Pak Heart J

NON-CONVENTIONAL APPROACHES FOR THE MANAGEMENT OF ANGINA

Qudsia Basri[1], Afsha Siddiq[2], Sadia Ghousia Baig[3]

[1-3]Department of Pharmacology, University of Karachi, Karachi, Pakistan.

Address for Correspondence:

Afshan Siddiq

Department of Pharmacology, University of Karachi, Karachi, Pakistan.

Emails: afshanpharma@gmail.com

Date Received: January 12, 2019

Date Revised: May 03, 2019

Date Accepted: June 04, 2019

Contribution

QB conceived the idea and designed the review. AS and SGB did litrature and helped in final drafting of the review. All authors contributed equally to the submitted manuscript.

All authors declared no conflict of interest.

This article may be cited as: Basri Q, Siddiq A, Baig SG. A review of non-conventional approaches for the management of angina. Pak Heart J 2019; 52 (03):193-9

ABSTRACT

Angina is usually classified as a symptom of an underlying cardiovascular disease which is one of the most common disorder that is affecting the human life now a days. It is presented as a throbbing chest pain that can radiate to left arm and back due to ischemia of major vessel supplying blood to heart. Several drug classes and their combination has long been used to treat angina for e.g. Nitrates, Nitrites, Calcium channel blockers, Beta blockers and sodium channel blockers to improve the demand vs supply ratio of oxygen so that the heart muscles can perform its function effectively. The increasing prevalence of disease and resulting resistance to conventional therapy has urged scientists to find other ways that can help in the management of this disease. Cardiovascular and consequently angina is thus the focus of many studies. In this review a number of strategies and their associated mechanisms has been discussed which include Life style modification, Yoga, Acupuncture therapy, Herbal treatment , L-arginine, L-carnitine, Omega 3 fatty acids, Gene therapy, Cell therapy, Chinese Medicine, and Interventions like Spinal cord Stimulation, Percutaneous coronary intervention, Enhance external counter pulsation, Extracorporeal shockwave myocardial revascularization, Transmyocardial laser revascularization, transcutaneous electrical nerve stimulation, percutaneous retrograde coronary sinus perfusion. Coronary sinus perfusion, Coronary sinus reducer, Video thoracoscopic sympathectomy (VTSY) may help in short term and long-term management of angina.

Key Words: Angina, Acupuncture, Cell Therapy, Coronary Interventions, Gene Therapy, Life style modification, Yoga

INTRODUCTION

Angina is a common condition that may arise due to the underlying Ischemic heart disease or coronary artery disease and it is the main cause of reducing the life's quality and leading to death in many developed countries. The major cause of angina is an altered balance between the demand and supply of oxygen to heart.[1]The heart is responsible to provide oxygen and nutrients to whole body and for this a considerable amount of energy in the form of ATP is required. An adequate oxygen supply ensures that the heart can generate enough ATP to maintain its function. The demand of oxygen can be increase by various causes such as hypertrophy of cardiac muscles, fluctuation in heart rate, increase afterload, high systolic or diastolic pressure, positive ionotropic effects and increase tension in cardiac walls. If the demand is not fulfilled it can lead to angina. It can aggravate with exercise and emotional stress especially in patient who have a blockade in their major coronary artery, further the flow in coronary artery also depends on the capacity of blood to carry oxygen and patients Hemoglobin level. [2]

The major factor that can lead to ischemia of myocardium is acute coronary syndrome and treatment of this underlying cause can greatly improve the cardiovascular functions of individual. Mental stress is also a contributing factor to pathogenesis of angina due to increased oxidative stress on myocardial wall and can subsequently cause ischemia. Many therapies that can reduce stress ca also be helpful in angina.[4] The presentation of chest pain in various hospital administration is related to coronary dysfunction in almost 15 % of the patients and the percentage can increase further in cardiac care centers and emergency wards.[5] A timely and correct diagnosis is particularly important to improve the survival rate of patients suffering from coronary heart disease.[6]

Stable angina that is provoked by exertion and exercise, can be relieved by nitroglycerin (sublingual) or rest but health negligence converts it into chronic angina.[7] Chronic angina is a big challenge to the society now a days that is impairing the quality of life and its proportion is rising day by day due to increasing industrialization and resulting increase in prevalence of coronary artery disease, frequent use of medicinal agents, and rising population of obese people that is why new therapeutic strategies are continuously being designed for the treatment of angina one such approach is a new drug Ranolazine, a late sodium channel blocker.[8]

Microvascular Angina is a type of angina that is a big challenge for physicians both in term of diagnosis and treatment strategies. It is a condition in which the cause of angina pain is not associated with disease of coronary artery blockage rather it is associated with an abnormal function of coronary microvasculature that leads to an imbalance in blood supply and distribution to heart.[9]

Conventional Treatment

Calcium Channel blockers, Beta blockers and Nitrates are most commonly used drug for angina, and newer drugs like late sodium channel blocker ranolazine and Ivarabine are second line drug for angina. Anti-inflammatory agent canakinumab is a new investigational drug that is being studied for the treatment of angina as inflammation also has a role in the progression of angina and other coronary diseases.[10] Aspirin and statins also have role in controlling various aspect of coronary disease.[11] Conventional drugs along with modification of life style and Percutaneous coronary revascularization are usually suggested to improve the survival and quality of life.[12] Table 1 summarize some conventional agent for controlling angina and the side effect profile of these agents as summarized in table 1.

Table 1: Conventional Treatment of Angina and its Associated Risk

DRUG	MECHANISM OF ACTION	SIDE EFFECTS AND RISK
Nitrates	Provide Nitrous oxide required for vascular dilation thud improve oxygen supply to heart	It may cause headache, dizziness, nausea, flushing and severe hypotension. Use with other vasodilator like Phosphodiesterase inhibitors may worsen the side effects.
Beta Blockers	Block B1 receptor mediated stimulation of heart thus reduce cardiac load and oxygen demand	A few side effects are associated with beta blockers in which sexual dysfunction, stomach upset, and dry mouth are common. It may worsen asthma if non-selective, and is contraindicated in diabetes and acute heart failure
Calcium Channel Blockers	Block L-type Calcium channels thus produce vascular dilation and also reduce workload on heart by decreasing its contractility	Gingival hyperplasia, dizziness and hypotension are most common side effects with calcium channel - blocker. It is also contraindicated in second and third degree heart block.
Ranolazine	New Drug that Block late sodium channels and reduce metabolic load of heart	It can cause spinning sensation, GI disturbance and QT prolongation and may interact with cytochrome 3A4 enzyme inhibitors and inducer

Novel Approaches

Refractory angina, a serious condition cause by progressive coronary artery disorder and is a big challenge for physicians now a dayand in majority of cases the management strategies to improve the quality of survival and decreasing the chances of mortality is individualized for the patient according to the expertise of health care professionals and available resources. A number of novel therapeutic methods such as angiogenesis by therapeutic means, modulation of metabolism, and innovative techniques of interventions has been suggested in several studies.[13]

Some studies show that older people are more responsive to surgical techniques as compare to the commonly prescribed medication therapies for unstable angina and non-ST elevation myocardial elevation.[14]

Stellate ganglionic blockade (SGB), implantation of coronary sinus reducer (CSR), Cardiac Rehabilitation, and cognitive behavioral therapy (CBT) are some other means to control angina. Behavioral and psychological therapies are particularly important as the angina itself cause depression and anxiety in patients. Number of sessions areregularly planned with the patient and appropriate counselling is provided to the patients so that they can understand their disease that will aidin decreasing the stress level and helps in the management of pain to improve the sleep time and its quality. Furthermore, rehabilitation phenomenon can also help to improve aerobic and other functional capabilities.[15]

Some other non-conservative approaches for the management of angina are spinal cord stimulation, percutaneous laser revascularization, Enhancement of external counter pulsation (EECP), combination of opioids with analgesics, cell therapy and transcutaneous electrical nerve stimulation.[16]

In the coming paragraphs we will discuss some of these approaches that can be used for the management of angina safely and effectively.

Life style modification

Several non-pharmacological approaches by simply having moderate changes in life style has always been the focus of researchers for the management of stable angina to prevent worsening of disease and avoid the untoward effects of drug therapy. A major risk factor to coronary artery disease is smoking thus discouraging the use of smoking by counselling of patient in angina patients can be beneficial. Obese patients are more prone to disease worsening so weight management with the help of diet and exercise can also be beneficial in angina.[17]

Music therapy can produce a relaxing effect and thus provide relieve in angina and other ischemic disease, a randomized trial performed to evaluate the effect of music therapy on heart function, chest pain and discomfort, and the resulting improvement in the symptoms unlocked a new path for the management of angina.[18]

Co-Enzyme Q10:

Some trials also suggest that Co enzyme q10 also found to be effective in the management of angina and ischemic heart disease with minimum side effect. The effect is produced by providing enough energy to heart for its functions.[19]

Acupuncture therapy

In a study performed in china it was found that the acupuncture therapy can be beneficial in the improvement of angina symptoms by relieving pain, it improves the ECG changes and decrease the progression towards myocardial attack. In this study the groups were divided into 1) Control Using Conventional Therapy-Nitrates, 2) Acupuncture group and 3) A group receiving both (conventional and acupuncture therapy). The last group Shows better improvement as compare to other two while acupuncture group shows a delay in action as compare to conventional, this leads to the conclusion that acupuncture cannot be use in acute cases but can be beneficial instable angina.[20] In one trial the effect produced by acupuncture therapy and resulting electro cardio graphic changes were better than commonly use anti anginaldrugs, but more trials are required forvalidating these results.[21]

YOGA

Smoking is one of the reasonfor many cardiovascular diseases, renal diseases and hypertension. Exercise can help in reducing the craving for smoking and Yoga has profound benefit in smoking cessation. Other health benefits of Yoga are improvement in mood and reduction in anxiety. It is also suggested that inclusion of YOGA in daily activities is helpful to improve heart function by decreasing heart rate and Arterial pressure, it also improve pulmonary function and causes smooth muscle relaxation.[22]

L- Arginine

One of the major goal of anti-angina therapy is to improve the supply of oxygen to heart muscles by dilating the vessels that is supplying blood to heart. Nitrous oxide is a potent vasodilator present endogenously and L-arginine has found to have role in increasing the production of nitrous oxide in the body. Oral use of L- Arginine in experimental animals is found to be very effective in the treatment of angina. Other mechanism involve in its action may includereductionof oxidative stress in the body, decrease progression of atherosclerosis and inhibition of platelet plug formation. L- Arginine can also improve the lipid profile of the patient and prevent myocardial damage due to peroxidation.[23]

In another approach the development of vessel via mechanism like gene therapy, cell therapy use of growth factors were tried in some studies and were suggested as future goals for management of chronic stable angina. But further trials are required to establish a valid treatment plans.[24]

Cell Therapy

Therapy with CD 34 positive receptor as an autologous cell therapy can also improve angina and exercise tolerance.[25] The therapy promotes angiogenesis by enhancing microcirculation at low doses but at high dose the response was not as effective as a slow dose therapy due to rise in density of cell from high dose The therapy was also found safe during trials.[26]

Omega 3 Fatty Acid

Omega 3 Fatty acids also has cardio protective role, which is evident by decrease in level of cardiac biomarker in several trials

after therapy with omega 3 fatty acid. Its beneficial role in myocardial infarction also support its use in angina.[27]

L- Carnitine

It can help in angina by providing energy required by myocardium for its function. It increases the level of fatty acid and also promote oxidation of glucose by which it provides heart with its substrate for oxidative metabolism. It also Prevent the accumulation of ester of fatty acid further protecting heart muscles.[28]

Herbal and Chinese Medicines

Hawthorn plant belong to family Rosacea and specie Crategus is long been use as an herbal remedy for diseases of cardiac origin. Research shows that the hydro alcoholic extract obtained from the flowers and leaves of this plant has protective action on vessels and heart which suggest the use of this herb in vascular and occlusive disease of coronary artery as a preventive and therapeutic measure.[29]

Shexiang Baoxin Pill is another Chinese medication that can be advantageous in management of cardiovascular disease safely and effectively by enhancing revascularization.[30]

Huoxue Huayuis a traditional Chinese medication that is use for coronary disorders and trials shows that it can improve revascularization and prevent redevelopment of stenosis by promoting circulation and preventing the immobility of blood.[31]

Injection of safflower yellow can improve the symptom of unstable angina by reducing myocardial damage and improve the effectiveness of therapy when given with conventional agent. It also improves angina signs in ECG when given without addition to any other agent.[32]

Other methods of neuronal modulation, invasive and noninvasive revascularization procedures may also provide benefit in angina.

Spinal cord Stimulation

Studies shows that Spinal cord stimulation provides long term benefits by alleviating the symptoms in Patients who are not responding to conventional therapies and revascularization. According to European Angina Registry Link spinal cord stimulation device can help in improving angina progression and decreased nitrate dependence.[33] It decreases the pain that has neuronal origin, the possible mechanism involve in this might be the blood stream reallocation, by reducing sympathetic nervous system activity and by mechanism related to endorphin production. It provides similar response to that of CAB-G and percutaneous myocardial revascularization.[34] This technique involves the placement of electrodes into the epidural space and the placement of electrode at the correct place is critical for the efficacy of this procedure. As the area that is controlling the heart rhythm and function must be stimulated for an ideal response to this therapy.[35]

Percutaneous coronary intervention

A study to analyze the effect of exercise in patients after percutaneous coronary intervention shown improvement in various angina associated effects such as ST segment depression, Recurring angina pectoris and better tolerance for exercise.[36]

Enhanced external counter pulsation

Enhance external counter pulsation is a technique to control the worsening of angina by applying pressure on lower extremities during diastole and systole respectively, the changes in electrocardiogram of the patient is recorded as a change in R wave. It enhances the function of collateral circulation, decrease atherosclerosis and also increase the venous return thus increases the supply of blood and oxygen to the heart. It has an additional advantage of being non-invasive yet safe and effective. It is effective in reducing the perfusion abnormalities and stress associated with angina.[37]

The main mechanism of action by which it improves angina is increased release of vasodilator agent such as 6-KetoProstaglandin and nitric oxide, it also decreases vasoconstrictive mediator such as C- reactive protein, endothelin 1 and tumor necrosis factor and it is a recommended choice of treatment by American heart association and American college of cardiology for management of refractory angina.[38]

Extracorporeal shockwave myocardial revascularization (ESMR)

In this technique shock wave of small magnitude directed towards heart tissue that has ischemia. The stress cause by waves leads to conversion of hydrogen peroxide and L-arginine into nitrous oxide. Release of vascular endothelial growth factor is another mechanism by which it improves vascular function, neo vascularization and improve the survival time and quality of life.[39]

Trans myocardial laser revascularization

In this techniques channels are created across the myocardial wall with the help of a laser (Xenonmonochloride or carbon dioxide) which promote angiogenesis. It also decreases the sensation of pain by abolishing the response of nerve fibers. It can be use with other techniques like bypass grafting of coronary artery to increase efficacy and safety. Other technique related to it are use of catheter and direct revascularization of myocardium and TMLR also have more benefits and survival rate as compare to percutaneous myocardial laser revascularization.[40]

Transcutaneous electrical nerve stimulation (TENS)

The application of electrical current having low voltage can help to reduce angina symptom and associated pain. There are many mechanisms proposed for this behavior such as increase in concentration of endorphin or stimulation of opioid pathway. The response found was good enough to produce tolerance to most of the symptoms and improved performance of the patient metabolic activities.[41]

TENS is a technique to improve the flow in vessels and supplying sufficient blood to heart for performing its function. As the name indicate that this method involves the stimulation of neurons, it can reduce the ischemia in patients who are non-responsive to pharmacological therapy. The overall effect is decrease in frequency of angina pain and improve presentation of electrocardiogrambut the exact mechanism to improve the disease condition need more research to be evaluated.[42]

Another major contributing factor to coronary disease is hypertension that can lead to multi organ damage.[43]

The use of transcutaneous electrical nerve stimulation also helps in improvement of resistant hypertension by blocking the afferent pathway.[44]

Percutaneous retrograde coronary sinus perfusion

This technique is being used to deliver autologous bone marrow derived mononuclear cells (ABMMC) to the heart, for transplantation of stem cells. The resulting improvement in myocardial function may be due to the improved contraction, increased coronary perfusion and increased angiogenesis as the bone marrow cells help to promote differentiation of cardiac myocytes and smooth muscle cells and promote angiogenesis All these mechanisms together improve the function of left ventricles by reducing end diastolic volume and can be beneficial in acute as well as chronic angina and even heart failure.[45]

Coronary sinus reducer

The use of a sinus reducer device is a recent approach to treat angina. It involves the use of an elastic balloon stunt that create a pressure on coronary veins, this will improve the coronary collateral circulation and improve the blood supply to the region of ischemia.[46]

This belief of altering the venous pressure and improving angina symptom was first used by Beck and Leighniger in 1954 by ligation of coronary sinus invasively. The back pressure produced by sinus reduction cause dilation of the endocardial vessels which further improve the flow and redistribution of blood within the myocardium and therefore effective in decreasing the symptoms of angina. During a trial conducted to establish the efficacy of this procedure it was found that the patient treated with coronary sinus reducer has a significant improvement in their cardiac performance according to Canadian cardiovascular classification.[47]

The possible mechanism might be an elevation in back pressure that leads to the improvement in flow between the affected and non-affected areas of myocardium and increase in flow to oxygen deprived myocardial tissues.[48]

Another method that is related to this mechanism is coronary sinus occlusion, the major effect produce by this method is not only due to elevation of pressure in coronary sinus but other mechanisms like removal of toxin and noxious metabolite, microvasculature opening and regeneration may also be responsible for this effect.[49]

Video Thoracoscopic sympathectomy (VTSY)

Blocking of sympathetic system at the level of thoracic cavity is also an approach for the management of angina by improving the supply of oxygen to heart and decreasing cardiac workload due to sympathetic inhibition. The procedure involves the insertion of ports after general anesthesia to the thoracic region and cause gangleoctomy in that region.[50] Alist of non-conventional approaches for angina treatment is given in Table 2.

Table 2: Non-Conventional Treatment Strategies for Angina

Revascularization Procedures		Non-Pharmacological Approaches	Medicinal Agents	Other Therapies
Stellate Ganglionic Blockade	Percutaneous Coronary Intervention	Cardiac Rehabilitation	Combination of Opioids with Analgesics	Gene Therapy
Coronary Sinus Reducer	Extracorporeal Shockwave Myocardial Revascularization (ESMR)	Cognitive Behavioral Therapy	Co Enzyme Q10	Cell Therapy
Spinal Cord Stimulation	Trans Myocardial Laser Revascularization	Acupuncture Therapy	Herbal & Chinese Medicine	
Percutaneous Laser Revascularization	Transcutaneous Electrical Nerve Stimulation.	Yoga	Omega 3 Fatty Acid	
Enhancing of External Counter Pulsation (EECP)	Percutaneous Retrograde Coronary Sinus Perfusion	Music Therapy	L -Arginine	
Transcutaneous Electrical Nerve Stimulation	Video Thoracoscopic Sympathectomy (VTSY)	Diet	Omega 3 Fatty Acid	

CONCLUSION

With the advancement in diseases its treatment should also be advanced, in most of the case the advancement in therapy is brought about with an addition of a drug but selective addition of a new drug to any regimen is also a big challenge as number of factors like side effects and drug interaction can arise. This leads to the development of newer and safer therapeutic strategies that can provide maximum benefit with minimum unwanted effects. Life style modification Acupuncture therapy, Yoga, Cell therapy and Gene therapy are very constructive in this aspect as these therapies have affirmative effects and have shown remarkable improvement of cardiovascular health with minutest compliance issues. Supplements like Omega 3 fatty acids, L-arginine and L-carnitine are also a focus of many studies with proven benefits. Herbal and Chinese medicines also shown remarkable effects

when used in different trial but must be use cautiously as they are also chemicals. Other interventions also shown benefits in majority of trial but patient support and compliance must be focused, One advantage of these methods is their long term benefit that can help in counselling of patients to adopt these treatment. The mechanism of action in all these therapy is variable but major goal is to reduce the stressor response of heart and to improve the supply of oxygen to promote normal functioning of heart. All these methods can be use along with conventional therapies and can also be used alone for management of angina. Further studies and randomized control trials can validate the therapeutic efficacy and establish facts that can promote the use of these methods in clinical practice.

REFERENCES

1. Tarkin JM, Kaski JC. Pharmacological treatment of chronic stable angina pectoris. Clin Med 2013;13(1): 63-70.
2. Ferrari R, Camici PG, Crea F, Danchin N, Fox K, Maggioni AP, et al. A 'diamond' approach to personalized treatment of angina.Nat RevCardiol2018;15(2):120-32.
3. JenniferNS, Jenna MN,ManekMB, Emily MH, AnthonyJV. Diagnosis and management of acute coronary syndrome: an evidence-based update. JAmBoardFamily Medicine 2015;28(2):283-93.
4. Pimple P, Shah AJ, Rooks C, Bremner D, Nye J, Ibeanu I. Angina and mental stress-induced myocardial ischemia. JPsychosomRes 2015;78(5):433-7.
5. Ayerbe L, Gonzalez E, Gallo V, Coleman CL, Wragg A, Robson J. Clinical assessment of patients with chest pain; a systematic review of predictive tools. BMC CardiovascDis2016;16(18):1-9.
6. a fingerprint for diagnosis of acute myocardial infarction and angina pectoris. BMC MedGenomics 2013;6(16):1-9.
7. Wee Y, Burns K,Bett N. Medical management of chronic stable angina. AustPrescr 2015;38(4):131-6.
8. Wilson SR. Efficacy of Li C, Fang Z, Jiang T, Zhang Q, Liu C, Zhang C. Serum microRNAs profile from genome-wide serves as Ranolazine in patients with chronic angina observations from the randomized, double-blind, placebo-controlled MERLIN-TIMI (Metabolic Efficiency withRanolazine for Less Ischemia in Non-ST-Segment Elevation Acute Coronary Syndromes) 36 Trial.JAmCollCardiol2009;53(17):1510-6.
9. Marienescu MA, LofflerAI, Ouellette M, Smith L, Kramer CM, Bourque JM. Coronary Micro vasculardysfunction, microvascular angina, and treatment strategies. JAmCollCardiol2015;8(2):210-20.
10. Balla C,PavasiniR,FerrariR. Treatment of angina: where are we?Cardiology 2018;140:52-67.
11. Gayet JL,Paganelli F, Cohen-Solal A. Update on the medical treatment of stable angina. ArchCardiovascDis 2011;104(10):536-44.
12. Windecker S, Kolh P, Alfonso F, Collet JP, Cremer J, Falk V. ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). EurHeart J2014;35(37):2541-619.
13. HenryT,Satran D, Jolicuer EM. Treatment of refractory angina in patients not suitable for revascularization. NatRevCardiol2014;11(2):78-95.
14. Tegn N, Abdelnoor M, Aaberge L, Endresen K, Smith P, Aakush S. Invasive versus conservative strategy in patients aged 80 years or older with non-ST-elevation myocardial infarction or unstable angina pectoris (After Eighty study): an open-label randomized controlled trial. Lancet 2016;387(10023):1057-65.
15. Ali N, Patel P.Non-pharmacological interventions in refractory angina. Heart ResOpen J 2018;5(1):1-7.
16. Cheng K. Sainsbury P, Fisher M, De-Silva R. Management of refractory angina pectoris. EurCardiol Rev 2016;11(2):69-76.
17. WinchesterDE,Pepine CJ. Angina treatments and prevention of cardiac events: an appraisal of the evidence. EurHeart JSuppl 2015;17;G10-G8.
18. Siritunga S,Wijewardena K,Ekanayaka R,Mudunkotuwa P. Can music improve the symptoms of stable angina? A randomized controlled trial. Health 2013;5(6):1039-44.
19. Kulmov AD, Murzina TA. Coenzyme q10 in complex therapy of patients with ischemic heart disease Kardiologiia2013;53(8):40-3.
20. Chen J,Ren Y, Tang, Y, Li Z, Liang F. Acupuncture therapy for angina pectoris: a systematic review. JTradChinese Med 2012;32(4):494-501.
21. Zhang Z, Chen M, Zhang L, Zhang Z, Wu W, Liu J. Meta-analysis of acupuncture therapy for the treatment of stable angina pectoris. IntJClinExp Med Sci2015;8(4):5112-20.
22. Dai C, SharmaM.Between inhale and exhale: yoga as an intervention in smoking cessation. J EvidBased Complementary AlternMed2014;19(2):144-9.
23. Tripathi P, Chandra M,Misra MK. Protective role of l-arginine against free-radical mediated oxidative damage in patients with unstable angina. Indian JClinBiochem 2010;25(3):302-6.
24. Chaitman BR,Laddu AA. Stable angina pectoris: antianginal therapies and future directions. NatRevCardiol2012;9(1):40-52.
25. Khan AR,Farid TA,Pathan A. Impact of cell therapy on myocardial perfusion and cardiovascular outcomes in patients with angina refractory to medical therapy: a systematic review and meta-analysis. CircRes 2016;118(6):984-93.
26. Losordo DW, Henry TD, Davidson C, Lee JS, Costa MA, Bass T. Intramyocardial, autologous cd34 cell therapy for refractory angina. CircRes 2011;109(4):428-36.

27. Heydari B, Abdullah S, Pottala JV, Shah R, Abbasi S, Mandry D. Effect of omega-3 acid ethyl esters on left ventricular remodeling after acute myocardial infarction the OMEGA-REMODEL randomized clinical trial. Circulation 2016;134:378-91.
28. DiNicolantonio JJ,Lavie CJ, Fares H,Menezes AR, Keefe JH. L-Carnitine in the secondary prevention of cardiovascular disease: systematic review and meta-analysis. MayoClin Proceeding 2013;88(6):544-51.
29. KochE, Malek F. A standardized extracts from hawthorn leaves and flowers in the treatment of cardiovascular disorders - preclinical and clinical studies. Planta Med2011;77(11):1123-8.
30. Tian PP, Li J,Gao J, LI Y. Efficacy and safety of the ShexiangBaoxin Pill for the treatment of coronary artery disease not amenable to revascularization: study protocol for a randomized, placebo-controlled, double blinded trial. BMJ Open 2018;8:1-6.
31. Chen R, Xiao Y, Chen M, He J, Huang M, Hong X, et al. A traditional Chinese medicine therapy for coronary heart disease after percutaneous coronary intervention: a meta-analysis of randomized, double-blind, placebo-controlled trials. BiosciRep2018;38(5):1-11.
32. Kong D, Xia W, Zhang Z, Xiao L, Yuan D, Liu Y. Safflower yellow injection combined with conventional therapy in treating unstable angina pectoris: a meta-analysis. JTradChinese Med2013;33(5):553-61.
33. Andrell P, Yu W, Gersbach P, Gillberg L, Pehrsson K, Hardy I. Long-term effects of spinal cord stimulation on angina symptoms and quality of life in patients with refractory angina pectoris--results from the European Angina Registry Link Study (EARL). Heart 2010;96(14):1132-6.
34. Taylor RS, De-Vries J,Buchser E,DeJongste MJL. Spinal cord stimulation in the treatment of refractory angina: systematic review and meta-analysis of randomized controlled trials. BMC CardiovascDis2009;9(13):1-13.
35. Ranganadhan K. Kumar KK,Jayapraksah K, Panayappan L. Spinal cord stimulation: a dominant therapy for refractory angina pectoris. IntResJPharm2015;6(8):489-92.
36. Yang X, Li Y, Ren X, Xiong X, Wu L, Li J. Effects of exercise-based cardiac rehabilitation in patients after percutaneous coronary intervention: a meta-analysis of randomized controlled trials. SciRep2017;7:44789.
37. Manchanda A,Aggarwal A,Aggarwal N, Soran O. Management of refractory angina pectoris.EurCardiol2011;18(4):343-351.
38. Braith RW, Conti CR, Nichols WW, Choi CY, Khuddus MA, Beck DT. Enhanced external counter pulsation improves peripheral artery flow-mediated dilation in patients with chronic angina: a randomized sham controlled study. Circulation2010;122(16):1612-1620.
39. Cheng R, Henry TD. Nonpharmacological approaches to refractory angina. Heart Metab2017; 72:18-24.
40. Briones E,Lacalle JR, Marin-Leon I, Rueda JR. Transmyocardial laser revascularization versus medical therapy for refractory angina. Cochrane Database SysRev2015;27(2):CD003712.
41. Montalescot G, Sechtem U, Achenbach S, Andreotti F, Arden C, Budaj A. ES guidelines on the management of stable coronary artery disease: The Task Force on the management of stable coronary artery disease of the European Society of Cardiology. Eur Heart J 2013;34(38):2949-3003.
42. Hallen K, HrafnkelsdoTT, Jern S, Biber B, Mannheimer C, DuttaRoy S. Transcutaneous electrical nerve stimulation induces vasodilation in healthy controls but not in refractory angina patients. JPainSymptom Manage 2010;40(1):95-101.
43. Oppenheimer GM. Framingham heart study: the first 20 years. ProgCardiovascDis 2010;53(1):55-61.
44. Vilelea-Martin JF, Giollo-junior LT, Chiappa GR, Cipriano-Junior G, Vieira PJC, Ricardi FDS. Effects of transcutaneous electrical nerve stimulation (TENS) on arterial stiffness and blood pressure in resistant hypertensive individuals: study protocol for a randomized controlled trial. Trial2016;17(168):1-13.
45. Tuma J, Fernández-Viña R, Carrasco A, Castillo J, Cruz C, Carrillo A. Safety and feasibility of percutaneous retrograde coronary sinus delivery of autologous bone marrow mononuclear cell transplantation in patients with chronic refractory angina. J TranslMed 2011;9(183):1-7.
46. Verheye S, Jolicœur EM, Behan MW, Pettersson T, Sainsbury P, Hill J.Safety and feasibility of percutaneous retrograde coronary sinus delivery of autologous bone marrow mononuclear cell transplantation in patients with chronic refractory angina. New EnglJMed2015;372:519-27.
47. Abawi M, Nijhoff F, Stella PR, Voskuil M, Benedetto D, Doevendans PA. Safety and efficacy of a device to narrow the coronary sinus for the treatment of refractory angina: a single-centre real-world experience. Netherland Heart J2016;24:544-51.
48. Stoller M, Traupe T, Khattab AA, De-Marchi SF, Steck H, Seiler C. Effects of coronary sinus occlusion on myocardial ischemia in humans: role of coronary collateral function. Heart 2013;99(8):548-5.
49. Mohl W, Gangl C, Jusić A, Aschacher T, De Jonge M, Rattay F. PICSO: from myocardial salvage to tissue regeneration. CardiovascRevasc Med2015;16(1):36-46.
50. JavidiD, Saffarian N. Nonconventional therapeutic modalities in refractory angina pectoris. Medical J Islamic Repub Iran 2009;23(2):96-104.