be the cause of an S4 gallop in patients with HF and maintained EF.

Major Criteria

- Acute pulmonary edema
- Cardiomegaly
- Hepatojugular reflex Neck vein distention
- Paroxysmal nocturnal dyspnea or orthopnea
- Pulmonary rales
- Third heart sound (S3 Gallop)

Minor Criteria

- Ankle edema
- Dyspnea on exertion
- Hepatomegaly
- Nocturnal cough
- Pleural effusion
- Tachycardia (heart rate greater than 120 beats per minute)

Other Evaluations

When assessing a patient with HF, a thorough evaluation is necessary. Complete blood count, iron profile, renal profile, and liver profile are all included in this. Depending on the aetiology and clinical stage, patients may need further studies after the baseline metabolic and blood panel [35].

CBC: A CBC might indicate leukocytosis or anaemia, which could indicate an infection that is causing CHF.

Complete Renal Profile

All HF patients require a comprehensive renal profile. It directs the selection of medications and shows the extent of renal damage linked to HF. Prior to initiating medication, such as renin-angiotensin-aldosterone (RAAS) inhibitors, sodium-glucose transporter-2 (SGLT-2) inhibitors, or diuretics, it is imperative to ascertain the patient's baseline renal function. In patients with chronic heart failure, serum sodium level is a useful prognostic indicator for death prediction. "The Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure" (OPTIME-CHF) experiment showed that patients with HF who came with hyponatremia had a considerably higher risk of 30-day death in addition to in-hospital mortality.

Liver Profile

Usually, a liver profile is taken. Elevated levels of gamma-glutamyl transferase, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) can be caused by hepatic congestion owing to HF.

Urine Studies

Studies on urine can help with diagnosis. Monoclonal light chain tests and urine and serum electrophoresis should be carried out if amyloidosis is suspected. Bone scintigraphy can be used if tests for light chains come back negative but the clinical suspicion is still strong [36].

Serum B-type Natriuretic Peptide (BNP) or N-terminal Pro-BNP (NT-ProBNP)

In individuals with unclear demonstrations, serum B-type natriuretic peptide (BNP) or N-terminal pro-BNP (NT-ProBNP) levels can help distinguish cardiac from noncardiac causes of dyspnea. BNP is utilised to evaluate the risk of death in patients with HF as it is a distinct indicator of elevated left ventricular end-diastolic pressure. BNP levels are largely utilised as a marker to evaluate the effectiveness of therapy, as they are correlated with NYHA classification. With a longer half-life, NT-ProBNP is the chemically inert N-terminal segment of BNP. Depending on underlying comorbidities, the NT-ProBNP/BNP ratio fluctuates and might prove to be a valuable tool in the future. Treatment regimens should not be based on natriuretic peptides in individuals who have an obvious clinical presentation of heart failure. It is crucial to keep in mind that elderly patients, those with renal failure, and those with atrial fibrillation may have increased BNP and NT-ProBNP levels. On the other hand, individuals with progressive heart failure (HF) brought on by myocardial fibrosis, obesity, and hypothyroidism may have deceptively low BNP values.

Troponin-I or T levels

When troponin-I or T levels are consistently high, they indicate a chronic myocardial damage and indicate poor prognoses and death.

Electrocardiogram

Evidence of a previous infarction, chamber enlargement, intraventricular conduction delay, or arrhythmia may be shown on an ECG. It could also provide hints about particular aetiologies. Heart amyloidosis is characterised by a low voltage and pseudo infarction pattern of the ECG. In ARVC, an epsilon wave is observed. With a QRS length of more than 120 msec, the ECG also indicates the existence of ventricular desynchrony, which predicts how the patient will react to device treatment for heart failure.

Chest Radiographs

Chest radiographs are used to evaluate heart shape (to identify the existence of cardiomegaly) and the degree of pulmonary congestion. Edoema around the bases of the lungs, vascular congestion, and an enlarged cardiac silhouette are all signs of congestive heart failure (CHF) on chest radiographs. Chest radiographs may show Kerley B lines in patients with florid HF. In individuals with a suspicious clinical presentation, the lack of these signs does not rule out CHF [37].

Echocardiography

When a patient has suspected heart failure, echocardiography is the first modality that is used since it is a readily accessible bedside tool. Echocardiography is used to measure the function of the left and right ventricles, identify anatomical irregularities in the heart's chambers and valves, and detect localised abnormalities in the heart's motion. However, getting appropriate acoustic windows may be difficult for people who are extremely obese, pregnant, or on mechanical breathing. For these individuals, transesophageal echocardiography (TEE) is an option. For individuals with tachyarrhythmias, sufficient rate control is required in order to produce satisfactory echocardiographic pictures.

Cardiac Catheterization

The diagnosis of ischemic cardiomyopathy frequently requires cardiac catheterization, which is also helpful in precisely assessing intracardiac pressures such pulmonary artery pressures and left ventricular end-diastolic pressure [38].

Computed Tomography

When evaluating coronary artery disease in a young patient experiencing ventricular failure, computed tomography may be utilised (older individuals are likely to have baseline calcifications). Patients with congenital cardiac problems that result in HF may also utilise it. Finding tumours that are causing heart failure may be aided by cardiac CT. CT can also be utilised to assess graft quality and stent patency.

SPECT-Myocardial Perfusion Imaging

When a patient does not have coronary angiography and has just been diagnosed with left ventricular failure, SPECT-Myocardial Perfusion Imaging can be used to determine whether or not ischemia is present. When evaluating CAD in individuals who have never had ischemia but have increased troponin levels, it is very helpful. ECG-gated myocardial perfusion imaging is employed to assess regional wall thickness, motion, and LV EF. Patients with poor count density, extracardiac radiotracer uptake, and irregular heart rates may have different results from the EF assessment in this research. Additionally helpful in identifying artifactual flaws shown on SPECT imaging, such as diaphragmatic attenuation and breast tissue, are ECG-gated pictures.

Cardiac Magnetic Resonance Imaging

When there is a difference between the echocardiographic results and the clinical stage of the disease, cardiac magnetic resonance imaging has become a crucial tool. It facilitates the accurate assessment of ventricular function, chamber diameters, and volume. It also provides a detailed assessment of the valvular heart disease stage. Evaluation of complicated congenital cardiac conditions is another benefit of cardiac MRI. Additionally, the device may be used to examine disorders including arrhythmogenic right ventricular dysplasia, dilated cardiomyopathy, infiltrative cardiomyopathy, and myocarditis noninvasively.

Radionuclide Multiple-Gated Acquisition (MUGA)

A dependable imaging method for assessing EF is the radionuclide multiple-gated acquisition (MUGA) scan, which is applied to patients when EF readings from several investigations don't match.

Treatment and Management

Reducing hospitalisations, increasing cardiac mortality, and improving symptoms and quality of life are the objectives of treatment for chronic CHF. Pharmacologic treatment aims to manage symptoms and start and increase medications that lower mortality and morbidity in heart failure. The American Heart Association and the American College of Cardiology provide guidelines for managing each stage of heart failure [39].

For Stage A (At-Risk for HF)

- The treatment of hypertension in patients ought to be accomplished through the use of guidelinedirected medical therapy (GDMT).
- SGLT-2 inhibitors are recommended in people with type 2 diabetes to lower hospitalisations for heart failure.
- It is recommended to make lifestyle changes such as eating a balanced diet, getting regular exercise, keeping a healthy weight, and quitting smoking.
- It is advised that patients with HF utilise prognostication scores to determine their likelihood of experiencing future HF episodes. ARIC Risk Score (2012), Health ABC Heart Failure Score (2008), Framingham Heart Failure Risk Score (1999), and PCP-HF score (2019) are a few examples.
- When a patient has coronary artery disease, their cardiovascular conditions should be optimally managed.
- Patients who have been exposed to cardiotoxic drugs (such as chemotherapy) and are at risk for heart failure (HF) should get multidisciplinary care.
- Screening for natriuretic peptides and routine assessment are advised [40].

For Stage B (Pre-HF)

Preventing clinical heart failure and lowering mortality and severe cardiovascular events are the main goals of managing stage B.

- ACEi should be given to reduce mortality and avoid clinical HF in patients with left ventricular EF of less than 40%.
- The use of a beta-blocker plus statin is advised for patients with LV EF < 40% and evidence of recent or past acute coronary syndrome or myocardial infarction in order to lower mortality, congestive heart failure, and adverse cardiovascular events.
- A primary prevention ICD is advised for patients with LV EF < 30%, appropriate medical treatment, NYHA-class I, and an anticipated meaningful survival of more than a year.
- To avoid symptomatic HF, patients with LV EF < 40% are advised to take beta-blockers, regardless of the cause.
- It is recommended to avoid using thiazolidinediones and non-dihydropyridine calcium channel blockers in patients with LV EF < 50% due to the increased risk of adverse events and heart failure hospitalisations.
- The recommendations for asymptomatic valvular heart disease patients as well as those with congenital heart disease are related to valve replacement, repair, or treatments [41].

For Stage C (HF)

- It is recommended that multidisciplinary management be used to increase HF patients' self-care and mortality.
- For the best possible care, social support and patient education are necessary.
- Vaccination against respiratory diseases lowers death rates.
- During medical visits, it makes sense to evaluate patients for depression, low literacy, limited social support, frailty, and resource and transit constraints.
- A diet low in salt is advised.
- You can improve your functional class and quality of life with exercise training.
- Diuretics lessen the course of HF and relieve symptoms in people with congestion.
- Patients who are not responding well to a moderate or high dose of loop diuretics should be the only ones to receive a thiazide diuretic, such as metolazone.
- To lower mortality and morbidity, an ARNi is advised for individuals with HFrEF. Patients who are intolerant of ACEi should not be given ARNi; instead, an ARB should be administered. When a patient's finances prevent them from taking an ARNi, using an ACEi or ARB is advised. It is not recommended to utilise ARNi for 36 hours after the previous ACEi dose. It is highly advised, and has a great economic benefit, to transition to ARNi for patients who are tolerating ACEi/ARB well. Similar to ACEi, people with previous instances of angioedema shouldn't be administered ARNi. The beta-blockers carvedilol, bisoprolol, or sustained-release metoprolol are useful in lowering hospitalisation and death rates for patients with HFrEF [42].
- The use of MRA is advised for patients with HFrEF, NYHA class II–IV, an eGFR of more than 30 mL/min/1.73 m2, and a serum potassium of less than 5.0 mEq/L. MRA usage is dangerous for people whose blood potassium level is more than 5.0 mEq/L.
- SGLT-2 inhibitors, regardless of diabetes status, are advised for patients with HFrEF in order to lower hospitalisation rates and death.
- To lower morbidity and mortality, it is advised that African American patients with HFrEF and NYHA class III–IV who are currently receiving optimum medical treatment (OMT) add hydralazine and nitrate. This has significant economic worth.
- Hydralazine and nitrate combined may be useful for individuals with HFrEF who are intolerant to RAASi or for whom RAASi is contraindicated because of renal insufficiency.
- To get the desired results, it is advised to titrate drugs vigorously. As often as 1-2 weeks, depending on tolerance, this can be repeated.
- Ivabradine can be helpful in lowering HF hospitalisation rates and improving mortality in patients on OMT with heart rates over 70 bpm.
- Although its utility in lowering the all-cause hospitalisation rate is restricted, digoxin may be taken into consideration in symptomatic patients with sinus rhythm who do not respond well to goaldirected treatment.
- An oral soluble guanylate cyclase stimulator (Vericiguat) may be helpful in lowering mortality and HF hospitalisation in individuals with HFrEF and recent HF. Vericiguat is a soluble guanylate cyclase stimulant that acts as a strong vasodilator by stimulating the intracellular endogenous NO receptor.
- Moreover, it enhances cardiac contractility.

Device Therapy

- When a patient with heart failure (HF) is receiving goal-directed medical therapy and has an LVEF of less than or equal to 35% and a NYHA functional class of II to III, an implanted cardioverter-defibrillator (ICD) is recommended for the primary prevention of sudden cardiac death. Additionally, if a patient is receiving appropriate medical care and has an EF of below or equal to 30% while in NYHA functional class I, it is advised.

- Patients with HFrEF and a NYHA functional class of II to III or ambulatory class IV with an LVEF below or equal to 35%, QRS duration ≥ 150 msec, and sinus rhythm with left bundle branch block (LBBB) morphology are advised to undergo cardiac resynchronization therapy (CRT) with biventricular pacing. It can also be taken into account for QRS > 150 msec and nonLBBB shape [43].
- In certain patients receiving GDMT and having coronary artery disease and HFrEF, revascularization is recommended.
- Patients with HF and on GDMT may benefit from valve disease interventions such as transcatheter edge-to-edge mitral valve repair or mitral valve surgery.

For Stage D (Advanced HF)

- It is recommended to refer to an HF expert.
- In patients awaiting mechanical cardiac support or transplant, it makes sense to use inotropic support and device treatment. Patients who are not suitable for a transplant or mechanical cardiac assistance can use inotropic support alone.
- As a stopgap measure before a transplant, mechanical cardiac assistance including an ECMO or a durable left ventricular assist device (LVAD) may be helpful.
- A heart transplant is recommended for individuals who meet strict criteria in order to increase survival and quality of life.
- Care goals ought to be determined through collaborative decision-making. This involves taking frailty, concomitant conditions, and socioeconomic support into account. After a collaborative decision-making process, palliative care ought to be provided as needed [44].

Plant Derivative Compounds in the Treatment of CVD

The prevention or treatment of cardiovascular disease has drawn a lot of study attention to natural products and herbal therapies. This momentum is driven by several reasons. Specifically, the possibility of an affordable remedy has been contrasted with the prevalent conventional therapies and the widespread perception of their safety and efficacy. These findings have led to the use of several medicinal plants in the treatment of cardiovascular disease. There is a wealth of data linking dietary practices to the emergence of metabolic and cardiovascular diseases. Health is improved by consuming less highly processed foods and substituting them with fruits, vegetables, nuts, seeds, and legumes. The dietary components are low in salt content, devoid of food additives, high in unsaturated fats, minerals, fibres, carotenoids, and phenolics. In this sense, common dietary plants utilised for the treatment of CVD include tea and coffee. Research from epidemiological, clinical, and experimental settings has shown a connection between consuming green tea and better cardiovascular health [45].

Different Compounds Used in CVD

1. **Flavonoids**

One heterocycle and two phenyl rings make up the polyphenolic structures of the bioactive chemical class known as flavonoids. It was just recently found that flavonoids are compounds with strong biological effects that may help prevent chronic illnesses like cardiovascular disease. Flavonoid consumption has demonstrated an inverse relationship with events associated to cardiovascular disease in a number of epidemiological and experimental studies. There have been several reports of the protective effects of flavonoids from drinks, spices, fruits, vegetables, and medicinal plants on CVD [46].

Polygonum minus contains myricetin, quercetin, and methyl-flavonol, which act as antioxidants and antiinflammatory agents on the cardiovascular system to treat cardiovascular disease. The antioxidant, antiinflammatory, and antihypercholesterolemia properties of ajigua iva flavonoids, such as naringenin and apigenin-7-O-neohesperidoside, are utilised in the treatment of cardiovascular disease. Heart disease can be avoided by using the traditional Chinese herb Dracocephalum rupestre, which contains naringenin-7-Oglucoside [47]. In addition to being used to treat CVD, quercetin may be found in tea, wine, apples, and onions. The principal mode of action of flavonoids and polyphenols was thought to be their antioxidant activity.

2. **Plant Sterols**

Plant sterols are bioactive substances that function similarly to animal cholesterol. They are alkaloids, and unlike cholesterol, they have a different side chain structure. The primary sources of plant sterols, making up 50–80% of daily plant sterol consumption, include vegetables, cereals, bread pieces, spreads and margarine, and vegetable oils. Fruits make up the remaining 12%.In a normal Western diet, 300 mg of plant sterols are consumed daily on average; however, vegetarians can consume up to 600 mg. Plant sterols have been more widely used in these products lately because of their ability to decrease cholesterol. Plantsterol-rich foods are a useful dietary supplement for lowering cardiovascular risk since they can lower blood levels of total cholesterol and low-density lipoprotein cholesterol by up to 15% [48].

3. **Terpenoids**

One can extract sesquiterpenes, diterpenes, and monoterpenes from specialised structures such ducts, cell schizogenous glands, and lysigenous glands. They are found in the following families: Rutaceae, Piperaceae, Zingiberaceae, Umbelliferae, Lauraceae, and Labiataceae. Citral is one of the terpenoids that has been studied for its bioactivity, along with salvinorin-A,

camphor, menthol, and other plant terpenoids that are commonly used for their aromatic qualities. Uses the myocardial I/R rat model to investigate the impact of ginsenoside Rd on CVD [49]. The outcome showed that when LVSP and LVEDP drop, CVD changes. Glycyrrhetinic acid demonstrated its impact on CVD in a different research by raising HLD-c, insulin, and Hb while lowering PL in serum, FFA, VLDL-c, LDL-c, TG, TC, and BG.

As naturally occurring NF-κB inhibitors, terpenoids can regulate the impact of cardiovascular disease by blocking the NF-κB signalling cascade via p65 translocation, DNA binding, and IκB phosphorylation. Naturally occurring in Artemisia annua, artemisinin reduces inflammation by preventing NF-B activation. Ginkgolide C, a substance obtained from the leaves of Ginkgo biloba, can be used to treat ischemic and thromboembolic conditions. It also possesses anti-inflammatory and antiallergy qualities. The preliminary treatment with ginkgolide C decreases NF-B p65 subunit translocation, phosphorylation of IB, and IKK activity, increasing the survival of H/R-induced ventricular myocytes and their reactivity to inflammatory injury. Arjunolic acid, a potent ingredient in Terminalia arjuna bark, is used to treat ischemia-reperfusion damage, coronary artery disease, myocardial necrosis, angina, atherosclerosis, and congestive heart failure [50].

4. **Alkaloids**

Alkaloids are a fascinating class of plant compounds that are present in nature and include basic nitrogen atoms. About 12,000 nitrogen-containing cyclic chemicals, known as alkaloids, are a structurally diverse category present in about 20% of plant species. They belong to the plant families Papaveraceae, Acanthaceae, Apocynaceae, and Solanaceae.

Certain alkaloids have demonstrated cardioprotective qualities, as evidenced by their capacity to lower cholesterol and their potential for antioxidant and anti-inflammatory effects. The most prevalent alkaloids include propane, purine, acridone, indole, imidazole, purine, and morphine. Strong adrenergic agonists found in shrub extracts from the genus Ephedra have a major impact on the heart and circulatory system [51].

5. **Quinones**

The aforementioned classes of secondary metabolites from plants are also used by people as traditional medicine. In the rat experiment, pyrroloquinoline preserved mitochondrial activity and prevented oxidative stress in the rat cardiac myocytes, demonstrating the cardioprotective characteristics of quinones. Nigella sativa seeds, Nepeta distans, Thymus vulgaris, Calocedrus decurrens, Eupatorium ayapana, Origanum, and Satureja species are among the plants that contain thymoquinone, another quinone [52]. These substances have cardioprotective qualities, as demonstrated by a rat trial wherein they improved mitochondrial function by raising ATP generation.

Generalized Mechanism of Action

According to reports, phytochemicals may prove to be clinical trial candidates for antioxidants with cardioprotective properties. Fruits and vegetables include phytochemicals that have been shown to have preventive benefits against CVD through mechanisms that are still mostly unknown. Many studies have suggested that distinct phytochemical substances derived from plant extracts have cardioprotective effects through vasodilation through interactions with calcium channels, inhibition of platelet formation, and reduction of inflammation and serum lipids [53, 54]. Additionally, several research shown that the mechanism of phytochemicals' cardioprotective impact includes the capacity to block calcium and regulate irregular cardiac speed and blood pressure rise.

It has been observed that the use of phytochemicals in the therapy of atherosclerosis inhibits important pathological development processes, including oxidative stress, lipid deposition, endothelial dysfunction, and proliferation of vascular smooth muscle cells. For instance, it has been suggested that some oxygenated substances, such polyphenolics, may act as reducing agents and free radical scavengers, which may be the realistic processes behind cardioprotection [55]. Because many medicinal plant items come from natural sources, most customers assume that they are safe for treating CVD, even when research on their toxicity and safety has not yet been conducted. Plants do, however, contain a variety of active chemicals that can have negative pharmacological consequences. Thus, further clinical and preclinical investigations are still needed to address the effectiveness, safety, and toxicity problems connected to the phytochemicals found in therapeutic plants [56].

CONCLUSION

Globally, CVDs are the primary cause of mortality. Because they have fewer adverse effects and are less expensive than synthetic medications, phytochemicals have been utilised for quite some time to treat this illness. In order to identify possible bioactive chemicals with a wide range of functional groups and characteristics that might be utilised to treat CVD, researchers are currently looking to medicinal plants. The ability of bioactive substances derived from different plant sections to exhibit cardioprotective effects has received significant use. The majority of identified possible phytochemicals with notable cardioprotective effects include phenolics, flavonoids, terpenoids, glycosidic derivatives, alkaloids, iridoids, and saponins. These phytochemicals have been studied the most and have been shown to be beneficial in lowering cardiovascular risks, especially when it comes to lowering blood lipids, obesity factors, glucose and type 2 diabetes impacts, oxidative stress factors, inflammation

regulation, and platelet aggregation inhibition. The majority of the intricate processes by which phytochemicals exert their cardioprotective benefits are currently unknown. Large-scale research is still needed to examine the chemical compounds of medicinal plants and their pharmacological characteristics, including their cardiovascular effects, even though the preclinical and clinical studies that are currently available indicate a positive correlation between their intake and a decrease of cardiovascular factors. Therefore, more thorough clinical research is needed to determine the safety, toxicity, and effectiveness of the majority of phytochemicals in therapeutic plants.

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