CHAPTER 05

Cardiovascular Pharmacotherapy: Balancing Efficacy and Safety

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SUMMARY

Cardiovascular disorders (CVDs) are a leading cause of mortality globally. Depression, hypertension, smoking, high lipid profile, stress, alcohol consumption, and obesity are the primary factors underlying the development of CVDs. There are various types of CVDs including myocardial infarction (MI), peripheral artery disease (PADs), atherosclerosis, cardioembolic stroke, coronary artery disease (CAD) and hypertension instigated valvular dysfunction. These conditions are highly fatal and need multiple pharmacotherapeutic approaches. Advancement in pharmacotherapy plays a pivotal role in averting CVDs. Membrane coated nanoparticles, nano-drug delivery systems (NDDSs) and natural flavonoids showed promising results to counteract the adverse effects of CVDs. These approaches enhance the drug targeted efficacy, reduce thrombosis as well as protect the cardiac tissues from oxidative stress via scavenging free radicals. In conclusion, the CVDs burden requires urgent and effective therapeutic interventions to counteract the progression of these diseases. However, the abovementioned pharmacotherapies provide efficient results in CVDs patients. This chapter will comprehensively highlight primary CVDs and possible pharmacotherapeutic approaches to maintain cardiac health.

INTRODUCTION

Cardiovascular disorders (CVDs) are one of the top-notch life threating conditions and considered as leading cause of death globally (Correa-Rodriguez et al., 2020). CVDs are a group of impairments which include acute myocardial infarction, valvular, structural, and vascular heart defects, chronic hypertension, acute coronary syndrome as well as congenital diseases (Iung et al., 2007; Rehan et al., 2021). Approximately one-third of global deaths are reported due to CVDs (Richards et al., 2018). A recent report by WHO revealed that cardiovascular disorders account for 17.7 million deaths worldwide (Allabadi et al., 2019). Owing to advanced treatment options, death rates are significantly reduced in Western countries. However, developing countries are still combating these disorders due to high consumption of tobacco, lack of physical exercise and unsustainable lifestyles (Zhang et al., 2020).

There are various factors underlying the development as well as progression of CVDs. Depression is considered the leading cause of psychiatric diseases in cardiac patients which ultimately affects the quality of life as well as increases the death rate among these patients (Feng et al., 2019). It is observed that cardiac patients suffer from severe anxiety owing to unexpected chest pain and lack of information about the severity of the disease (Dehghani et al., 2013). Despite the standard treatments, these patients suffer from the fear of disability and death. Anxiety in cardiac patients is associated with sweating, cramps, low blood pressure, palpitations, fear of imminent death, flushed face and abnormal circadian rhythms (Ghods et al., 2019). Since the last 20 years, various studies have reported the association between CVDs and depression. Depression is not only linked with an elevated risk of getting CVDs, but it also acts as an indicator of high mortality and morbidity in cardiac patients. Therefore, depression is designated as an independent risk factor behind the development and progression of heart failure, myocardial infarction, anxiety, angina, and coronary heart diseases (Mavrides & Nemeroff 2015).

VARIOUS CARDIOVASCULAR DISORDERS (CVDS) AND THEIR IMPLICATIONS

As discussed earlier, CVDs are a group of cardiac diseases. The following are some important CVDs and their potential implications.

Coronary artery disease

Coronary Artery disease (CAD) is a common cardiac impairment owing to an inadequate supply of oxygen and blood to the myocardium. This imbalance between supply and demand occurs due to plaque formation in the lumen of coronary arteries which ultimately halts the normal circulation of blood (Komilovich, 2023). Atherosclerosis is the major reason behind the onset of CAD in the majority of patients (Libby, 2013; Hiatt et al., 2015). Moreover, Fig 1 provides a

How to Cite: Bushra, T Batool, N Asif, A Manzoor, A Tahir, Z Nassar, M Arif & Q Sattar, 2024. Cardiovascular pharmacotherapy: balancing efficacy and safety. In: Zoology: Advancements and Research Trends (Ijaz MU, N Ehsan, M Imran & S Yousaf, eds): FahumSci, Lahore, Pakistan, pp. 31-36. ISBN: 978-627-7745-02-8. https://doi.org/10.61748/Zool.2024/05

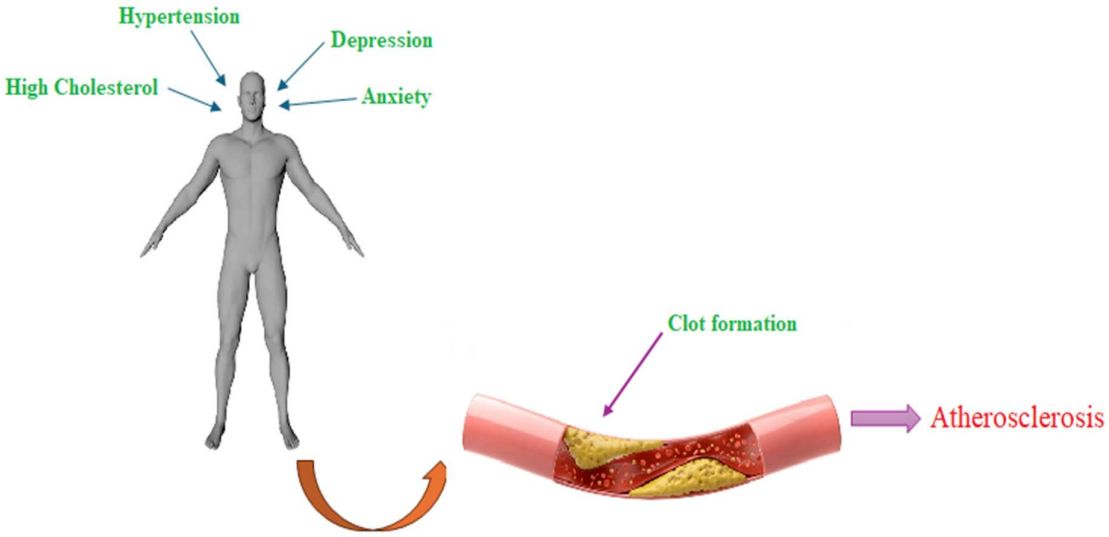

Fig 1. Basic mechanism behind the development of Atherosclerosis

brief illustration of the basic mechanism behind the development of atherosclerosis. The formation of plaque is characterized by general symptoms including low-grade inflammation, disrupted endothelium as well as lipid accumulation (Libby et al., 2011). The presence of plaque formation can provoke vessel occlusion which leads to various cardiovascular events including stroke, myocardial infarction, and limb ischemia (Bauersachs & Zannad 2018). There are numerous risk factors that worsen the severity of CAD such as hypertension, smoking, dyslipidemia, and diabetes mellitus (Bhatt et al., 2006). Different treatments such as clot inhibitors, anti-thrombotic therapies as well as lifestyle modifications reduce the CAD burden however, still it is the leading cause of death worldwide (Libby et al., 2011). An atherosclerotic clot is composed of cellular debris, cholesterol and its esters, inflammatory cells, and different types of cholesterol crystals. The over saturation of inflammatory cells translocases to the walls of arteries and weakens the fibrous cap which tears the cap. The deterioration of fibrous cap exposes the thrombogenic lipid layer leading to the formation of coronary thrombus (Srikanth & Ambrose 2012).

Cardioembolic stroke

Twenty-six million individuals are experiencing cardiac stroke every year worldwide which makes it a leading cause of death after cancer. One-third of cardiac strokes involve subarachnoid or intracerebral hemorrhage while two-thirds represent cerebral ischemia (Krishnamurthi et al., 2013). There are certain factors behind the occurrence of stroke such as occlusion of cerebral small vessels, plaque in cerebral circulation and cardiac embolism (Adams et al., 1993). Cardiac embolism provokes severe cardiac arrest as compared to other ischemic cardiac strokes (Bogiatzi et al., 2014). Despite the advancement in pharmacotherapy, cardioembolic strokes increased three times in a few decades and are estimated to become triplet by 2050 globally (Yiin et al., 2014). Early detection of embolic stroke can prevent the complexities of cardiac arrest. Echocardiography is one of the fundamental screening techniques to detect stroke (Sabín et al., 2020). Moreover, various biochemical analysis such as metabolomics, echocardiographics, genomics and transcriptomics are potential methods to identify cardioembolic strokes (Markus et al., 2021).

Peripheral artery disease (PAD)

Peripheral artery disease (PAD) is an obstruction of the antegrade flow of blood or narrowing of arteries which disrupts the normal flow of blood. It is reported that 30% of older populations in the USA, Australia and other Western countries are diagnosed with PAD (Newman et al., 1991; Hiatt et al., 1995). An investigation conducted by Global Burden of Disease revealed that PAD caused forty-thousand deaths in 2013 which is 155% greater as compared to deaths in 1990. Hiatt et al. (2001) elucidated that PAD is a potential cause of death as compared to myocardial infarction or other ischemic strokes. The mortality rate exceeded 45% in chronic PAD patients. Hypertension, smoking, diabetes mellitus, family disorder history, hyperlipidemia and obesity are potential risk factors underlying the progression of PAD. A survey executed by the National Health and Nutrition Examination showed that 95% of PAD patients have at least one of these major risk factors while more than 70% have more than two of them (Selvin & Erlinger 2004). Diabetes mellitus and smoking are considered as the strongest risk factors of mortality and morbidity each conferring more than 2.5 times higher risk of morbidity and mortality from PAD (Lu et al., 2014). A wide range of investigations were conducted to assess the relationship between PAD and oxidative stress (OS) (Husain et al., 2015; Siti et al., 2015; Barbagallo et al., 2013). OS plays a pivotal role in the pathophysiology of PAD (Novo et al., 2011). Different markers of OS such as C-reactive protein, beta 2 microglobulin and cystatin are primary indicators of PAD (Brevetti et al., 2010; Cooke & Wilson 2010). It is reported that OS escalates the levels of inflammatory cytokines during PAD that impairs the production of nitric

oxide which ultimately reduces vasodilation in the atherosclerotic arteries of lower limbs (Pastori et al., 2014).

Hypertension induced cardiac impairments

Hypertension (HTN) is a common risk factor behind various CVDs including hypertrophy, valvular impairments, atrial fibrillation and arrhythmia (Pickering, 1972). HTN is 30-45% prevalent in European countries which is continuously increasing with age (Pereira et al., 2009). Recent data suggested that HTN is the primary cause of fatal cerebral stroke in patients (Wolf-Maier et al., 2003). Various investigations documented that HTN is directly associated with cardiovascular health. HTN escalates the risks of getting heart failure, myocardial infarction, PAD, sudden death as well as stroke (Britton et al., 2009; Kalaitzidis & Bakris 2010). It is found that systolic blood pressure is a stronger indicator of cardiac events as compared to diastolic blood pressure (Vishram et al., 2012). Moreover, patients with escalated systolic while reduced diastolic blood pressure are reported to be vulnerable to cardiovascular disorders (Kannel et al., 1981). Various metabolic alterations such as type-II diabetes and glucose intolerance are common factors during HTN (Kannel, 2000).

Myocardial infarction

Myocardial infarction is specifically a severe manifestation of CADs which leads toward chronic myocardial ischemia owing to a low supply of oxygen to cardiac muscles. The myocardial infarction is characterized by alteration in wall motion, disrupted echocardiogram (ECG) and abnormal levels of cardiac injury markers (Tracey, 2002; Hayat et al., 2024). Severe and prolonged chest pain is one of the clinical signs of myocardial infarction. It frequently coexists with dyspnea, nausea, and sweating. Major complications due to myocardial infarction include angina, ischemic episodes, severe to potentially fatal arrhythmias, and chronic cardiomyopathy. The key factors influencing the prognosis are the degree of present clinical symptoms, the existence of any concomitant diseases, and the patient's reaction to the first course of treatment (Lawrence et al., 2002). Small intramural pockets of necrosis from coagulation and perinuclear edema in the cardiac myocytes, together with enlarged mitochondria and inflated sarcoplasmic reticulum, are the histological hallmarks of myocardial infarction. Moreover, severe alterations in the mitochondria, the incorporated disc's dehiscence, lamellar deterioration, and granular degeneration were noted (Funk, 2001). Infracted myocytes exhibit apoptosis, histological and organellar shrinking, and oncosis, or cellular and organellar swelling. Oncosis results from increasing cardiac membrane damage and malfunction, which lowers adenosine triphosphate (ATP) levels and depletes energy (Serrano-Mollar & Closa 2005).

POTENTIAL TREATMENT OPTIONS

Massive death rates from cardiac disorders urge a need for potential treatments. Following are some valuable pharmacotherapeutic approaches to treat cardiovascular disorders.

Nano-drug delivery systems (NDDSs)

Nano-drug delivery systems (NDDSs) are materials that show at least a one-dimensional range of nanometer scale (1-100 nm) (Cooke & Atkins 2016; Zhou et al., 2018). NDDSs are a prominent topic for study in the fields of pharmacy and contemporary biomedicine because they are an efficient way to optimize medication delivery. Over 40 years have been spent in investigating NDDSs, which has resulted in the production of several nano-drug carriers. The nanomaterials employed in NDDSs can be categorized as organic, inorganic, or composite materials based on their material makeup. For the prevention and treatment of CVDs to be effective, early, fast, and precise identification is essential. There has been an increasing focus on the use of molecular imaging in the detection of cardiovascular diseases. New contrast agents are essential for quick, high-sensitivity, excellent quality diagnostics that may be performed in real time, in addition to the ongoing advancement of various imaging methods. The following benefits of using nano-contrast agents over traditional contrast agents are: (1) stabilization of contrast agents or drugs in vivo, controlled distribution, and extension of their half-life; (2) controllable physical and chemical properties (e.g., chemical composition, size, and imaging performance); (3) specific identification of certain biomolecules; (4) capability of multimodal imaging realization; and (5) expected utilization of values in personalized diagnosis and therapy (Attia et al., 2016).

Membrane coated nanoparticles

New developments in nanomedicine have the possibility to significantly reduce long-term contamination, off-target adverse effects, and restricted therapeutic or diagnostic effectiveness (Patra et al., 2018). For instance, there are hazards associated with thrombosis and restenosis when using stents conventionally. In order to induce strong endothelium repair and control the drug-releasing characteristics of stents, nanoparticles have been added to their formulations. Advanced DES consisted of PLGA nanoparticles loaded with nitric oxide (NO) donor and collagen (Liu et al., 2013). Consequently, the platform lessened the creation of intima and showed a persistent release capacity of NO, which considerably decreased platelet aggregation in rabbit blood and consequently mitigated thrombosis. Traditional diagnostic contrast agents, like gadopentetic, work by making the vascular constriction, or stenosis, visible. On the other hand, by active targeting, a molecular contrast agent based on nanotechnology might reveal the precise location of atherosclerotic plaques (Palekar et al., 2015). An osteopontin antibody coupled up conversion nanoplatform, for instance, was created by Qiao et al. (2017) to enable noninvasive targeting and imaging of susceptible plaques. Dextran-coated superparamagnetic nanoparticles were described as having an affinity for macrophages and being able to be used to measure the number of macrophages in atherosclerosis. This might be a helpful tool for determining which plaques are inflamed and for keeping an eye on medical issues (Morishige et al., 2010). These nanoparticles were originally developed cell membrane cloaking innovation by coating poly-(D, L-lactic-co-glycolic) acid (PLGA) nanoparticles with red blood cell membranes,

thereby extending their circulation for up to 72 hours (Hu et al., 2011). To synthesize cell membrane coated nanoparticles, this method is often broken down into three steps: inner core nanoparticle manufacturing, cell membrane extraction, and the fusing process (Zou et al., 2020).

It is anticipated that cell membrane-coated nanoparticles will display some inherent cell characteristics, such as precise targeting to inflammatory sites, immune evasion, and binding affinity to specific cells or receptors. CMCNPs are used to simulate peripheral cells, such as immunological cells (Silvestre-Roig et al., 2020), platelets and erythrocytes (Pernow et al., 2019) which have been shown to play a critical role in the development of cardiovascular disorders. The erythrocyte membrane encapsulation was originally applied to PLGA nanoparticles by Zhang et al. (2020). In their investigation, RBC membrane-camouflaged nanoparticles (RBC-NPs) with an average diameter of 80 nm were synthesized by extracting the RBC membrane using hemolysis in a hypotonic media and fusing it with PLGA nanoparticles. They also demonstrated the effective transfer of RBC membrane proteins to PLGA nanoparticles. When appropriate small-molecule medicines are put into the inner PLGA core, this nanostructure-with its extended circulation time functions as a drug delivery platform against CVDs that is universally efficacious (Zou et al., 2020).

Natural flavonoids as cardioprotective

Foods rich in flavonoids are well researched and regarded as powerful bioactive substances with a variety of biological actions that contribute to many key signaling pathways associated with chronic illness (Khoo et al., 2017; Akbar & Ijaz 2024). Flavonoid-enriched herbal supplements are often claimed to have ameliorative benefits in the management of metabolic syndromes, such as diabetes mellitus and cardiovascular diseases. It is documented that regularly consuming 100 mg of total flavonoids daily may lower the risk of CVD-related morbidity and mortality. Owing to the flavonoid structure's many hydroxyl groups (-OH), they have a potent antioxidant action and counteract oxidative damage throughout a variety of clinical events (Iwashina, 2013). Free radicals oxidize flavonoids to produce a more stable, less reactive radical, which is the fundamental antioxidant action of flavonoids (Panche et al., 2016). Flavonoids may directly scavenge superoxide via scavenging very reactive radicals produced from oxygen, such as peroxynitrite ions (Kackov et al., 2013). The potential of flavonoids to protect against cardiovascular illnesses has been extensively researched. It is commonly recognized that these chemicals' antioxidant action reduces oxidative damage which causes cardiomyocytes to undergo apoptosis (Corcoran et al., 2012).

CONCLUSION

CVDs are one of the leading causes of death around the world. There are numerous factors underlying the development as well as the progression of CVDs. These factors include smoking, hypertension, high lipid profile and depression. Various sorts of CVDs including Cardioembolic stroke, Hypertension, Myocardial infarction, and Peripheral artery disease (PAD) are leading cardiac disorders. However, pharmacotherapy plays an essential role in mitigating the overburden of CVDs. Different pharmacotherapy potentials including the use of NDDSc, membrane coated nanoparticles and natural flavonoids exhibited marvelous results in counteracting CVDs.

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