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Original Article

Novel Drugs Approach in Treatment of Angina

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ABSTRACT

Angina Pectoris is a common symptom of ischemic heart disease. In 1772 according to William Heberden Angina is characterized by the painful and disagreeable sensation that occurs in the breast during walking. This is caused as the result of the myocardial oxygen supply and demand imbalance. The oxygen demand increases due to tachycardia, hypertension, left ventricular hypertrophy. Tissue ischemia leads to series of metabolic changes which includes elevated intracellular lactate production and acidification that produces anginal symptoms. Besides coronary obstructive diseases, it also occurs following coronary vasospasm and with coronary microvascular diseases. Vasospastic angina also known as Prinzmetal's angina results due to vasoreactivity of epicardial coronary arteries. Microvascular angina is also referred as Syndrome X resulting from constriction of coronary microvasculature. In 2-4% of adult population silent ischemia occurs in void of anginal manifestations.This review article discusses current and novel antianginal strategies under development. It focuses on the molecular mechanisms that may complement traditional therapies. The understanding of the clinical trials and endpoints is important in the evaluation of the new antianginal agents. Primary endpoints comprise exercise-based variables. Secondary endpoints comprise of amount of nitrate consumption and self-reporting of anginal frequency. Anti-anginal drugs are the pharmacological agents that reduce the frequency and severity of the anginal episodes.

Keywords: Angina Pectoris, myocardial oxygen, Prinzmetal's angina, tachycardia, hypertension, left ventricular hypertrophy

INTRODUCTION

Vital healthcare:

In US Coronary Artery Disease is the foremost cause of mortality, which accounts 1 in 4.8 deaths. The American Health Association (AHA) 2002 consensus guidelines assessed 6 million peoples in US experience Anginal signs. According to AHA 2010 data the prevalence of angina has estimated around 9.8 million. Advancement in ageing is a significant risk factor in development of angina. Arterial Revascularization study has shown that the 83% of patients who undergone post-percutaneous coronary angioplasty requires anti-anginal drugs for the 1-month duration. Traditional class of anti-anginal medications includes β-blockers, nitrates and calcium channel blockers. Their uses are confined due to its adverse hemodynamic effects. Due to the negative inotropic effects and severe conduction abnormalities the usage of β-blockers are limited. β-blockers are contraindicated in asthmatic conditions. In CCBs particularly non-dihydropyridines possess transduction abnormalities, negative inotropic activity and peripheral edema. Systemic Vasodilation and severe headache are caused by nitrates and its prolonged use leads to tachyphylaxis. Primarily anti-anginal agents relieve the signs of angina and contradictly leads to commence ischemia leads to cardiac injury. The optimal anti-anginal drug should have anti-ischemic properties and lower haemodynamic effects.

Standard treatment:

Heart rate lowering agents:

The anti-anginal drugs are conventionally classified as heart rate lowering agents and vasodilators. The heart rate lowering agents decreases myocardial oxygen demand and increases myocardial perfusion. In Goteborg a city located in Sweden has conducted Multifactor Primary Prevention Trial and discovered

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that threefold increase of total mortality in individuals of heart rate greater than 90 BPM compared to individuals who have less than 60 BPM. After the study was conducted of having 25,000 individuals for 25 years shown that the heart rate has the direct relationship with the total mortality.

Calcium channel blockers:

CCBs are classified as phenylalkylamines (Verapamil), dihydropyridines (amlodipine, felodipine, nicardipine, nimodipine), benzothiazepine (diltiazem). These agents block the L-type calcium channels located in peripheral vascular bed which leads to decreased systemic arterial pressure and low cardiac afterload. The oxygen supply is enhanced through the vasodilation. In usage of non-dihydropyridines leads to negative chronotropic and inotropic response and this results in LV contractility and reduced heartrate. Due to their negative inotropic effects, it is contraindicated in heart failure.

Nitrates:

It was launched in the year 1867, which relaxes the coronary arteries, venous capacitance vessels result in reduced myocardial oxygen demand. It is a direct endothelium -independent vasodilator. The combination of CCBs and Nitrates produces Synergistic effect. The continuous use of nitrates leads to tolerance

β-blockers:

They are sympatholytic agents launched in 1962. They block the β-adrenergic receptors and inhibit the action of epinephrine and norepinephrine. It leads to the negative inotropic, chronotropic and dromotropic response. The present uses include hypertension, IHD, and heart failure. It is used as a first line drug to treat stable angina. The side effects include hypotension, bradycardia, AV conduction abnormalities. Since it blocks the β-1 adrenergic receptor leads to increased bronchospasm so it is contraindicated in asthmatic patients.

Active research targets:

As characterized above the conventional anti-anginal medications act by heartrate reduction and coronary vasodilation. Due to their hemodynamic effect the use such medications are constrained. The use of CCBs and -blockers leads to hypotension and decreased heart rate.

The latest research in the advancement of anti-anginal drugs are

*To establish a method that use novel mechanism of action

*Build medications with lowered hemodynamic effects

*To exhibit mortality benefit when it is included in standard therapy.

*To conduct clinical trials emphasized in combination therapy.

Biomedical rationale:

Late Na^+current inhibition:

Activation of voltage-gated sodium channels leads to upstroke in Phase 0 of ventricular depolarization which leads to inward Na^+ current. During this phase sodium channels open, allowing sodium ions rush into cell. As the action potential reaches its peak, sodium channels undergo inactivation, closing and preventing further Na^+ influx. A small fraction of sodium channels fails to inactivate property, remaining open and allowing a slow, sustained Na^+ influx which leads to activation of late Na^+current. So, it allows sodium ions to continue entering the cell, even after the initial upstroke phase. So, it prolongs the depolarization phase, increasing action potential duration. Prolonged influx Na^+ncreases intracellular Na^+ concentrations which triggers the influx of Ca^{2+} ions through sodium-calcium exchanger (NCX) results in calcium overload. The sustained sodium and calcium influx leads to prolonged action potential duration. Ranolazine is a is a US approved potent inhibitor of late inward sodium current.

Cardiac bioenergetics and metabolic control mechanisms:

Partial fatty acid oxidation inhibitor is a category of medication used in angina. They partially inhibit the fatty acid oxidation pathway and reducing the amount of energy produced from fatty acid breakdown. Fatty acid metabolism accounts 60-70% energy of cardiomyocytes. Glucose serves as secondary origin of energy for myocardium. Glucose oxidation provides 10-20% of ATP production. In case of angina

* Glucose oxidation is increased.
* Citric acid cycle is impaired and leads to reduced generation of NADH and FADH2
*Decreased activity of election transport chain results in reduced ATP production.
The glucose oxidation leads to the production of more ATP and reduces the myocardial oxygen demand. It produces less amount of lactate when compared to fatty acid oxidation, which helps to reduce lactate accumulation and acidosis.

Sinoatrial f current inhibition:

The f channels were also known as hyperpolarization-activated cyclic nucleotide-gated (HCN) channels which was discovered in 1970. f current inhibitors are new class of drug that inhibits f channel located in SA node which promote bradycardia. These channels are activated by influx of sodium and potassium ions into cell. The I_f current was built by the ionic influx resulting in increased depolarization and heart rate. Ivabradine is a selective f channel inhibitor used as anti-anginal medication.

Rho kinase inhibition:

Rho kinase is activated by binding of GTP to the RhoA subunit which in turn leads to increased myosin light chain phosphorylation, resulting in vasoconstriction leads to reduced blood flow to myocardium. Rho activation also results in inflammation and cardiac remodelling by promoting cardiac fibrosis and hypertrophy. So, the GDP binding to Rho kinase inhibits its activity, reducing the ability to phosphorylate and activate downstream targets.

Targeted gene therapy for growth factor activation:

Gene therapy is an emerged as a promising therapeutic strategy for managing angina. Growth factors, such as vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF) promote angiogenesis. So, it improves the blood flow to myocardium, alleviating angina symptoms. Plasmid based gene therapy involves use of plasmids to deliver growth factor genes to cardiac cells. Viral vector-based gene therapy involves the use of viral vectors, such as adenovirus or adeno-associated virus, to deliver growth factor genes to cardiac cells. Adeno virus has the affinity to bind with several tissues its use is restricted. Adeno virus type 5 shows cardiac selectivity than other strains used earlier. The main demerit is the high immunogenic response which leads to severe inflammation and drastic myocarditis. Stem cell-based gene therapy involves the use of stem cells to deliver growth factor gene to cardiac cells.

Ranolazine:

Ranolazine is a derivative of piperazine and shares similarities with trimetazidine. It was originally believed to function by enhancing glucose metabolism in heart cells. But the drug mainly works by blocking the late sodium (Na^+), which helps to improve heart function and manage angina symptoms. When it is taken in doses ranging from 500 to 1500 mg per day, patients experienced better exercise performance and reduction in ST-segment depression. Ranolazine in combination with atenolol, amlodipine, or diltiazem lowered the frequency of angina attacks. Early studies raised concerns about QT interval prolongation (by 6-8 milliseconds). However, the MERLIN trial, which is involved 6,560 patients with acute coronary syndrome, found no increase in cardiovascular mortality compared to placebo. The trial also confirmed a notable reduction in ischemia, reinforcing its role in chronic angina treatment. Significantly, no additional risk of arrhythmia was observed, proving its safety profile. The drug's side effects are usually mild to moderate and often appear within the first two weeks of use. Common symptoms include dizziness, nausea and constipation. Ranolazine results in the prolonged QT interval by blocking the potassium channels leads to risk of dangerous arrhythmias.

Ivabradine:

Ivabradine is the first drug that preferentially block the I_f current in the heart. It slows the heart rate without affecting blood pressure or heart muscle contraction strength. The recommended dose is 2.5-10 mg twice daily (b.i.d). In the INITIATIVE trial 7.5 mg of twice-daily dose worked just as well as atenolol in reducing angina and improving blood flow. BEAUTIFUL study was conducted on 10,000 patients which didn't significantly lower death rates after a heart attack, it helped patients with heart rates above 70 BPM by reducing heart related complications. The

side effects include bradycardia, visual disturbances like "flashing lights" known as phosphenes occur in up to 16% of users. Other side effects include headache, dizziness and arrhythmias. 21% of patients stop taking Ivabradine because of side effects, which is similar to amlodipine (22%) but slightly higher than atenolol (16%).

Trimetazidine:

Trimetazidine acts as a metabolic modulator, enhancing glucose utilization in heart cells. It works by partially inhibiting fatty acid oxidation (pFOx inhibition). Trimetazidine affects the enzyme 3-ketoacyl CoA thiolate, which is involved in fatty acid breakdown, through the exact process is not fully understood. It was found to be effective in combination therapy with other heart medications. The Poland II study had confirmed that it improves angina symptoms and ST-segment changes in patients taking metoprolol. A 2005 study review validated its role as a reliable anti-anginal treatment. A review of 12 randomized trials demonstrated that it reduces angina episodes and decreases the oxygen demand during exercise. Research from Cochrane Collaboration indicates Trimetazidine helps to decrease the frequency of angina attacks and improves ST-segment changes in patients with stable angina. Unlike some other heart medications, it does not impact heart contraction strength (inotropic effect) or cause blood vessel dilation (vasodilation). Perhexiline, a similar metabolic agent introduced in the 1970, also inhibits pFOx but was largely discontinued due Oliver toxicity and nerve damage. Despite being withdrawn in the US, perhexiline is still used in Australia, New Zealand and parts of Europe. The common side effects include gastrointestinal disturbance, dizziness and headache. The latest review of European Medicines Agency mentioned that the Trimetozine leads to movement disorders similar to Parkinsonian symptoms. These side effects are rare, occurring in about 0.36 cases per 100,000 patient each year. The symptoms usually go away within a few weeks or months after stopping the medication.

Nicorandil:

Nicorandil is an anti-anginal medication used primarily in Europe and Japan. It has two main actions that is it acts as nitrates, leading to widening of blood vessels (vasodilation) in heart and activates ATP-sensitive K^+ (K_{ATP}) channels, which hello to relax arteries by allowing potassium to flow out of cells. These K^+ channels are mostly inactive under normal conditions but open when energy (ATP) levels drop. A study on 5,126 angina patients with heart disease risk factors compared to nicorandil versus placebo, along with standard angina treatment resulted in 17% reduction of heart attack, cardiovascular death and hospitalizations in nicorandil groups. The common side effects include headaches (seen more than 10% of patients), dizziness. In rare cases (less than 0.01% of patients), mucosal ulcers may develop.

Hydroxyfasudil/Fasudil:

Hydroxyfasudil is a medication used in Japan to treat vasospasms, particularly those affecting the CNS. It is commonly prescribed for vasospasms following subarachnoid haemorrhage (bleeding in the brain). Hydroxyfasudil works by blocking Rho-kinase, an enzyme that causes blood vessels to contract leads to relaxation of blood vessels. Research shows that hydroxyfasudil can increase exercise tolerance in heart patients. It has been found to reduce ST-segment depression (a sign of poor blood supply to the hearty during exertion) and improve the coronary blood flow. The hydroxyfasudil has been tested in patients with vasospastic angina by injecting it directly into heart arteries (intracoronary infusion) resulted in inhibition of acetylcholine-induced coronary vasospasm. The intravenous use of hydroxyfasudil in individuals with subarachnoid haemorrhage is resulted in the incidence of intracranial haemorrhage. The common side effect is headache.

Growth factor gene therapy:

Growth factor gene therapy is a technique that aims to stimulate the formation of new blood vessels (angiogenesis) in patients with heart disease. This is done by delivering specific growth factors, such as Fibroblast Growth Factor (FGF) and Vascular Endothelial Growth Factor (VEGF), into the heart.

1. **Fibroblast Growth Factor (FGF) Therapy – AGENT Trials**

AGENT-1 trial was involved with 79 patients with severe angina and exihibited that catheter-based Ad5FGF injections leading to increased cardiac uptake which were technically feasible. AGENT-2 Trial was conducted in 52 patients in a randomized, placebo-controlled study resulted in enhanced perfusion imaging when analysed to the baseline. AGENT-3 & AGENT-4 Trials was involved with large-scale Phase IIb/III trials conducted in Europe, Latin America, and Canada and their goal was to increase exercise time and reduce angina symptoms however, the results did not show significant improvement compared to placebo. The side effects include thrombocytopenia and increased levels of liver enzymes.

2. Vascular Endothelial Growth Factor (VEGF) Therapy

VEGF gene therapy was tested to see if it could improve blood supply to the heart through direct intramyocardial injections. Phase II Trial (Stewart et al.) was involved with 67 patients demonstrated an increase in exercise time and a reduction in ST-segment depression (a sign of improved blood flow). Other Phase II Trial (Euroinject One Trial) was conducted in 80 patients who received intramyocardial VEGF Plasmid through Percutaneous route of administration. At 3 months, perfusion imaging and heart function were not significantly better than in placebo-treated patients.

Beanlands and Co-workers examined VEGF plasmid injections for patients undergoing LAD revascularization and the patients received VEGF plus L-arginine or placebo for 3 months resulted in VEGF and L-arginine improved the heart wall motion and contractility. When it is injected with G-CSF leads to mobilization of bone marrow stem cells.

Challenges in development:

Like any cutting-edge medical breakthrough, new drug classes come with uncertainties—especially in how different populations might respond and what hidden risks might emerge.

I_f Inhibitors:

The Race to Tame the Heart's Rhythm

Scientists have been on a 30-year quest to develop I_f inhibitors that slow heart rate without causing major side effects. Earlier frontrunners, Zatebradine and ZD7288, faced a hard stop due to unwanted side effects. Zatebradine is not only blocked heart channels but also messed with vision by interfering with Ca^{2+} and K^{+} channels. ZD7288 is Crossed into the brain, affecting the substantia nigra, hippocampus, and thalamus—areas linked to movement, memory, and alertness. Ivabradine is a newer, smarter generation of I_f blockers that avoids most of the pitfalls of its predecessors. However, while current studies look promising, long-term safety checks remain crucial.

Fasudil:

Fasudil packs a serious punch in lowering blood pressure, making it a superstar candidate for hypertension rather than angina. This drug targets Rho kinases, which control nerve remodelling and synaptic connections a fascinating, but risky, intersection between the heart and brain. Animal studies suggest that tweaking Rho kinases could influence neurodegenerative diseases. Short-term use (2 weeks) in humans seems safe and well-tolerated. The long-term clinical trials are important to predict the incidences of nervous diseases.

Metabolic Regulators & Mitochondrial Function:

Drugs, like Trimetazidine, operate at the heart of the cell's energy production—mitochondria. These tiny powerhouses are insanely complex, hosting over 3000 different proteins, yet science has only mapped 10% of them. This uncharted territory makes it difficult to predict how a drug will truly behave in the long-term use. Mitochondria play a role in neurodegenerative diseases, metabolism, and cell division. Perhexiline, a mitochondrial CPT-1 inhibitor, has been used outside the U.S. for 40 years. Studies suggest that the biggest problem with mitochondrial inhibitors is phospholipidosis (a buildup of phospholipids in cells) and this happens due to slow drug clearance, leading to toxic drug accumulation. Trimetazidine, a weaker mitochondrial regulator, may be safer than CPT-1 inhibitors.

Intake and monitoring protocol:

These new medications for angina are taken orally twice daily. The initial dose may be lower for those over 75. Experts suggest checking progress within 2-4 weeks after starting or adjusting the treatment to see if it's working and to spot any side effects. For those using ivabradine, doctors should watch for slow heart rate symptoms like dizziness, tiredness, or low blood pressure if these issues continue, the medication should be stopped. Ranolazine users need heart monitoring through ECGs to check for heartbeat irregularities. Elderly individuals on trimetazidine be observed for signs of movement disorders; if these appear, the drug must be discontinued. NICE guidelines recommend to monitor 2-4 weeks of taking or changing any anti-anginal medications to supervise the adverse drug reactions.

CONCLUSION: A range of therapies exists for managing angina, with β-blockers, Ca^{2+}channel blockers and nitrates serving as foundational treatments for years. The introduction of Ranolazine has expanded the landscape of available solutions, offering a fresh mecahnaism of action. The other novel medications include Rho kinase inhibitors, I_f channel modulators, pFOX suppressors and gene based therapies showing potential in enhancing patient outcomes. Some groundbreaking treatments are already making an impact globally, while others remain in experimental phases, awaiting further validation. While genetic interventions hold great promise, overcoming technical complexities remains a key challenge before widespread option. Extended research is vital to fully grasp the long-term impact and sustainability of these novel medications

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