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Recent Trends in the Pharmacotherapy of Angina Pectoris

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Abstract
Background and Objectives: Angina pectoris,a pain from the heart felt in the pectoral regionsof the upper chest,is a predominant symptom of ischemicheart disease caused by transient episodes ofmyocardial ischemia. The traditional medications for the treatment were discovered about 60years ago. The current presentations and complications associated with angina are hardly well catered for by such medicines and present daymanagement keeps evolving. The need for bringing health practitioners and researchers up to speed with recent advances in drug management of angina pectoris becomes essential.
Methods: This review examines published literature of the last 3 decades on the recent pharmacotherapeutic approaches to angina pectoris management.Online search of published literature from reputable sources of pubmed, researchgate and google scholar were used as well as offline search from the pharmacy library resource centre of the Faculty of Pharmacy, University of Uyo, Nigeria.
Results: This work reveals that currently, while the beta blockers, calciumchannel blockers and nitrates are conventional first-line drug of choice, their limitation in being transitory is significant. Newer techniques are more effective in refractory angina cases and are typically a combination of more than just pharmacotherapeutic agents.
Conclusion: Poorly controlled angina still poses serious concern in a number of patients with ischemic heart disease and current strategies is a combination therapy that targets cellular processes, altering lipid metabolism or promoting angiogenesis, thus resulting in sustainable benefit that can improve not just the clinical outcome of the diseasebut also add to patients quality of life.
Keywords: Pharmacotherapy, angiogenesis, angina, lipoprotein apheresis

I. INTRODUCTION

In humans, the heart is a muscular structure that serves as two separate pumps *i.e.* the right heartthat pumps blood through the lungs, and the left heartthat pumps blood through the peripheral organs. Descriptively, both the right and left hearts function distinctly asa pulsatile two-chamberpump composed of an atrium and a ventricle.Eachatrium is a weak primer pump for the ventricle, and aids blood movement into the ventricle. The ventricles then supply the mainpumping force that propels the blood either (1) through the pulmonary circulationby the right ventricle or (2) through the peripheral circulation by the leftventricle.The very essence of these muscular pumps is to ensure adequate tissue perfusion (supply of oxygen and nutrients) and removal of waste materials. Since tissue perfusion is necessary for optimal cellular health, the heart which is an aggregate of tissues must be perfused and this is done by the coronary arteries.

The narrowing or eventual blocking of the coronary arteries due to plaque formation otherwise known as coronary artery diseases (CAD) predisposes an individual to many cardiovascular disorders including ischemic heart disease, coronary heart disease (CHD), myocardial infarction, congestive heart failure (CHF) amongst others. Angina pectorisis the primary symptom of ischemicheart disease and is caused by transient episodes ofmyocardial ischemia (Michel and Hoffman, 2011).

Worldwide, angina is a highly prevalent condition. In the United States alone, it is estimated that more than 8.2 million patients suffer from angina(Rosamond *et al.*,2008; Mozaffarian *et al.*, 2016).Most certainly, the

condition is a major cause of poor quality of life, disability, and high heath care cost. Treatment for angina is challenging, especially in the face of recalcitrant cases, thus priority has been to evolve newer and improved strategies on the management of the condition (Balla*et al.,* 2018). This work is thus aimed at examining medicines of choice in the management of angina and brings readers up to speed with the current advanced pharmacotherapeutic options. This will help practitioners to choose effective, evidenced-based current options for positive clinical outcomes as well as improved quality of life of patients.

II. MATERIAL AND METHODS

Published articles on the pharmacotherapeutic approaches to the management of angina pectoris,in the last 20 years were sourced for in this review.Online search of published literature from pubmed, researchgate and google scholar were used as well as offline search from the pharmacy library resource centre of the Faculty of Pharmacy, University of Uyo, Nigeria. Search terms used were 'angina pectoris', 'management of angina', 'medicine use in angina', 'type of angina and medicine use in them' and these revealed altogether more than 1270 articles. Similar search words were checked in indexes and appendices of hard copies of books on pharmacology and therapeutics consulted. Some of the articles in one search engine were duplicated in the other hence the duplicates excluded. Other exclusion criteria were articles older than 30 years containing recommendations for drug therapy of angina, articles on surgical approaches to angina management as well as those on alternative methods to orthodox management of angina.

Aetiology of Angina Pectoris

Angina pectoris is a consequence of an imbalance in themyocardial oxygen supply-demand relationship. Thisimbalance may be caused by an increase in myocardial oxygen demand or by a decrease in myocardial oxygen supply or sometimes by both (Figure 1). Myocardial oxygen demand is determined by the heart rate, contraction of the ventricles, and tension on the walls of the ventricles while coronary blood flow is the primary determinant of myocardial oxygen supply. However, this supply may be occasionallymodified by the oxygen-carrying capacity of the blood.Oxygenated blood is delivered to the myocardium via epicardial coronary arteries that branch into arterioles, and the latter further branches into a network of capillaries. Physiologically, the epicardial coronary arteries are a low resistance system and changes in the tone of the arterioles is responsible for the auto regulation of blood flow. Also, circulation of blood through the coronary arteries is chiefly determined by cross sectional stenosis. Once developed, the arterioles dilate to maintain myocardial blood flow. When there is increase in myocardial oxygen demand, arterioles dilate in response to nitric oxide, prostaglandins, carbon dioxide, hydrogen ion, adenosine, and other nucleotides (Duncker and Bache, 2008). Through this mechanism, blood flow to normal myocardium can be augmented four to five-fold. This is the coronary flow reserve or myocardial perfusion reserve. Plaques resulting from atherosclerosis, narrow the lumen and increase the resistance of the epicardial coronary arteries. Despite its physiological usefulness, persistent epicardial coronary stenosis (>70%), might result in inadequate blood supply to the myocardium even at rest, culminating in ischemia and primary angina (Epstein*et al*., 1985; Talbert,2014).

Myocardial oxygen supply also depends on some other factors such as collateral blood flow, left-ventricular end diastolic pressure (known to reduce the perfusion pressure from epicardium to endocardium capillaries), and diastolic-perfusion time (which is related to the heart rate and aortic diastolic pressure-product). This is so especially as myocardial perfusion mostly occurs during diastole. Oxygen is the critical substrate for energy production as adenosine triphosphate (ATP) in cardiac muscle cell. Myocardial oxygen requirement depends on myocardial wall stress, myocardial contractility, systolic blood pressure, and the heart rate. In addition, myocardial energy need depends on the systolic wall stress and left-ventricular mass. For example, the myocardial energy need may increase up to four-fold in aortic stenosis and three-fold in essential hypertension (Strauer, 1979).

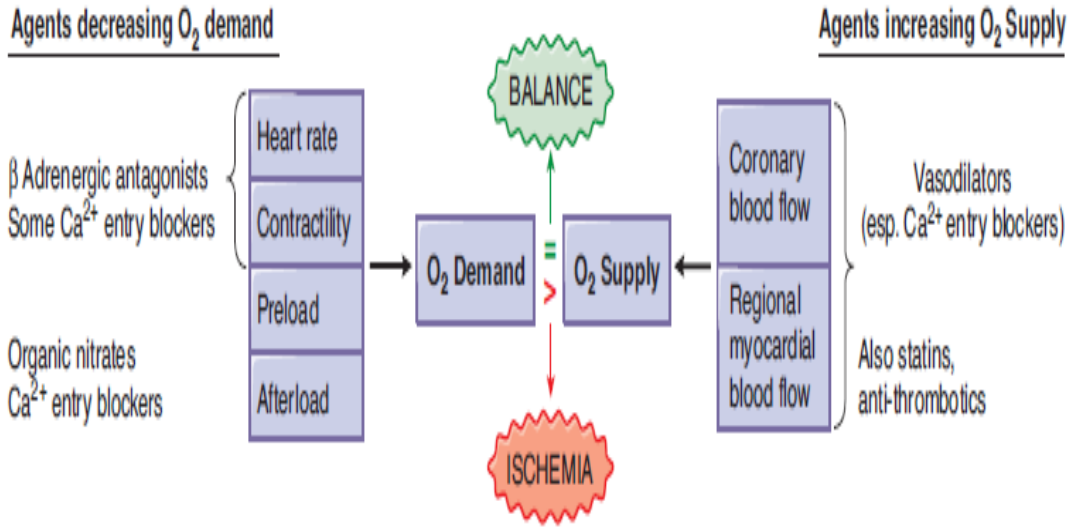

Figure 1. Myocardial oxygen supply-demand relationship showing the hemodynamic sites for therapeutic agents.

(Source: Bruntone*t al.*,2011)

Angina pectoris refers to the pain from the heart felt in the pectoral regionsof the upper chest (Guyton and Hall, 2006). This pain usually radiates intothe left neck area and down the left arm (Figure 2). Put simply, this is a visceral pain whose specific underlying mechanisms for pain generation are not entirely understood. Myocardial ischemia leads to acidosis and loss of normal ATP sodium-potassium pump and membrane integrity (Jain *et al.*, 2017). Release of substances such as adenosine, lactate, serotonin, bradykinin, histamine, and reactive oxygen species stimulate chemo-sensitive receptors (Figure 2). Stimulation of afferent sympathetic fibres in the upper thoracic spinothalamic tract leads to chest and arm pain symptoms,while the stimulation of vagal afferent fibres leads to excitation of cervical spinothalamic tracts which may result in neck and/or jaw pain symptoms.

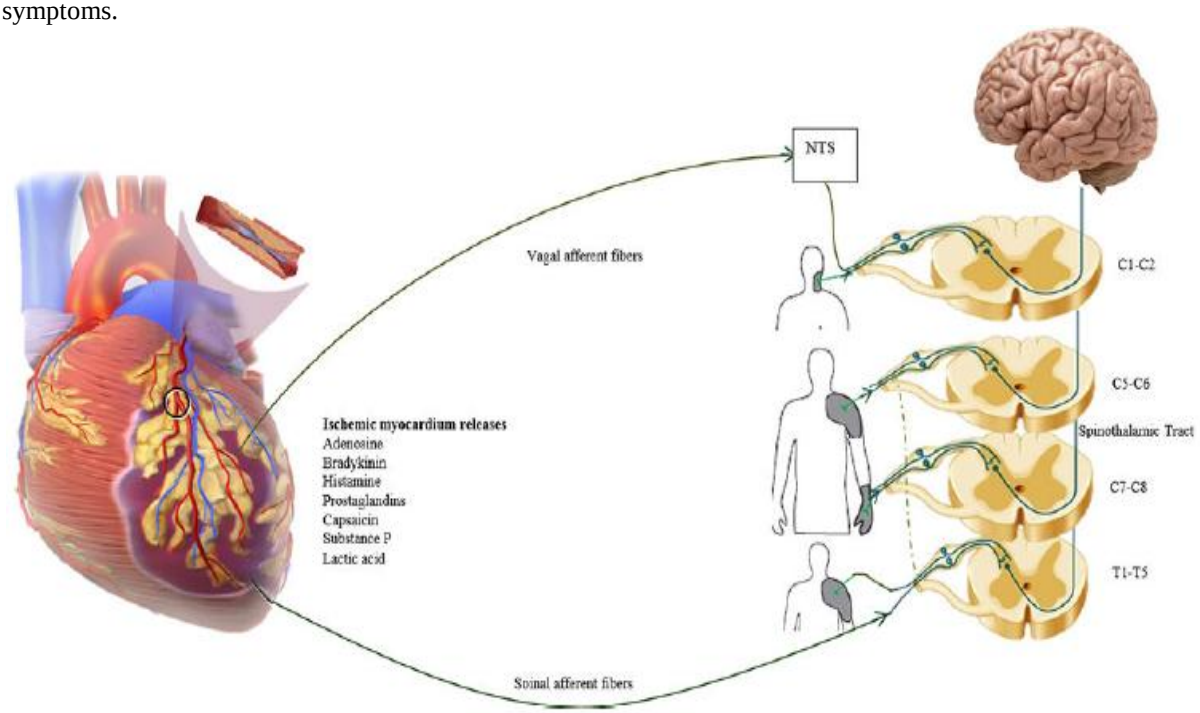

Figure 2. Schematic presentation of mechanisms and pathways involved in cardiac chest pain: Ischemic myocardium releases nociceptive mediators that stimulate excitatory spinal and vagal afferent fibres. Somatic fibres also converge on upper thoracic and cervical spinal segments as shown, leading to referred pain. NTS = Nucleus TractusSolitarius.
(Source: Jain *et al.*, 2017).

The biophysics of circulation suggests an inversely proportional relationship of blood flow to the fourth powerof the artery's luminal radius, thus the progressive decreasein the radius or diameter of the coronary arteries due to atheroma impairs coronary blood flow and lead to symptomsof angina when myocardial oxygen demand increases,as with exertion, cold or excitement (Michel and Hoffman, 2011; Rang *et al.*, 2012).In most cases, there is a weak relationship between pain severity and degree of oxygen supply. In other words, there can be severe pain but minimal disruption of oxygen supply or no pain, yet severe cases. As reported by Fisher (2015), the traditional risk factors for coronary artery disease include the following:

- High levels of LDL cholesterol
- Low levels of HDL cholesterol
- Smoking
- High blood pressure
- Family history
- Obesity and
- Age (men above 45 years and post-menopausal women)

Historical background of Angina Pectoris and its Pharmacotherapy

Medical history points to the first mention of angina pectoris in 1772 by William Heberden during his paper presentation entitled "Some account of the disorders of the breast" at the Royal College of Physicians in London (Zhou *et al.*, 2005). He wrote "There is a disorder of the breast…the seat of it, and sense of strangling and anxiety, with which is attended, may make it not improperly be called angina pectoris. Those, who are afflicted with it, are ceased [sic] while they are walking and most particularly when they walk soon after eating, with a painful and most disagreeable sensation in the breast, which seems as it would take their breathe away, if it were to increase or to continue; the moment they stand still, all this uneasiness vanishes".

Despite his first attempt at describing this heart condition, Heberden, obviously did not fully comprehend the pathogenesis and pathophysiology of angina pectoris. In fact, he had inaccurately describedoccurrence of angina pectoris as a strong cramp, an ulcer, or both.

According to Jain *et al.* (2017), for some 3,500 years ago, pain felt within the chest area and arm, in relation to heart disease were experienced by the ancient Egyptian mummies. Furthermore, Liang *et al.* (2012) reported that these mummies had atherosclerosis as was revealed by computed tomography.Of interest to us is the fact that this finding was observed in renowned and highly placed Egyptian mummies. Though it is difficult to pinpoint exactly when the civil society first became aware of heartconditions associated with ischemia, however, as reported by Liu *et al.* (2007), Leonardo da Vinci (1452–1519)investigated the coronary arteries; William Harvey (1578– 1657) described the blood circulation, while Friedrich Hoffman (1660–1742) observed a "reduced passage of blood within the coronary arteries," though none of these investigations closed the link with the condition now known as angina pectoris.

Angina was first linked with cardiovascular disease (CAD) by Edward Jenner, and he described the coronary arteries with these words: "a fleshy tube with a considerable quantity of ossific material dispersed irregularly through it" (Liu *et al.*, 2007). Lauder Bruntonimplicated the spasm of coronary vessels in the aetiogenesis of angina, while other theories linked the condition to irritation of the nervous elements of the cardiac plexus (Liu *et al.*, 2007).

The varying ideas as regards the aetiology of angina pectoris potentiated diverse treatment options. Heberdenoffered a "quiet, warmth, and spirituous liquors" as well as opium, administered in the evenings as prophylaxis. According to him, opium prevents nocturnal anginal crises.In 1867, Thomas Brunton suggested amyl nitrite to cause symptomatic relief of angina pectoris, and this was the first treatment option with scientific credence (Liu *et al.*, 2007). In 1879, W.M. Morrell had reportedthat nitroglycerineadministered in alcohol could relieve the symptoms of angina pectoris (Gauthier*et al*., 1996). James Black correctly associated episodes of angina with emotions, exercise or physical exertion and strongly proposed the usefulness of beta blockers in the management of angina pectoris, thus, in 1965 propanolol became the first clinically available beta-receptor blocker (Elgendy*et al.*, 2014). Albert Fleckenstein and colleagues, while investigating the properties of prenylamine and verapamil (coronary dilators), observed that besides the expected coronary vasodilation, the drugs provoked a negative inotropic effect on the heart, which was obliterated by calcium. Following their conclusion that the observed negative inotropic action was due to the ability of prenylamine and verapamil to block excitation-induced calcium influx, drugs tagged as calcium channel blockers or calcium antagonists were introduced (Lertora*et al.*, 1975). Subsequently, these 3 classes of drugs (nitrates, beta blockers and calcium channel blockers) are currently labelled by the guidelines as"first-choice" in the management of angina pectoris.

Types of Angina Pectoris

Basically, there are four types of angina pectoris, namely: Stable angina, unstable angina, microvascular angina and prinzmetal's angina.

i. **Stable Angina**: This is otherwise known as typical, classic or effort-induced angina, and refers to a predictable chest pain on exertion. It is produced by an increased demand on the heart and is caused by a fixed narrowing of the coronary vessels, almost always by atheroma.Classic angina is the most common form of angina and, therefore, is also called typical angina pectoris. It is usually characterized by a short-lasting burning, heavy, or squeezing feeling in the chest. Some ischemic episodes may present "atypically"—with extreme fatigue, nausea, or diaphoresis—while others may not be associated with any symptoms (silent angina). Atypical presentations are more commonin women, diabetic patients, and the elderly.Classic angina is caused by the reduction of coronary perfusion due to a fixed obstruction of a coronary artery produced by atherosclerosis. Due to the fixed obstruction, the blood supply cannot increase, and the heart becomes vulnerable to ischemia whenever there is increased demand, such as that produced by physical activity, emotional stress or excitement, or any other cause of increased cardiac workload.

ii. **Unstable Angina**: Unstable angina is classified between stable angina and myocardial infarction. In unstable angina, chest pain occurs with increased frequency, duration, and intensity and can be precipitated by progressively less effort. Manifestations of unstable angina could be expressed in the following ways: Any episode of rest angina longer than 20 min, any new-onset angina, any increasing (crescendo) angina, or even sudden development of shortness of breath. The symptoms are not relieved by rest or nitroglycerine. Unstable angina is a form of acute coronary syndrome and requires hospital admission and more aggressive therapy to prevent progression to MI and death. This is characterised by pain that occurs with less and less exertion, culminating in pain at rest. The pathology is similar to that involved in myocardial infarction, namely platelet–fibrin thrombus associated with a ruptured atheromatous plaque, but without complete occlusion of the vessel.

iii. **Microvascular Angina**:Acute coronary syndrome is an emergency that commonly results from rupture of an atherosclerotic plaque and partial or complete thrombosis of a coronary artery. Most cases occur from disruption of an atherosclerotic lesion, followed by platelet activation of the coagulation cascade and vasoconstriction. This process culminates in intraluminal thrombosis and vascular occlusion. If the thrombus occludes most of the blood vessel, and, if the occlusion is untreated, necrosis of the cardiac muscle may ensue. MI (necrosis) is typified by increases in the serum levels of biomarkers such as troponins and creatine kinase. The acute coronary syndrome may present as ST-segment elevation myocardial infarction, non–ST-segment elevation myocardial infarction, or as unstable angina. (Note: In unstable angina, no increases of biomarkers of myocardial necrosis are present).

iv. **Prinzmetal's Angina**: Prinzmetal angina is an uncommon pattern of episodic angina that occurs at rest and is due to coronary artery spasm. Symptoms are caused by decreased blood flow to the heart muscle from the spasm of the coronary artery. Although individuals with this form of angina may have significant coronary atherosclerosis, the angina attacks are unrelated to physical activity, heart rate, or blood pressure. Prinzmetal's angina generally responds promptly to coronary vasodilators, such as nitroglycerineand calcium channel blockers. This is uncommon. It occurs at rest and is caused by coronary artery spasm, again usually in association with atheromatous disease.

Strategic Management of Angina Pectoris

Generally, the goal of therapy is to reduce myocardial oxygen demand, which is achieved via reduction in the heart's firing rate (HR), and to increase coronary blood flow via vascular smooth muscle relaxation. Since atherosclerotic plaque is implicated in the pathogenesis of angina, management of risk factors for progression of atherosclerosis becomes essential. Therefore, lifestyle modification and prevention of progression of underlying atherosclerosis isthe mainstay of management.

First-line Pharmacotherapy Options

The 3 classes of drugs currently labelled by the guidelines (Figure 3) as"first-choice"or "traditional drugs" in treatment of angina pectoris are:

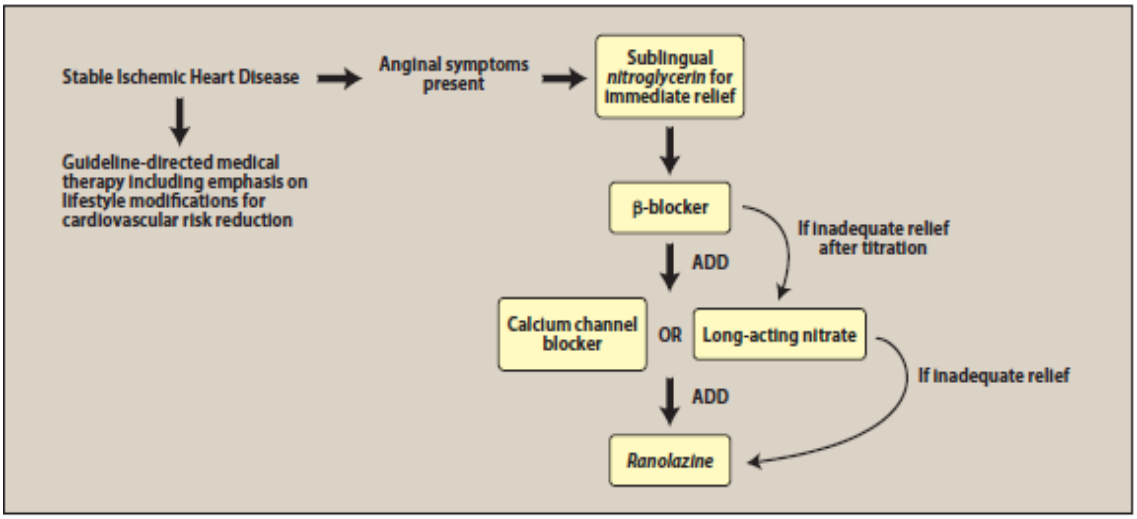

Figure 3. Algorithm for the management of stable angina pectoris

Source: Whalen*et al.*, (2015).

iBeta-adrenergic Blockers

These drugs are known to modulate and/or inhibit the endogenous ligand binding to the beta adrenergic receptors. There are three types of beta receptors. B_1 receptors, found primarily in the heart, and their activation leads to increased contractility and heart rate (HR). B_2 receptors are primarily located in the bronchial and peripheral smooth muscle. Their activation results in vasodilation and bronchodilation. B_3 receptors are mainly found in adipose tissue but also in the heart, and their activation helps with thermoregulation and decrease myocardial contractility (Elgendy*et al.*, 2014; 2016). Beta adrenergic inhibitors decrease myocardial oxygen demand by slowing down the heart rate, reducing myocardial contractility, and blood pressure. They also increase the time for coronary perfusion by decreasing HR and increasing diastolic time, thus favourably altering the determinants of collateral perfusion.

The beta blocking drugs can be classified according to the adrenergic receptors that they block. Drugs that principally block B_1 receptors, preferentially to B_2 or B_3, are commonly referred to as "relatively" cardio-selective. The qualifier "relatively" is fitting because at higher doses the selectivity may become partially or completely lost (Lertora*et al.*, 1975; Jain *et al.*, 2017). The non-selective beta blocker *propranolol* was first introduced for clinical use and was shown to reduce angina episodes by more than 50% when compared with placebo (Warren *et al.*, 1976). *Carvedilol*is another commonly used drug. Althoughnot approved for the management of angina pectoris, it is a non-selective beta blocker with α-1 receptor blocking properties. Non-selective beta antagonists should be avoided in patients with asthma because of their ability to cause bronchospasms. As reported by previous studies (Yong*et al.*,2015; Furberg*et al.*, 1978; Jackson *et al.*, 1978), cardio-selective agents such as *atenolol* and *metoprolol* were effective in improving exercise tolerance and decreasing angina, with minimal and tolerable side effects compared to other non-selective agents like propranolol. These cardio-selective agents (*i.e.*,*metoprolol* and *atenolol*) are considered the first line therapy for angina. *Nebivolol* is another newer agentwith selective antagonism for $B_1$and a vasodilating effect made possible by the stimulation and release of nitric oxide (Kobusiak-Prokopowicz*et al.*, 2008).Though not approved as an antianginal drug, *nebivolol*is being investigated for microvascular angina relief in women in an on-going trial [NCT01665508]. Beta blockers are recommended as first-line therapy for patients with angina chiefly because they improve angina, reduce the risk of re-infarction, sudden cardiac death as well as all-cause mortality in post-myocardial infarction and systolic heart failure patients (Packer *et al.*, 1996). Because of fair tolerance profile, beta blockers (cardio-selective) are widely used. Generally, the pharmacologically action of the beta blockers and its attendant effect on angina pectoris are thought to be dose-dependent (Alderman *et al.*, 1975; Jackson *et al.*, 1980).Common adverse effects of this class of drugs include:

- Depression,
- Fatigue,
- Male sexual dysfunction,
- Enhancement of hypoglycaemia and
- Increase weight gain.

ii Calcium Channel Blockers

Calcium is essential for muscular contraction. Influx of calcium ion into the cardiomyocytes triggers intracellular release of calcium, potentiating myocardial contractility. During ischemia, the amount of calcium entering the myocardium increases, primarily due to the membrane depolarization produced by tissue hypoxia. This in turn, worsens the ischemia due depletion in energy stores brought about by enhanced activities of several ATP-consumingenzymes (Mulqueen, 2015). Calcium channel blockers inhibit the entry of calcium into the cardiac and smooth muscle cells of the coronary and systemic arterial beds. The overall effect of this is seen as a reduction in the heart's firing rate, decreased myocardial contractility, vasodilation anddecreased blood pressure. All calcium channel blockers are, therefore, tagged "arteriolarvasodilators that cause a decrease in smooth muscle tone and vascularresistance"(Mulqueen, 2015). Calcium channel blockers exert their effects primarily by decreasing vascular resistance, thereby decreasing afterload leading to a reduction in myocardial oxygen consumption.Therefore, they are efficacious in the treatment of effort-induced angina. Their efficacy in vasospastic angina is due to relaxation of the coronaryarteries.

Traditionally, calcium channel blockers are classified based on their chemical composition either as:

i. Dihydropyridines (*e.g.,nifedipine, amlodipine, and nicardipine*) or
ii. Non-dihydropyridines (*e.g., verapamil and diltiazem*).

Dihydropyridinesexert greater effect on the vascular smooth muscle than the cardiac musculature. As a result, they cause vasodilation of the peripheral vasculature including the coronary arteries. However, these agents elicit reflex adrenergic stimulation of the heart; hence they do not significantly affect contraction of the cardiac muscles and the heart rate.On the other hand, non-dihydropyridinespreferably act on the calcium channels in the myocardium, provoking a relatively more coronary vasodilation, against myocardial contractility and heart rate. Though a non-dihydropyridine, diltiazemisintermediary in its actions (Mulqueen, 2015; Jain *et al*., 2017).

As reported by earlier researchers, calcium channel blockers are more effective in relieving angina and increasing exercise tolerance (Krikler, 1987; Taylor 1994).When combined, beta blockers and calcium channels antagonists exert synergistic but not additive effects compared to monotherapy(Strauss andParisi,1985; Leon *et al.*, 1985; Dunselman*et al.*, 1997). It is worthy of note that though the combination of non-dihydropyridines with beta adrenergic antagonists proves to be more effective, it is with higher risk of adverse effects like heart palpitations,bradycardia, syncope as well as GIT intolerance (Strauss andParisi,1985;Knight and Fox,1998). In patients who cannot tolerate the beta antagonists, then non-dihydropyridines are considered as safe alternatives. Also, inpatients with vasospastic angina, the calcium antagonists are considered as the 'choicest drugs'(Harris *et al.*, 2016). Due to their negative inotropic effects, non-dihydropyridines worsens heart failure, and must be avoided in patients with congestive heart failure.

iiiNitrates

Organic nitrates (*Isosorbide-5-mononitrate, Nitroglycerine and Isosorbide dinitrate*) are among the first line therapy for angina pectoris because of their relaxation effects on the vascular smooth muscle. On entering the smooth muscle cells, they are usually converted to nitrites and finally to nitric oxide. The nitric oxide activates the enzyme guanylate cyclase and increases cyclic guanosine monophosphate(cGMP) production in the smooth muscle cells. This provokes dephosphorylationof the myosin light chain, culminating in vascular smooth muscle relaxation. According to Abrams (1985; 1992), at very low, low to moderate and high doses, cGMP causes venodilatation, arterial dilatation, and arteriolar dilatation respectively. For example, nitroglycerindilates larger veins, reducing the venous return to the heart (preload), and this ultimately reduces myocardial contraction or the work load of the heart (Mulqueen, 2015). Nitrates also reduces myocardial oxygen demand by dilating the coronary vasculature, thus blood supplyto the heart muscle is greatly increased.

Mostly, headache is the common adverse effect of nitrates reported (Wei*et al.*, 2011). However, at doses high than normal, postural hypotension, facial flushing, andtachycardia may occur. These adverse events are potentiated by the 5-phosphodiesterase inhibitors (*e.g.*,sildenafil), and thus such combination is contraindicated.Nitrate tolerance (*i.e.* the desensitization of the blood vessels to vasodilation), is a major problem with long-term use of this class of drug. This can be alleviated by ensuring a daily "nitrate-free interval (10 – 12 hours)" to restore sensitivity of the blood vessels to thedrug. However, the drug-free interval poses the theoretical risk of a rebound angina. As reported by Giuseppe *et al.* (2015), chronic or long-term use of organic nitrates is implicated to induce oxidative stressand endothelial dysfunction (due to increase sympathetic stimulation).Takahashi *et al.* (2015) associated the combination of long acting nitrates with calcium channel blockers patients with increased risk of adverse cardiovascular events in patients with vasospastic angina. Figure 4 summaries the drugs commonly used in therapy in patients with concomitant or other underlying disease conditions.

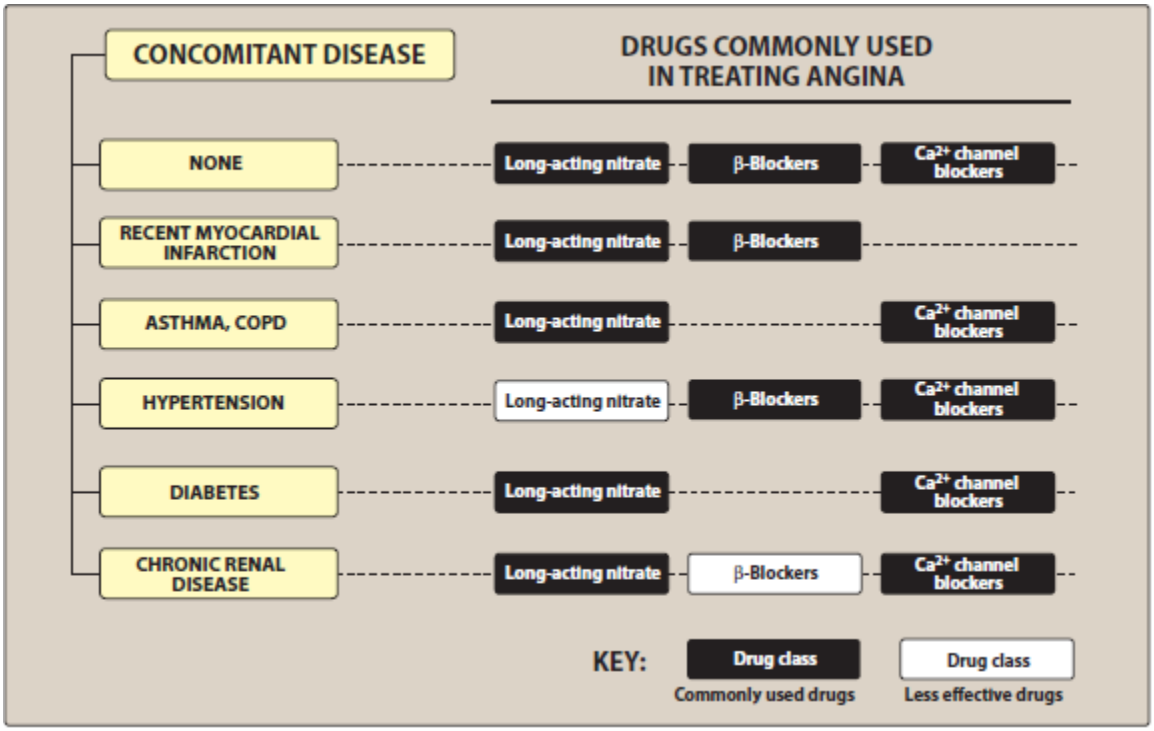

Figure 4. Therapy for angina in patients with comorbidities
(Source: Whalen*et al.*,2015).

Second-line Pharmacotherapy Options
The following drugs are considered internationally as second line for the therapy of angina pectoris:

iSodium Channel Antagonists

*Ranolazine*is a sodium channel blocker used in the treatment of angina pectoris. It inhibits the late phase of the sodium current (I_{Na}), reducing myocardial intracellular sodium and calcium overload, balancing the myocardial oxygen supply and demand equation, and ultimately improving diastolicfunction (Chaitman, 2006; Mulqueen, 2015; Saad*et al.*, 2016). The drug is indicated for the treatment of chronic angina and may be usedas a monotherapy or in combination with other traditional therapies. However, the drug is oftenused in patients that failed to respond to the first-line therapies. Ranolazineis extensively metabolized in the liver, mainly by the CYP3A family andalso by CYP2D6. It use necessitate caution especially in polypharmacy involving QT interval prolonging medications. This is so because ranolazine itself prolongs the QT interval.

a ***Direct Sinus Node Inhibitor***

Elevated heart rate is often associated with heightened risk of cardiovascular crises in patients with stable ischemic heart disease. This class of drug is believed to inhibit the activities of the pacemaker of the heart or the sinoatrial node, thereby reducing the heart rate. The sinus node has some channels tagged as "funny" channels (f-channels), and these channels are the target site for drug action. The only drug in this class that has been approved for this purpose is *Ivabradine*®.

b ***Metabolic Modulation***

Agents known to inhibit fatty acid metabolism have been exploited in the treatment of ischemic heart disease. One of such drug is *Trimetazidine*®which is recommended in the European guidelines as a second-line antiaginal drug (Montalescot*et al*., 2013). The drug inhibits fatty acid metabolism while stimulating glucose metabolism (secondary action) thereby increasing cellular tolerance to ischemia.As reported by Szwed*et al.*, (2001), the addition of trimetazidine to metoprolol in a randomized controlled trial demonstrated 46% reduction in nitroglycerin consumption, 47%reduction in frequency of anginal crises as well as 15% increase in exercise tolerance. Furthermore, Ciapponi*et al.*, (2005) reported that a meta-analysis of 23 studies demonstrated trimetazidine to be a potent antianginal agent; based on its ability to reduce the frequency of the attacks and reduction in the use of organic nitrates regardless of whether or not it is administered alone or in combination with other anginal medications.

iiPotassium Channel Stimulants

A typical example of this class of drug is *nicorandil*. It is a potent vasodilator and causes vasodilation by stimulating the potassium channels. The drug is recommended inthe European guidelinesas a second-choice drug for the treatment of angina pectoris.In a randomized angina trial, nicorandilsignificantly reduced the risk of the composite primary endpoint of cardiovascular death, non-fatal myocardial infarction, or unplanned hospital admission for chest pain. This was primarily due to a reduction in the risk of angina requiring hospital admission (Jain *et al*., 2017).

Miscellaneous Agents

The following are other agents seldom used in the treatment of angina:

i. **Allopurinol/Febuxostat:** *Allopurinol* decreases the amount of uric acid produced either directly or indirectly. By inhibiting the enzyme xanthine oxidase, the production of uric acid is directly reduced. Whereas the decrease in purine synthesis by feedback inhibition of amidophosphoribosyltransferase, is the indirect approach. The exact mechanism of this anti-ischemic effect of allopurinol is unclear, but xanthine oxidase inhibition can reduce oxidative stress. Rajendra*et al.*, (2011) reported that in patients with stable coronary artery disease, 600 mg/day of allopurinol significantly improved vasodilation of the coronary vesselland completely abolished oxidative stress related with the condition. *Febuxostat*is also a potent xanthine oxidase inhibitor. Specifically, it is a non-purine selective inhibitor of this enzyme, which is actively involved in uric acid production. Thus, by potently and selectively inhibiting it, Febuxostatreduces formation of uric acid and its effect is comparatively greater to that of allopurinol. The agent significantly reduces and/or improved oxidative stress (seen in virtually all disease conditions, including angina). However, there is paucity of evidence from clinical trials to validate its use in the therapy of angina pectoris. Perhaps, on its completion, the on-going double-blind randomized trial on the therapeutic usefulness of febuxostat in CAD patients (https://clinicaltrials.gov/ct2/show/NCT01763996) may provide more details on its possible use in the therapy of angina pectoris.

ii. **Testosterone:** Evidence suggests that hormones may be good candidates for angina therapy. For example, Chou *et al.* (1996) reported testosterone to cause significant coronary artery dilatation and a corresponding increase in coronary blood flow in man. The mechanism of this action very likely relates to the physiology of ionic channels on vascular smooth muscles. According to Rosano*et al.*, (1999), testosterone improves endothelial dysfunction and may be an effective candidate for angina pectoris. Earlier studies revealed the anti-ischemic benefits of testosterone delivered transdermally (English *et al.*, 2000), intramuscularly (Jaffe, 1977), and orally (Wu and Weng, 1993). Webb *et al.*, (1999) demonstrated increased coronary artery diameter and coronary blood flow in male patients with coronary artery disease with intracoronary infusion of testosterone, confirming its coronary vasodilation effect. Till date, the therapeutic value of testosterone replacement for angina pectoris remains an important lacuna.

Novel Therapies for Angina Pectoris

i. **Therapeutic Angiogenesis:** this is a novel promising approach (still under investigation) for the management of refractory angina. It is focused on the regeneration of the dysfunctional or damaged coronary microvasculature. Despite advances in medical and revascularization management of angina, some patients remain refractory to therapy, and thus, are not suitable candidates for revascularization (Mukherjee *et al.*, 2001). In corroboration with the findings of Carmeliet*et al.*, (2000), by enhancing neovascularization, therapeutic angiogenesis, may potentially raise the threshold for ischemia and hence improve angina. Admittedly, use of angiogenic genes therapy, proteins and stem cell therapy are options with promising outcomes. However, the associated challenges includes: (1) isolation of key genes and cells, (2) identifying the relevant intracellular signalling processes, (3) development of compounds that alter genetic expression, (4) autologous extraction and isolation of effective progenitor cells (Jain *et al*., 2017), (5) identifying the optimal route and timing for delivery of active compounds/cells, (6) the presence of co-morbid conditions (diabetes, atherosclerosis, amongst others) that can inhibit angiogenic signalling (Simons, 2009) as well as (7) advanced patient age (Tirziu and Simons, 2005). Aberrant vascular proliferation in adjacent and/or distant non-targeted tissues, triggering the growth of coexisting neoplasms or the development of de novo tumours; hazards associated with viral vectors; and hazards associated with direct myocardial delivery of angiogenic factorsare the several potential complications associated with therapeutic angiogenesis.As earlier noted by Jain *et al*. (2017), there are multiple clinical trials with different agents and varied results. Some angiogenic factors that have been extensively investigated and being tried include the *Vascularendothelial growth factors* (*VEGF), fibroblast growth factor(FGF), platelet-derived growth*

factors, PDGF and the angiopeitin-1. Therefore, despite the numerous potential complications, only few significant complications have been observed in angiogenesis trials to date.

ii. **Lipoprotein Apheresis:** This process of removal of lipoprotein from the blood circulation either by filtration, adsorption or precipitation is a modern effective method for angina therapy, particularly those related to resistant hypercholesterolemia.This procedure is made possible using pharmacotherapeutic agents. This is so whether it is used before (A*lirocumab*, *Evolocumab*), with the LA methods (using heparin and citrates)or post apheresis procedure to reduce concomitant LA(Lomitapide, a microsomal transfer protein inhibitor) (Ulrich 2018). As reported by Khan (2016), lipoprotein apheresis resulted in significant improvements compared to sham therapy in patients with refractory angina who had elevated lipoprotein Lp(a). The author reported a study of randomized 20 patients with refractory angina and Lp(a) levels >500mg/L to weekly lipoprotein apheresis or sham treatments over a 3-month period with a 1-month washout period, and reported a significant increase in myocardial perfusion reserve, improved carotid wall volume and dispensability after apheresis, improved exercise capacity, angina as well as improved quality of life (Khan, 2016).This is the first evidence that shows a link between the reduction of lipoproteins and improved circumstances in patients with refractory angina.

iii. **Other Novel Therapies:** other novel therapies for angina still under investigation include coronary sinus reduction (Banai*et al*., 2007), external counter-pulsation - ECP (Arora *et al.*, 1999; Soran*et al.*, 2006),spinal cord stimulation – SCS(Mannheimer*et al*., 1996) and trans-myocardial laser revascularization – TMLR (Frazier *et al.*, 1999).

III. CONCLUSION

The goal of pharmacotherapy for angina is to correctthe mismatch between perfusion and workload. Till date, the beta-adrenergic receptor blockersare the most studied as well as the only antianginal drugs with clear evidence for reduction in mortality. However, this is limited to those with recent myocardial infarction or severe systolic left-ventricular dysfunction. Like the beta blockers, the calcium channel inhibitors and nitrates are also mostlystudied and reliable for therapy of angina. They provide symptomatic relief and are better tolerated than the beta blocking drugs. The issue with these classes of drugs is that they often times do not seem to reduce frequency of mortality. Despite the applauded advances in medical therapy and revascularization techniques, poorly controlled angina still poses serious concern in a greater number of patients with ischemic heart disease. Most recent strategies target cellular processes to alter metabolism or promote angiogenesis, and thus result in a sustainable benefit that can improve not just the clinical manifestations of the disease, but also the patient's quality of life and reduction in mortality. The on-going researches in this field are promising with keen anticipation for tremendous breakthroughs.

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