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Current Updates on Therapeutic Advances in the Management of Cardiovascular Diseases

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Abstract: Despite the significant advances in the medical research and treatment methods, the rate of mortality associated with cardiovascular disease (CVD) is continuously rising and it remains the leading cause of death worldwide. There are several treatment methods for CVD and associated complications that have been considered till now. The current treatment methods cannot produce rapid cure, but could prevent or reduce the progression of this devastating disease. In the current article, we have summarized the use of various pharmacological agents viz. HMG-CoA reductase inhibitors (statins), antihypertensive, thrombolytic and anticoagulation agents that are currently being used for the management of CVD which targets different biochemical or molecular events. Based on our article, more research in this field is advocated which will provide the rapid and effective treatment methods in order to avoid fatal complications associated with CVD.

Keywords: Anticoagulation agents, antihypertensive agents, antithrombolytic agents, Statins.

INTRODUCTION

Despite the significant improvement in medical care lately, cardio vascular disease (CVD) contributes to the growing burden of life-limiting complication and remains the leading cause of death worldwide [1, 2]. There are limited reports on specific and effective treatment methods that raise concern about the cardiovascular protection and its long-term management plan. As per the latest WHO report, CVD contributes approximately 31% of all deaths in the global population and nearly 50% of non-communicable diseases (NCDs) associated deaths [3]. The continuous rise in CVD cases worldwide advocates the need of adequate preventive measures in order to avoid fatal complications related to this disease. Moreover, in patients with diabetes, cardiovascular complications are the principal causes of morbidity and mortality and account for up to 65% of diabetic fatalities [4]. It has been reported that 33% of diabetic patients on insulin therapy could die from CVD by the age of 50 years [5]. It is thought that glycation process which leads to the formation of advanced glycation end-products (AGEs) has a central role in the pathophysiological processes that lead to the development of such cardiovascular complications observed in diabetes [6]. More specifically the glycation of lipo-proteins predominantly of low density lipo-proteins (LDL) leads to the formation of advanced lipoxidation end-products which has significant role in the pathophysiology of CVD [7]. Thus, glycation process is a non-enzymatic addition of free amino groups of nucleic acids, lipids and proteins to the reducing sugars, ultimately leading to the formation of AGEs [8, 9]. Recent reports suggest that the prevalence of auto-antibodies against glycated biomolecules in diabetes subjects in turn implicates the aggravation of the glycation and the diabetes [10-12]. However, PubMed search revealed that no study has been performed to probe the presence of auto-antibodies against glycated biomolecules in cardiovascular or diabetic cardiovascular subjects till date. Until now scientists across the world are more concerned about the oxidative stress and thus have probed the auto-antibodies against oxidized biomolecules in CVDs and atherosclerosis subjects. Keywords used for the PubMed search were glycation, auto-antibodies, diabetic and cardiovascular disease. Looking at the severity of the reaction, the need of the hour for researchers is to curb the menace of glycation reaction which is gaining weightage by leaps and bounds [13-15]. The increasing prevalence of major and emerging cardiovascular risk factors such as tobacco smoking, physical inactivity, unhealthy diets and harmful use of alcohol also accounts for the potential catastrophic complications of CVD [16] In addition, the lifestyle changes and co-existing risk factors, such as hypertension, dyslipidemia etc. make the current problem more complicated. In view of the present data on mortality rate associated with CVDs, there is an urgent need to develop an effective translational treatment strategies from bench to bedside which could promote timely and appropriate management and possible treatment of CVD. Even though, current scientific knowledge does not completely elucidate the complex pathophysiology underlying CVD, it has been widely accepted that the atherosclerotic plaque rupture and subsequent thrombocyte aggregation are the crucial causatives of different cardiovascular complications and clinical consequences [17]. To achieve the above mentioned goal, various contributory conditions associated with pathophysiology and molecular pathology of cardiovascular complications of CVD could be targeted.

Cardiovascular complications are a complex and multi factorial process, the mechanism of initiation, progression and complications involves several pathological events that lead to fatal outcome. It should be highlighted here that targeting single pathological mechanism might not be an effective therapeutic strategy for CVD

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management. Moreover, selection of treatment strategy should be strictly adhered according to the clinical manifestations and proper diagnosis. Different pharmaceutical agents play a major role in the management and prevention of atherosclerosis and its consequences such as myocardial infarction (MI), stroke and heart failure. Recent developments in coronary care and timely reperfusion strategies have made remarkable improvements in the survival rates of patients suffering from various cardiovascular complications [18, 19]. In this review, we have outlined various therapeutic strategies for the prevention and management of CVD by different pharmacological agents, such as HMG-CoA reductase inhibitors (statins), antihypertensive and thrombolytic agents and agents used for antiplatelet and anticoagulation therapies.

CONTRIBUTORS OF CARDIOVASCULAR DISEASE

Even-though, all the pathogenic components associated with CVD have not been completely elucidated, atherosclerosis has been suggested as a fatal, complex and multifactorial condition and proposed as the primary causative agent of this devastating disease [2, 20]. The lipid accumulation in the coronary arteries and associated inflammatory responses are proposed as the crucial triggering factor of atherosclerosis, which ultimately leads to acute myocardial infarction (AMI) [21]. Moreover, dysfunctional endothelium, lipid-laden macrophages, smooth muscle cells and T lymphocytes have been proposed as the lethal contributors of atherosclerotic plaque formation and their pathological remodeling could lead to different cardiovascular complications [22, 23]. In addition to acute coronary blockage, chronic non-occlusive obstruction of the coronary arteries from atherosclerosis may also lead to disabling chest pain (angina) [24]. Chronic atherosclerotic process may lead to the enlargement or remodeling of heart that causes large or multiple small MIs and ultimately results into heart failure with several clinical symptoms, such as exertion related breath shortness, fluid accumulation in the legs and lungs, or both. Moreover, some alternative mechanism viz. hypertension and inherited problems that decrease the functioning of heart muscle has been also proposed as the reason of heart failure. Another complication of cardiovascular pathology is reported as stroke which is characterized by cerebro-vascular occlusions due to ischemic cerebral tissue that causes tissue infarction. Approximately, 80% of strokes are ischemic and 10-20% infarcted tissues could consequently lead to brain hemorrhages [25, 26]. The most important pathophysiological mechanism associated with stroke are thrombosis, embolism, or altered coagulation [26]. Several epidemiological studies have proposed hypertension as a significant contributing factor of CVD [27-29]. Moreover, a linear relationship between stroke and coronary heart disease has been suggested in patients with high blood pressure [30]. Hypertension promotes endothelial dysfunction by inducing mechanical stress on blood vessels and increase permeability of the intima that has a significant role in the progression of atherosclerosis and plaque rupture [30]. We all know that the incidence and prevalence of hypertension increases with age [31]. Moreover, hypertension is often asymptomatic, unlike other forms of CVD [24] and predisposes to all the major atherosclerotic clinical events, including stroke, cardiac failure, peripheral arterial disease and coronary artery disease (CAD) [27]. Understanding these profound mechanisms could be helpful in the development of novel strategies for CVD management.

THERAPEUTIC AGENTS THAT TARGET CARDIOVASCULAR DISEASE

Several strategies have been suggested on the use of pharmacological agents for the prevention and management of CVD. Various contributory conditions targeting associated with cardiovascular complications have been considered as the primary focus of CVD treatment. Although, these agents do not produce rapid cure, they could prevent or reduce the progression of disease. The efficacy of these treatments in mortality decline in stroke, heart attack and heart failure has been highlighted in literature. In the following section, we will try to cover some specific agents that are currently being used for the management of CVD.

HMG-CoA REDUCTASE INHIBITORS (STATINS)

Observational studies have shown the association between blood lipids and coronary artery pathology. Hypercholesterolemia has been proposed as an important modifiable risk factor for CVD [32]. Statins are the most commonly prescribed agents that have revolutionized hypercholesterolemia treatment because of their efficacy in reducing low density lipid with excellent tolerability and safety [33]. Angiographic studies have confirmed the crucial role of these agents in reducing the progression and regression of atherosclerosis [34, 35]. Moreover, statins also produce a wide variety of pleiotropic effects viz. endothelial dysfunction improvement, enhanced nitric oxide bioavailability, antioxidant and anti-inflammatory effects and atherosclerotic plaques stabilization that might significantly contribute to the treatment of CVD [36].

Statins are the competitive inhibitors of 3-hydroxy-3-methylglutarylcoenzyme A (HMG-CoA) reductase, in cholesterol biosynthesis which results in the reduction of hepatocytic cholesterol level through increased expression of LDL receptors [36]. Direct beneficial effect of statins in different pathological recovery such as reduced accretion of esterified cholesterol into macrophages, acceleration of endothelial NO synthetase activity, inhibition of inflammatory pathways, atherosclerotic plaques stabilization and restoration of coagulation process, have been reported in scientific literature [34, 37, 38]. The reduction in the atherosclerotic process by statins has been proposed via different mechanisms, such as inhibition of HMG CoA reductase, reduction of LDL susceptibility towards oxidation and inhibition of the expression of type A scavenger receptors [39]. Reduced HMG CoA reductase inhibits hepatic synthesis of apolipoprotein B-100 and decreases the synthesis and secretion of triglyceride rich lipoproteins through enhanced apolipoproteins B/E receptors production [36, 40, 41]. Several classification of statins have been proposed based on criteria such as the source of occurence, site of action, physico-chemical properties and specific activity. Atorvastatin, cerivastatin, pravastatin, fluvastatin, lovastatin and simvastatin are some examples of statins.

ANTIHYPERTENSIVE AGENTS

Epidemiological data indicate a strong and consistent linkage between hypertension and CAD. Hypertension has been considered as an important and independent risk factor for CVD in all ages, race and sex groups. Even-though, an exact definition of hypertension is difficult, a combined publication from American Heart Association, American College of Cardiology, and American Society of Hypertension reported as a systolic blood pressure (SBP) of $\geq$140 mm Hg or a diastolic blood pressure (DBP) of $\leq$ 90 mm Hg and/or the current use of antihypertensive medication are defined as hypertensive individuals.

It is well known that effective antihypertensive therapy significantly helps in combating the risk associated with CVD [42]. Several pathophysiological mechanisms that contribute in increasing hypertension have been reported in literature [42-44]. Involvement of altered sympathetic nervous system and renin-angiotensin aldosterone system (RAAS) activity with reduced release of prostacyclin, nitric oxide and other vasodilators have also been suggested as one of the major pathophysiological mechanisms of hypertension [42]. The presence of other disorders, such as diabetes mellitus, insulin resistance, and obesity could also results into the production of vasoactive adipocytokines that ultimately results in the rise of both blood pressure and CVD risks [42, 43].

Different classes of antihypertensive agents, such as thiazide and thiazide-type diuretics, β-blockers, calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, aldosterone antagonists and direct renin inhibitors

have been reported in scientific literature. Several clinical trials confirmed the antihypertensive potential of thiazide and thiazide-type diuretics [44-47].

β-blockers are the important class of anti-hypertensive agents and remain as the standard care of patients with angina pectoris. β-adrenergic receptors are the cell surface receptors mostly found in the heart, blood vessels and lungs. Their hormonal stimulation through catecholamines (norepinephrine, epinephrine) leads to increased blood pressure, heart rate, heart muscle contraction and relaxation of smooth muscle in the lung bronchial tubes [48]. Carvedilol, atenolol, metoprolol, betaxolol, bisoprolol and esmolol are some examples of currently used β-blockers. To maximize their potential they could be used in combination with other blood pressure-lowering drugs. In addition to hypertensive control, β-blockers could also be used to treat several other clinical conditions [48]. However, they should be used wisely, keeping in mind their long-acting, vasodilatory, and/or lipophilic properties [49].

Calcium channel blockers are another important class of anti-hypertensive agents currently used for hypertension management. This category of drugs typically works by preventing calcium ion influx through cell membranes. Calcium channel blockers inhibits L-type calcium channels found in vascular smooth muscles that results into relaxation of vascular smooth muscles. The ability of these drugs to manage arterial resistance with minimal effect on venous vessels makes them a frequently prescribed antihypertensive drug [50]. Keeping in mind their dual action on heart and blood vessels, they are widely used for the management of other cardiac complications including angina and supraventricular cardiac arrhythmias. The mechanism of calcium channel blockers includes interaction with three distinctive allosterically interacting receptors and according to their specific inhibitory action, three groups of inhibitors have been reported. This inhibitory agents are dihydropyridines, phenylalkylamines and benzothiazepines that have been developed to specifically bind with these sites [50].

Renin-angiotensin system (RAS) has a crucial role in the management of hypertension and suggested as a potential target of anti-hypertensive therapy. Pharmacological inhibition of RAS extends to distinct renoprotective and cardiovascular protection as well. Moreover, ACE inhibitors and angiotensin receptor blockers (ARB) are reported to be the most effective inhibitors of RAS, which dramatically attenuate the inevitable decline in hypertension, and other co-morbid conditions [51].

THROMBOLYTIC AGENTS

Acute myocardial infarction (AMI) is the ultimate fatal complication of atherosclerosis. It is reported as a significant complication developed due to total coronary occlusion [52]. The exact mechanism is still obscure, dynamics of plaque events has been suggested as a crucial step in the development of AMI with different clinical manifestations viz. unstable angina, stable angina or acute vessel closure. Moreover, early diagnosis and quick absolute therapeutic strategies are important to reduce the extent of myocardial damage. Till date, use of thrombolytic agents have been reported with some therapeutic impact and reduced mortality [53].

Pharmacological dissolution of the blood clot by intravenous infusion of thrombolytic agents has been considered as an important treatment strategy for AMI [53, 54]. These agents restore the circulation through occluded arteries by accelerating proteolysis of the thrombus. Targeting fibrinolytic system is valuable in various thromboembolic disorders viz. acute myocardial infarction (ST elevation, STEMI), acute ischemic stroke, peripheral artery occlusion, deep venous thrombosis and pulmonary embolism [55]. Moreover, extrinsic plasminogen activator has been suggested for its weak affinity towards plasminogen in the absence of fibrin. However, higher affinity in the presence of fibrin could be explained by surface assembly of plasminogen activator and plasminogen on the fibrin surface that promotes the plasminogen fibrin binding through lysine-binding site. Thus, it is quite clear that the level of plasminogen plays an important role in clot formation. The current insights into the physiological regulation of fibrinolysis highlight the importance of fibrin-selective thrombolytic therapy [56]. Various thrombolytic agents have been reported in the scientific literature based on their specific action on fibrin and/or non-fibrin specific thrombolytic pathway. Currently, several thrombolytic agents such as streptokinase, anistreplas, urokinase, tissue plasminogen activators (t-PA), alteplase, reteplase and tenecteplase are clinically used [44-50].

Streptokinase is a protein obtained from β-hemolytic streptococci which enables a complex formation with the proactivator of circulatory plasminogen and results into modulation of inactive plasminogen to activate plasmin and exhibits fibrinolytic activity [57]. Both fibrin-dependent and fibrin independent mechanisms of action for streptokinase have been reported in scientific literature [58]. Moreover, streptokinase is a first generation thrombolytic drug which has been widely accepted as a useful, cost-effective, easy to produce pharmacological agent in clinical practice. Lately, various chemical modifications of streptokinase have also been made to enhance its therapeutic efficacy [58].

Urokinase or urokinase-type plasminogen activator is a thrombolytic agent which is produced in human kidneys. This 54 KDa, human origin thrombolytic agent catalyzes the conversion of plasminogen to active plasmin. Urokinase holds a catalytic serine protease domain and a non-catalytic amino-terminal fragment specific to high-affinity cell-surface receptor. Urokinase is secreted as a single-chain molecule which can be converted to a two-chain form due to proteolytic cleavage by plasmin [59]. Due to their fibrinogensis property, urokinase has limited clinical use. Till date, only PROACT II is in phase III intra-arterial trial [60].

Tissue plasminogen activator (tPA) is a serine protease consists of a single chain of 527 amino acids found on the endothelial cells lining [61]. tPA are involved in the breakdown of blood clots that are composed of fibrin monomers. This activates fibrin-bound plasminogen and finally results into the release of fibrin molecules [60]. Advances in recombinant DNA technology led to the development of tPA (Alteplase) which promotes sufficient plasmin formation to overwhelm the limited circulating concentrations of α_2-antiplasmin. The intravenous administration of tPA is approved for the treatment of acute ischemic stroke within 4.5 hour of stroke onset [62]. Two different derivatives of tPA, reteplase (rPA) and tenecteplase (TNK-tPA) are used as third generation thrombolytic therapy. rPA is produced by removing several amino acid sequences from wild-type tPA. It is a non-glycosylated mutant deletion and due to the lack of fibrin binding domain and less fibrin specificity, reteplase is cheaper to produce as compared to tPA [61]. TNK-tPA, a mutant of tPA differs from rPA by only 6 amino acids sequence. Moreover, TNK-tPA has a longer half-life and slightly more fibrin-specific compared with tPA [63]. Although, the uses of thrombolytic agents are predominantly safer, it may cause some bleeding also. It should be highlighted here that thrombolysis is not advisable in contraindicative conditions, such as vascular lesions, severe uncontrolled hypertension, recent cranial surgery or trauma, brain tumor, ischemic stroke within 2-3 months, and in cases of active bleeding (except for normal menstrual bleeding) [61, 64].

ANTIPLATELET AND ANTICOAGULATION THERAPIES

Platelet-mediated thrombosis has been considered as the major pathophysiological mechanism underlying acute coronary syndromes (ACS), leading to fatal complications of CAD [65]. Anti-platelet therapy has gained increased attention in the treatment and prevention of thrombosis mediated consequences of atherosclerotic disease, heart attack and stroke by avoiding blood clot formation, which helps in long-term management of CAD and ultimately reduces cardiovascular associated morbidity and mortality [66]. Moreover, anti-platelet agents are also beneficial in the prevention

Table 1. Drugs used for the management of CVD and their mechanism of action.

Drug Category	Available Drugs	Mechanism of Action	References
HMG-CoA reductase inhibitors (Statins)	Atorvastatin, Cerivastatin, Fluvastatin, Pravastatin, Lovastatin and Simvastatin	Lowering of atherogenic Low Density Lipoproteins (LDL)	[20- 23]
Antihypertensive agents	Thiazide and thiazide-type diuretics, β-blockers, ACE inhibitors, Angiotensin receptor blockers, Aldosterone antagonists, Calcium channel blockers and Direct renin inhibitors	Prevention and management of hypertension	[29, 31, 35, 37, 39]
Thrombolytic agents	Streptokinase, Anistreplase, Urokinase, Tissue plasminogen activators, Alteplase, Reteplase and Tenecteplase	Restore the circulation through occluded arteries by accelerating proteolysis of the thrombus	[41, 45-46, 49-50]
Antiplatelet and anticoagulation agents	Cyclooxygenase1 inhibitor- Aspirin P2Y12 receptor inhibitors- Clopidogrel, Prasugrel and Ticagrelor Glycoprotein IIb/IIIa inhibitors - Eptifibatide, Ttirofiban and Abciximab Anticoagulants- Unfractionated heparin, Bivalirudin, Enoxaparin and Fondaparinux Oral anticoagulants - Warfarin, Rivaroxaban, Apixaban and Dabigatran	Prevent and manage platelet-mediated thrombosis	[54, 56, 58, 61]

of thromboembolism in atrial and/or venous fibrillation [67, 68]. Anti-platelet agents prevent the complete occlusion of an artery by the formation of blood clots and reduce the effect of thrombotic events. In the last 3 decades, anti-thrombotic agents have become one of the most prescribed medicines all across the globe. For several years, low dose of aspirin has been used as an effective anti-thrombotic agent for the management of chronic and acute CAD and its complications, such as MI and stroke [69]. The mechanism of action of aspirin includes the irreversible inhibition of enzyme cyclooxygenase-1 which results in the blockage of intraplatelet formation of thromboxane A2, the potent platelet aggregator [70]. Previously, clinical trials have also confirmed the potency of aspirin in reducing the rate of morbidity and mortality by 50% in the patients with ACS [71, 72]. P2Y12 receptor inhibitors are another example in this category which inhibits platelets by binding to P2Y12 receptors and blocks adenosine diphosphate mediated platelet activation. Clopidogrel, prasugrel and ticagrelor are well known P2Y12 receptor inhibitors [66]. Glycoprotein IIb/IIIa inhibitors are also anti-thrombotic agents which inhibit fibrinogen and von Willebrand factor and results in the blockage of platelet aggregation pathway. Eptifibatide, tirofiban and abciximab are some of the drugs listed in this class. In addition, parenteral administration of anticoagulants, such as unfractionated heparin, bivalirudin, enoxaparin and fondaparinux are also reported for the management of pathological thrombotic events. Heparin is an excellent inhibitor of factor IIa (thrombin), factor IXa and factor Xa, whereas bivalirudin is a direct thrombin inhibitor. Enoxaparin is known as low-molecular weight heparin and fondaparinux has been identified as a factor Xa inhibitor. Moreover, some oral anticoagulants, such as warfarin, rivaroxaban, apixaban and dabigatran have also been reported to provide ischemic benefit in patients with ACS [73]. Administration of combined anti-thrombotic agents have been widely accepted as an effective preventive measure of atherothrombotic complications, such as pathological platelet activation involving several receptor-mediated signaling mechanisms [74]. This multi drug approach enables the management of critical balance between anti-ischemic effect and bleeding risk. Dual anti-platelet therapy with aspirin and clopidogrel has been widely established as more effective preventive measure for the reduction of thrombotic events as compared to aspirin or clopidogrel alone [74]. We have summarized the currently used pharmacological drugs and their mechanism of action in the Table **1**.

FUTURE PERSPECTIVES

Based on our article, it is quite clear that there are some available drugs which could be used for the management of CVD with limited success. However, more research in this field is advocated which will provide the rapid and effective treatment methods in order to avoid fatal complications associated with CVD.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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