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RESEARCH ARTICLE

CORONARY ARTERY DISEASE: RECENT ADVANCEMENT IN THE TREATMENT AND DIAGNOSTIC MEASURES

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ABSTRACT

Coronary artery disease is still one of the leading causes of death around the globe even though the mortality is on the decrease since 1970 in most of the industrialized countries. This marked reduction in coronary artery disease was largely driven by the significance of advancement in the novel treatment modalities used in these western countries. These strategies have ranged from advanced diagnostic modalities to various novel treatment methods. This article will review the recent advancement in the treatment of Coronary artery disease in respect to therapeutics and diagnostic modalities.

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INTRODUCTION

Coronary artery disease (CAD) is one of the most common causes of death around the globe. Despite of significant advances made in the treatment, still millions of people are suffering from Coronary artery disease worldwide[1-3].CAD is responsible for one third of deaths in developing and developed countries in people over 35 years of age, with the percentage reaching close to 50% in western countries[4,5]. Most of the western countries are reporting cardiovascular problems, CAD in particular, are the leading cause of mortality, still. In united states, around 660,000 to 750,000 cardiovascular events has been reporting in every year. In every 43 seconds someone is suffering with acute coronary syndrome in the united states, as per the reports[6,7]. The prevalence of CAD among adults in the USA in 2005 was 7.3%.In the year of 2016, in the United States alone, 900,000 subjects suffered or die from CAD and its complications[8]. Recent estimates suggest that 16.5 million adults in the United States have chronic CAD. However over the past 35 years there is drastic decrease in both of the incidence and lethality of coronary artery disease in industrialized countries, which is well documented by large scale studies such as the WHO MONICA study[9],but the same cannot be held true for developing and underdeveloped countries.

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Increasing longevity of western population is the result of two major success stories in the prevention and treatment of human disease. The first milestone was eliminating the burden of communicable diseases via public health measures, improvement of public awareness of communicable diseases, provision of vaccines and antibiotic drug development. The second milestone was the drastic decline of cardiovascular mortality and morbidity, which began in the 1970[10]. Many clinicians and researchers are still trying to make a significant progress in developing novel strategies for patients suffering from coronary artery disease. These strategies have ranged from advanced diagnostic modalities to various novel treatment methods. This article will summarize the literature on the recent advances in coronary artery disease research in respect to therapeutics and diagnostic modalities.

Robots: The use of robots in the field of medicine was fairly recent even though it's application in industries are quite popular for a long time. In medical field, robots has been using in many surgeries and even in providing radiation for more than a decade. The use of robots in mitral valve repair, coronary artery bypass graft and septal defect closure are highly appreciable in terms of many benefits such as improved ergonomics, precision and sometimes shortening of intraoperative time, mini incision site, shortening hospital stay of patient[11]. Also, robotics are being used for many catheter based surgical procedures. Robotic guided surgery has potential to limit radiation exposure.For instance, the normal rate of conventional angiography radiation exposure for CAD patients is estimated at 7 mSV and in some complicated surgeries, this radiation exposure can be increased up to 5 times greater than the normal rate[12]. Moreover robotics can also reduce contrast induced nephrotoxicity and associated mortality among patients. In addition to, the robotic assisted surgery has some other benefits as it can accurately measure the size of the lesion, which can be miscalculated by other modes of procedure. Hence it can improve the long term health of the patient. A good number of research studies has proved the high efficacy of robotics in interventional cardiology especially percutaneous coronary intervention and coronary angioplasty[13]. Robotics use in performing Coronary artery bypass graft surgery also reported a high success. Robotically assisted hybrid coronaryrevascularization, which involves coronary artery bypass graft as well as percutaneous coronaryintervention, has also been developed as a treatment modality for CAD. The benefits over this therapy is reduced mortality and shortened hospital stay as it is minimally invasive in nature. However, the high cost of this procedures as well as mastery over the technical skill related to robotic application is the obstacles in it's regular use in surgery[14-18]. It remains to be determined, with furthertechnological advancement, whether this technology will be accepted into routine clinical practice andreplace conventional technologies.

Nanotechnology: The vision of nanotechnology introduced in 1959 by late Nobel Physicist Richard P Faynman. The word "Nano" comes from the Greek word for dwarf. Nanotechnology is defined as the research and development of materials, devices, and systems exhibiting physical, chemical, and biological properties that are different from those found on a larger scale (matter smaller than scale of things like molecules and viruses)[19]. Nanotechnology is using in different areas of cardiology: Invasive and non invasive(medical) treatment modalities, drug delivery applications, percutaneous coronary interventions, gene therapy, and coronary artery bypass graft. Nanotechnology has been using in reducing the low density lipoprotein level in the blood, which is one of the important reason for CAD. To be more specific, Consumption of high cholesterol food is one of the main reasons for coronary artery disease. Presence of high levels of low density lipoprotein in blood is a strong indicator of Coronary artery disease whereas high density lipoprotein has the protective role as it's involved in transportation of cholesterol away from peripheral tissues. Nanotechnology has been used in the synthesis ofa dimyristoyl phosphatidylcholine, which mimics the surface characteristics of HDL, thus it helps to the removal of cholesterol from the peripheral tissues and transport it to the liver. Efficacy of dimyristoyl phosphatidylcholine liposomes has proved in a study with mice[20]. Secondly, another drug Fumagillin, with anti-angiogenic property, has been proved to inhibit angiogenesis thereby promotingplaque regression in coronary arteries. But the problem with the application of this drug is the ability to cause adverse neurocognitive effects at high doses, which is required to achieve a therapeutic effect. Nanotechnology is useful to give fumagillin drug through_v_3 integrin targeted nano-delivery system, and which is able to achieve significant antiplaqueeffects at one-third of the usual dose[21]. A good number of nanoparticle based antithrombotic agents also have been tested for their efficacy. A potent antithrombotic agent, D-phenylalanyl-L-prolyl-Larginyl-chloromethyl ketone, is rapidly cleared from the body when it administered that questions it's clinical use[22]. But when this drug administered with a combination of a perfluorocarbon-core nanoparticle, it has been shown to have improved antithrombotic action, as shown by Myerson et al. in an animal model study[23]. Peters et.al used hirudin with fibrin binding micellar nanoparticles which exhibited greater targeting of fibrin clots in vivo[24].Similarly,another Gel-based nanoparticle combined with rapamycin, with antiproliferative and antiapoptotic properties, were studied in an animal model which were found to re-endothelialize injured arteries and reduce hyperplasia[25]. Tang et.al. has developed a smart nano particle such as a pH-dependent delivery of antioxidants has shownits effectiveness in treating cardiac diseases[26].

The use of nanotechnology in interventional cardiology is also highly appreciable. Nanotechnology has shown potential benefits when used in percutaneous coronary intervention[22]. They have been studied for their ability to release drugs as well as promote healing and reduce restenosis. Moreover, nanotechnology also has been useful in findingsynthetic alternatives for coronary artery bypass grafts. Researchers have studied the potentialof electrospunnanosized fibrous scaffolds, which may prove to be an alternative synthetic graft forcoronary artery bypass graft procedures [23,24]. Targeting drug-eluting stents in gene therapy isanother area where nanotechnology holds promise. Gene eluting stents can be used to overcomerestenosis, in-stent thrombosis, and delayed endothelialisation[25,26]. Several nano-coatings in theform of hyaluronic acid (to carry pDNA), nanobiohybrid hydrogel (to carry Tat peptide and DNA),and poly(lactic-co-glycolic acid) nanoparticles (carrying PDGF receptor-_ antisense RNA) have beenstudied in animal models and have shown promising results [27-33]. In the treatment of CAD, nanotechnology has led to an interesting and promising direction. It has valuable potential in delivering drugs that are otherwise limited by their pharmacokinetics.Its applications in stent and gene therapy are potentially useful for future therapeutics based on thesemodalities. Further randomized controlled trials need to be conducted to establish strong evidenceto support the use of these newer technologies for CAD treatments.

Stem Cell Therapy: Innovative stem cell (SC) therapies have the potential to fundamentally alter the conventional treatment of Coronary artery diseases by stimulating the regeneration of injured myocardium. In 2001, first encouraging pre-clinical study results, reporting the repair of infarcted cardiac tissue and the enhancement of ventricular function, led to the rapid translation of SC therapies within the same year [34-36]. Many number of pre-clinical and early clinical trials have demonstrated the safety and feasibility of some stem cell types since 2000. Nevertheless many questions has to be unanswered and so far no cell therapy has been unambiguously shown to be effective for the treatment of heart diseases. Therefore strategies have been developed in order to improve the potency of applied Stem cell therapies. Stem cell therapies are useful in many ways in the treatment of coronary artery disease. SC therapies are useful to improve the blood supply to ischemic areas of the heart as well as to promote cardiac cell regeneration. This can be achieved in one of two ways: by a direct effect of the stem cells, or by paracrine factors secreted by these stem cells[37].Studies conducted by using mononuclear cells and endothelial progenitor cells for acute myocardial infarction and chronic ischemic heart disease have been contradictory, although some studies has shown promising effect[38-41]. But this has led to the inclusion of other cell types, such as adipose derived stem cells. Another novel alternative is the creation of induced pluripotent stemcells, for which adult cells are transformed into pluripotent stem cells, similar to embryonic stemcells[42,43]. Even though it offers a promising alternative, cancerous transformation of the undifferentiated stem cells have to be taken into the immediate account before they can be tried in human subjects. The stem cells studied in cardiovascular research includes skeletal myoblasts, bone marrow derived SCs, Bone marrow derived mononuclear cells, Bone marrow derived HSCs and EPCs, BM derived MSCs, Mobilized stem and progenitor cells, Adipose derived stem and progenitor cells, cardiac stem and progenitor cells, Embryonic stem cells, Induced pluripotent stem cells etc.Among these,Cardiac stem cells are one source of interesting stem cells. From the past, heart is considered as the organ with little potential to undergo mitosis during adulthood[44-46]. But recent studies have shown a contrasting perspective that the heart isnow believed to have intrinsic regenerative potential and undergoes constant turnover throughoutadult life[47]. These types of cells are numerous in number in the apices of the atrium and ventricle[48]. However, the reparative potential of these cells is limited, especially in conditions with extensive damage such as myocardial infarction and chronic heart failure[49-51]. But, Cardio cluster are clusters of multiple stem cells which include cardiac progenitor cells, mesenchymal stem cells, endothelial progenitor cells and fibroblasts, that can communicate with eachother,, have the potential to promote cardiac cell regeneration even in extensive damage of the myocardium[52].

Many scientific studies and trials has been proving the distinct advantages of stem cell therapies over the cardiovascular disease especially in the management of coronary artery disease. The findings of the One non-randomized trial showed an improved left ventricularejection fraction (LVEF) function followed by the injection of mononuclear stem cells in patients with MIwithin three months[53]. Improved exercise tolerance, reduced death rate and scar tissue are visiblein a 5-year follow up[54]. A number of other studies also have shown the supporting results on their findings[55-57].For instance, a meta analysis showed an improvement in LVEF function by 2.99% followed by bone marrow transplantation in patients after myocardial infarction[58]. However, the meta-analysis did not include recent studies which has failed to show any improvement in LVEF. Another study of patients suffering from chronic ischemic heart disease showed an improvement on their cardiac function followed by the use of bone marrow derived stem cells[59-62].Similarly there have been many studies that have studied the clinical efficacy of mesenchymal stem cells for improving the cardiac function[63-66]. Cardiac derived stem cells also shown promising results[67-69] with an improvement in the left ventricular mass that was viable, improved quality of life, reduced scar mass, improved regional contractility and safety of the procedure. More surprisingly, a patient who treated with cardiac stem cells 14 months after myocardial infarction had shown similar therapeutic benefit as someone treated earlier[70]. This has been suggesting that cardiac stem cells could be beneficial in patients with chronic ischemic problems. However, it should be noted that the observed clinical benefit was less than the expected clinical benefit based on prior in vitro and animal studies.[71] Stem cell therapy continues to be a promising treatment modality for coronary artery disease of both acute and chronic in nature. A good number of experimental and clinical studies have shown promising results. However,further research is needed to understand the exact mechanisms of action and the ideal source of stem cells to derive optimum benefit and to further understanding.

Coated Stents

Stents coated with medication: These type of stents are very useful to protect the blood vessels from restenosis after percutaneous transluminal coronary angioplasty (PTCA). This new type of stent is on clinical trial and may be nearing food and drug administration approval. It's also increases the success rate of PTCA as well as reducing the need for later coronary artery bypass graft surgery.

Sirolimus: a stent coated with sirolimus, an antirejection agent, helps to reduce the growth of abnormal cells at the PTCA site. The SIRIUS study has examined the action of a stent coated with sirolimus. Results of the study shows that the client who received the sirolimus-coated stents had a restenosis rate of 3.2%, compared with 35.4% for patients who received uncoated stents. The FDA is expected to approve this stent for general use soon[72-73].

Paclitaxel: It is helpful in treating cancer and also it has the property of anti-inflammation. Therefore, it also helpful to protect the blood vessels from the growth of abnormal blood cells followed by the PTCA procedure. Results from current research studies on this product, look promising[74-75].

Cardiac Medicine: There have been many recent advances in drug developments for Coronary artery disease patients. Among them some of the important advances in medicine has been given below.

Antithrombotic Medications**:** One of the main class of drugs which is using among CAD patients is Antithrombotic drugs. The commonly using antithrombotic drugs, presently, among CAD patients are aspirin and clopidogrel[76]. But recently, a new group of drugs collectively known as novel oral anti-coagulants were discovered. The drugs which includes in "novel oral anti-coagulants" category areximelagatran, darexaban, dabigatran, rivaroxaban, and apixaban. Among the mentioned drugs dabigatran, edoxaban, rivaroxaban, apixaban are approved for clinical use. Dabigatran is a drug which inhibits the action of thrombin on clotting mechanism In contrast edoxaban, rivaroxaban, and apixaban are inhibitors of clotting factor Xa. The findings of research studies on dabigatran shows that it has significantly reduced the ischemic events with the higher doses of the drug(110 and 150mg), but this benefit was counteracted with a four-fold increase in bleeding risk[77]. However, the trials concluded that lower dosetherapy could be used without a significant increase in bleeding risk.

Proprotein convertase subtilisin/kexin type 9**(PCSK9):** Proprotein convertase subtilisin/kexintype 9 (PCSK9) plays an important role in the regulation of cholesterol homeostasis. By binding the hepatic low density lipoprotein receptors and promoting their lysosomal degradation, PCSK9 decreases LDL cholesterol levels in the blood[78-80.]

Alirocumab: It is a monoclonal antibody produced by recombinant DNAtechnology. Studies and trials on this drughas been proved effectiveness of this medicine to reduce the LDL level in the body81-82. First phase of a study report shows the reduction in LDL cholesterol levels, ranging from 28% to65% depending on the route of administration (subcutaneous or intravenous). In phase II studies(randomized controlled double blinded trials) cholesterol reduction rangedfrom 18.2% to 67% (depending on the dosage) compared to placebo83-90. When combined withatorvastatin, Alirocumab brought about a LDL cholesterol reduction of 66–73% whereas placebo andatorvastatin brought about a reduction of 17%. These results were confirmed in several phaseIII trials. Since high LDL levels are linked to CAD, the use of Alirocumab reduced adversecardiovascular events by 15–48%[90-97].

Anti-Inflammatory Therapies: It is generally believed that local or systemic inflammatory process is associatedwith greater cardiovascular risk.A good number of studies have supported the relationship between inflammation and cardiovascular risk[98].Nevertheless,still many interventional trials are needed to prove the association between inflammation and cardiovascular events[99]. Somesmall trials have suggested potential benefitsof anti- inflammatory agents such as colchicine on reducing the risk of CAD[100].And, indeed, severallarge-scale randomized trials are ongoing, testing various anti-inflammatorystrategies to reduce cardiovascular risk in patientswithCAD, such as canakinumab (an interleukin 1ßinhibitor), low-dosemethotrexate, etc[101,102]. If this approach has shown a positive result, therewould potentially be the ability to positively affect not onlythe substrate for acute events (by preventing plaque buildupwith LDL lowering) but also the phenomena leading to acutesuperimposed thrombosis.However, it will take many years to prove the effect of anti-inflammatory drug on CAD.

Advanced Diagnostic Techniques

A new test for heart disease risk: In the future, primary care providers may order a highlysensitive C-reactive protein level with routine lab workin an effort to identify patients at a higher risk for CAD.Recent research has shown that inflammation maylead to CAD development by weakening plaque buildupin the arterial walls, leading to thrombus formation. Determining the level of C-reactive protein in the bloodcan measure inflammation, but the test isn't specific forCAD. Any chronic infection can produce C-reactive protein, and the protein's serum levels also areelevated inpatientswith hypertension, other inflammatory processes, andpatients who smoke. A level less than 1 mg/dl is considered low risk for heartdisease; a level over 3 mg/dlplacesthe patient at high risk for CAD.Patients can reduce their C-reactive protein level witha low-fat, low-cholesterol diet; exercise; smoking cessa- tion; and certain medications such as cholesterolloweringagents and aspirin.

Beaming in on CAD assessment: Electron beam computed tomography (EBCT) is now being used for assessing the patient's risk for Coronary artery disease. Even before the appearance of symptoms, it can assess the patient risk for CAD, as per some studies. EBCT can give a more clearer and fasterthree-dimensional view of the heart and blood vessels when compared to a standard computed tomography scan. Moreover, the EBCT can shows the amount of calcium deposited over the coronary arteries. As a part of ageing process calcium normally appears in the arteries. Calcium is one of the many components of plaque, which is the reason for atherosclerosis and CAD. Based on the location and amount of calcium deposition, the cardiologist can assign a numeric scoreto each artery, that total score can determines the patient's risk category. For example, a patient with a scorebelow 10 isatverylow risk for CAD, a patient with a scoreof 11 to 100 is at mild to moderate risk, a patient with ascore of 101 to 400 is at moderate to high risk, and apatient with a score over 400 is at very high risk.Although it is not as specific as cardiac catheterizationfor showing the degree of vessel blockage, EBCT hassome advantages such as it is noninvasive and it can produce the 3D images with in 10 minutes.

3-D Printing: There are many 3-D imaging techniques in cardiology such as magnetic resonance imaging, computerizedtomography, and 3-D echography to diagnose and treat cardiovascular conditions. However, they can be viewed only on a 2-D computer screen or films even though these images are in 3-D. It is usually sufficient for most of the cardiac procedures. Hence the current imaging modalities are not effective formore complex interventions[103-104].3-D printing has been very useful in this circumstances, not only to overcome these difficulties but also allow for complete visualization, tactile sense, education andsurgical planning as well as simulation[105]. In the field of cardiology it has tremendous potential in thetreatment of congenital defects, cardiac tumors, cardiomyopathy, functional flow models, valvularheart diseases, stent placement for CAD and other cardiac surgeries[106-108]. 3-D printing also allows to identify the extent of occlusionand stenosis in CAD patients[109]. These models can be used in a pulsatile flow loop environment, notonly to visualize and understand complex flow patterns but also to simulate interventions. In research field, 3-Dprinted models areuseful to compare imaging and treatment modalities of CAD[110].It is identified from a study that3-D printing could be more effectivein planning and treating complex situations (bifurcation lesions) that require stent placement[111].

Conclusion

Cardiovascular diseases are still remaining one of the most common causes of morbidity and mortality worldwide even though the advancement in the treatment and diagnostic modalities are highly appreciable. Significant inter collaborative efforts between researchers, clinicians and other related professionals have led to many rapid progress in the diagnostic modalities and treatment of coronary artery disease. As we live the era of evidenced based practice, further evidence in the form of clinical trials and long term follow up studies are required to prove the efficiency of these novel treatment modalities and to include these strategies into mainstream practice.

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