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Precision Medicine in Cardiovascular Disease: A Systematic Review of Clinical Trials Evaluating Personalized Treatment Approaches

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ABSTRACT

Cardiovascular diseases (CVDs) have accounted for 93-% of all disease prevalence, 54-% of all deaths, with 60-% of debility-attuned living years over the prior three decades. Cardiovascular diseases (CVDs), a collective term for issues with the heart and blood vascular system, are the main cause of death and morbidity globally. The complexity of these diseases continues to pose a challenge for health care professionals and researchers, despite significant advancements in medical science and treatment approaches. New methods of prevention, diagnosis, and treatment are needed as CVD prevalence is on rise. With ischemic heart disease and stroke, CVDs now account for one in four fatalities in India. Precision medicine, a ground-breaking strategy that adapts treatment choices and patient outcomes to unique patient characteristics, has emerged as a promising path to transform cardiovascular care. Precision medicine, as opposed to conventional "one-size-fits-all" treatment approaches, customizes medical interventions to the particular genetic, molecular, and clinical characteristics of each patient. Individuals who are at a substantial gamble of acquiring circulatory diseases conceivably identified with the help of precision medicine. Biomarkers and genetic markers can help with risk assessment, enabling early intervention and preventive measures. A significant development in cardiovascular precision medicine, targeted therapies for cardiovascular disease herald a new era of treatment personalization based on unique patient characteristics. These therapies optimize treatment outcomes while minimizing side effects by utilizing genetic insights and molecular knowledge.

Keywords: Cardiovascular diseases (CVDs), Precision medicine, Biomarkers, Viral vectors, Familial Hypercholesterolemia (FH).

INTRODUCTION

Cardiovascular diseases (CVDs) have dominated the worldwide illness burden during the previous three decades by 93-% ubiquity, 54-% death, and 60-% in debility-attuned living years. The heart and circulatory problems collectively known as cardio-vascular diseases (CVDs), which are the major trigger of fatalities moreover morbidity worldwide. As the prevalence of CVDs rises, novel techniques to prevention, diagnosis, and therapy are required. This is made worse by differences in the prevalence of diseases between and within continents, which result in annual costs for healthcare and lost productivity of $216 billion and $147 billion, accordingly. [(1)] India in 2016, CVDs were accountable for 28.1-% of all fatalities and 14.1-% of all debility-attuned living years, in contrast to 15.2-% and 6.9-

%, correspondingly, in 1990. In India, the ubiquity of cardiovascular disorders grew from 25.7 to 54.5 million occurrences between 1990 and 2016, according to a simple assessment of the disease burden. In India, CVDs present interpretation on behalf of single in four fatalities, among ischemic heart disease and stroke accounting for beyond 80-% of the entire liability. [2, 3] The field of cardiovascular disease faces complex challenges, given its multifactorial nature and the diverse range of diseases it encompasses, including coronary artery disease, heart failure, arrhythmias, and more. Historically, treatment approaches have often relied on broad guidelines, which may not fully account for the heterogeneity within patient populations. [4]

Precision medicine, sometimes established as "personalized medicine" is a groundbreaking tactic to healthcare, is transforming the landscape of cardiovascular disease management. Unlike traditional "one-size-fits-all" treatment strategies, precision medicine tailor's medical interventions to the unique genetic, molecular, and clinical characteristics of individual patients. This paradigm shift recognizes that each patient's response to treatment can vary significantly based on factors such as genetic makeup, lifestyle, and environmental influences. The aim of precision medicine is to focus the precise therapies to the precise patients at the precise time. [5]

In recent years, precision medicine has emerged as a promising solution to address these challenges. By analyzing genetic markers, biomarkers, and other patient-specific factors, healthcare practitioners can identify targeted therapies that offer greater efficacy and reduced risk of adverse effects. This individualized approach holds the potential to revolutionize cardiovascular disease treatment by optimizing outcomes and improving patients' quality of life. Our approaches for examining biological systems come to be significantly transmuted with OMICS, which is well-defined as the probing plus scrutiny of enormous quantities of data that signify the edifice and role of a complete makeup of a given biological system at a specific level. Developments in "OMICS" knowledges, including genomics, proteomics, in addition metabolomics, have expanded our understanding of disease mechanisms and potential biomarkers. High-throughput techniques enable the identification of biomarker patterns associated with specific cardiovascular conditions, paving the way for more accurate diagnostic and prognostic tools. [6]

In cardiovascular precision medicine, biomarkers, and genetic profiling guide treatment selection. For instance, certain genetic markers may indicate a patient's responsiveness to statins for cholesterol management. This ensures that patients receive treatments with a higher likelihood of success, reducing the need for trial-and-error approaches. Essentially, precision medicine tolerates health care practitioners and scientists to foretell the most precise therapy and anticipation tactics for an identifiable group of people anguish from or vulnerable to an exact illness. In simple words the capability of precision medicine in cardiovascular medicine concerns to all arenas of the disease enhancement and enters threat prediction, defensive measures, as well as targeted therapeutic tactics. [7]

Overview of Cardiovascular Disease

Heart illness (CVD) has emerged as India's leading culprit for mortality since the turn of the century. Compared to those of European origin, Indians possess CVD more than a decade sooner and during their most productive midlife years. For instance, just 23-% of CVD fatalities happen around the turn of 70 in Western nations, compared to 52-% in India. Furthermore, compared to nations with high and middle incomes, the case fatality rate associated with CVD appears to be higher in low-income countries like India. India is anticipated to lose an estimated amount of 237$-billion through a ten-year span (2005-2015) owing to lost productivity and increased medical costs as a consequence of the current CVD burden, based on a World Health Organization (WHO) prediction. [8]

Cardiovascular disease (CVD) represents a diverse group of disorders affecting the heart and blood vessels, encompassing conditions such as coronary artery disease, stroke, heart failure, arrhythmias, and more. It remains a leading source of morbidity and fatalities globally, imposing a substantial burden on health-care systems and economies. The pathogenesis of cardiovascular diseases remains often multifaceted, concerning intricate interactions between genetic predisposition, lifestyle factors (such as diet, exercise, and smoking), environmental influences, and underlying medical conditions (such as hypertension and diabetes). This multifactorial nature of CVD contributes to the variability in disease presentation, progression, and treatment responses observed among patients. Historically, the approach to managing CVD has been based on general treatment guidelines and standardized therapies. However, these approaches may not fully account for the individual variations in disease etiology, severity, and treatment responses. As a result, some patients may experience suboptimal outcomes, adverse effects, or treatment resistance, underscoring the need for a further precise and personalized methodology. By understanding the complexity and diversity of cardio-vascular maladies, we can appreciate the significance of precision medicine's role in optimizing treatment outcomes and improving the overall well-being of patients.

The emergence of precision medicine offers a transformative solution to these challenges. By focusing on the unique molecular and genetic characteristics of each patient, precision medicine aims to tailor interventions to maximize therapeutic efficacy while minimizing potential risks. This approach recognizes that a treatment that works well for one patient may not be equally effective for another, emphasizing the importance of targeted strategies based on individual patient profiles. Precision medicine addresses the limitations of traditional cardiovascular disease management approaches. By harnessing insights from genetics, molecular biology, and patient-specific data, precision medicine has the prospective to reshape the landscape of cardio-vascular care, ushering in an era of more effective, patient-centered treatments. [9]

Principles of Precision Medicine

Precision medicine is rooted in the understanding that individual patients possess unique genetic, molecular, and clinical characteristics that influence their responses to medical interventions. This approach contrasts with the

historical "one-size-fits-all" model, acknowledging that the effectiveness of treatments can vary significantly based on individual variability. The norms of precision medicine in the context of cardiovascular disease are multifaceted and encompass various key aspects. The core principle of precision medicine revolves around creating personalized treatment strategies. By considering genetic, molecular, and clinical information, healthcare providers can design interventions that are more likely to succeed. One of the underlying principles of precision medicine is the recognition of genetic diversity among individuals. Genetic factors play a pivotal role in predisposing individuals to cardiovascular diseases, influencing disease progression, and affecting responses to treatments. Advances in genetic sequencing technologies have enabled the identification of specific genetic variants associated with increased disease risk. Non-clinical versions such as the mouse and other non-human primate could be exploited to recognize genetic alteration and its potential translation to humans and are offered for healthcare practitioners and scientist for clinical development. By analysing an individual's genetic makeup, healthcare practitioners can identify genetic markers that inform risk assessment, prognosis, and treatment decisions. [10]

Precision medicine integrates the identification of biomarkers measurable indicators of physiological, molecular, or genetic processes with disease diagnosis and treatment. In cardiovascular disease, biomarkers can provide insights into disease severity, progression, and response to therapy. For example, certain biomarkers might indicate inflammation levels, myocardial damage, or lipid metabolism dysfunction. Conventional biomarkers for instance lipid profile, hormone level afterwards physiological biomarkers grounded on magnitude of levels of noteworthy biomolecules. By measuring biomarkers such as serum ferritin, triglyceride plus HDLp ratio, lipophorin plus cholesterol ratio, LDL-cholesterol level, HDLp in addition apolipoprotein levels, lipophorins-LTPs ratio, sphingolipids, Omega-3-Index, in addition ST2-level, health care practitioners can refine treatment strategies and monitor disease progression more accurately. [11, 12]

Precision medicine aids in identifying individuals at substantial risk of developing cardiovascular diseases. Genetic markers and biomarkers can assist in risk stratification, allowing for early interventions and preventive measures. These interventions might include lifestyle modifications, targeted pharmacotherapy, or interventions to address specific threat circumstances, for instance towering cholesterol or else hypertension.

Biomarkers and Genetic Profiling

The integration of biomarkers and genetic profiling lies at the heart of precision medicine's transformative impact on cardiovascular disease management. These tools empower health care practitioners with the ability to recognize individuals who are more liable to react positively to specific treatments, thus enabling a more targeted and effective approach. Here, we delve into the significance, advancements, and implications of biomarkers and genetic profiling within the context of cardiovascular precision medicine. Biomarkers are measurable indicators of biological processes, often reflecting molecular, cellular, or genetic changes associated with disease. In cardiovascular disease, biomarkers provide insights into disease progression, severity, and potential treatment responses. For instance, elevated levels of cardiac troponins are indicative of myocardial damage, guiding timely intervention for acute coronary syndromes. [13]

In order to anticipate and avoid the significant death and disability rates linked to cardiovascular illnesses, it is necessary to identify new furthermore early-stage-biomarkers for hypertension. Fluctuations in a certain indicator's demonstration concerning vigorous people and sick might identify biomarkers of such disorders or tendency to their development. These include adjustments to the amounts of microRNA (miRNA) and proteins. The identification of proteins as well as mi-RNA as potential biomarker-candidates has been made easier by the use of mass spectrometry for protein characterization and microarray and sequencing for miRNA screening. But the task is to uncover biomarkers that expose early-stage-CVD in order to ominously shrink morbidity and fatalities associated with cardio-vascular affairs and enhance prognosis. Presently, a number of clinical biomarkers are linked to heart attack and stroke. C-reactive-protein (CRP), cardiac troponins I, T (cTnI, cTnT), B-type-natriuretic peptides (BNP), plus D-dimer are a variety of examples of such biomarkers. [14] Biomarkers offer the advantage of non-invasiveness, as they can often be measured from blood, urine, or other easily accessible samples. This facilitates repeated monitoring and tracking of disease progression and treatment responses without subjecting patients to invasive procedures. [15]

Genetic profiling extends to pharmaco-genomics is the scrutiny of how genetic modifications manipulate individual responses to treatments. Pharmacogenomic insights guide the assortment of drugs besides doses that are more prone to be efficient and safe for a specific patient. In cardiovascular precision medicine, this is exemplified by the tailored use of antiplatelet medications based on genetic factors affecting drug metabolism. Gene interpretation is alleged to be pivotal to the pathogenesis or progression of coronary-artery-disease (CAD)/ atherosclerosis, congestive-heart-failure (CHF) as well as ordinary congenital-heart disease (CHD). A potent method for extraordinary throughput, universal trans-criptonomic profiling of gene expression is microarray analysis. It has significant potential for scrutinizing the genetic underpinnings of several byzantine disorders and enables the simultaneous investigation of hundreds of genes in together sick and healthy tissues or cell-lines. Suppression subtractive hybridization (SSH) technique was effectively employed in conjunction with microarray analysis to examine gene expression characteristics. [16, 17]

Targeted Therapies

The paradigm shift towards precision medicine has given rise to the development of targeted therapies that address the unique genetic and molecular characteristics of individual patients. In the realm of cardiovascular disease, these therapies hold the potential to revolutionize treatment outcomes by tailoring interventions to specific patient profiles. Here, we delve into the significance, advancements, and examples of targeted therapies within the context of cardiovascular precision medicine.

Personalized Drug Selection:

Targeted therapies in cardiovascular precision medicine aim to optimize treatment responses by identifying drugs that match a patient's genetic and molecular profile. This departure from traditional one-size-fits-all approaches acknowledges the variability in patient reactions to medications. For instance, the choice of antiplatelet therapy following coronary stent placement can be guided by genetic factors that influence the metabolism of these drugs. The keystone of treatment for atherosclerotic cardio-vascular along with cerebro-vascular disorders continues to be antiplatelet drugs. There is minimal evidence that any antiplatelet medication is beneficial in primary hindrance (those with cardio-vascular jeopardy but no documented measures, indications, or angiographic-illness), and such rehabilitation involves the peril of surplus haemorrhage. Patients gain from long-term anti-platelet monotherapy where there is documented ailment (secondary hindrance), with aspirin be there as the 1st-choice for those with coronary-heart ailment and Clopidogrel for those with cerebro-vascular ailment. Additionally, contemporary testimony illustrations that low-dose Rivaroxaban combined with aspirin deliberates additional benefits in patients with stable peripheral arterial and cardiovascular illness. [18] Notwithstanding the now well-established job of aspirin in secondary-cardiovascular prophylaxis, the benefit-risk ratio in primary hindrance is far less evident. In low-middle revenue inhabitants, Aspirin accommodating polypill tactics have endorsed effective in counteracting major cardiovascular events, for instance in the Poly-IRAN study. [19] However, a hefty meta-analysis steered by the Antithrombotic Trialists' (from 2009) collaboration interrogated the net pros of aspirin in primary prevention as an upshot of an observed augmented jeopardy of foremost extracranial along with gastro-intestinal (GI) haemorrhage hitches in spite of only a trivial defensive outcome beside vascular-events. [20] The furthermost current trials also that concentrated on foremost anticipation showed net gain of aspirin in just this configuration is minimal at best while posing a significant risk of excessive bleeding threat in subjects with cardio-vascular peril factors who are otherwise well, contradicting these judgments. These trials included ASPREE, which examined elderly subjects, and ARRIVE, which scrutinised patients with a moderate estimated gamble of a first cardiovascular outcome. [21,22]

Genetic Mutations: [23]

Many cardiovascular diseases are driven by specific genetic mutations or molecular pathways. Targeted therapies capitalize on this knowledge to design interventions that interfere with or correct these aberrant processes. For example, in cases of Familial Hypercholesterolemia caused by specific gene mutations, therapies are being developed to target the underlying molecular mechanisms responsible for the condition. Familial-Hypercholesterolemia (FH) is an inherited genetic disorder illustrated by exceptionally improved stages of low-density lipoprotein (LDL) cholesterol in the plasma. This circumstance arises due to mutations in genes that play a critical role in LDL cholesterol metabolic rate, chiefly the LDL-receptor (LDLR) gene, the apolipoprotein-B (APOB) gene, comprising the proprotein-convertase subtilisin/ kexin-type 9 (PCSK-9) gene. Precision Medicine in FH are as follows:

a) ***Genetic Testing and Diagnosis:*** One of the key aspects of precision medicine in FH is the use of genetic testing to identify the specific mutations responsible for the disorder. Genetic testing can confirm the diagnosis of FH and provide insights into the genetic basis of the condition in an individual patient. This information helps differentiate FH from other forms of hypercholesterolemia and guides treatment decisions.
b) ***Risk Stratification:*** Not all FH mutations are equal in terms of their effects on cholesterol levels and cardiovascular risk. Precision medicine allows for risk stratification based on the specific genetic mutation. Some mutations may result in more severe forms of FH, while others might be associated with a milder phenotype. Understanding the genotype-phenotype correlation assists healthcare providers in predicting disease progression and implementing appropriate interventions.
c) ***Tailored Treatment Approaches:*** Precision medicine enables healthcare providers to design personalized treatment designs grounded on a patient's genetic-profile. For instance, some individuals with FH may respond better to certain types of cholesterol-lowering medications, while others may require a combination of therapies. Knowing the genetic mutation helps guide the selection of medications and dosages, optimizing treatment outcomes.
d) ***Early Detection and Family Screening:*** Identifying the specific genetic mutation in a patient with FH opens the door to proactive screening of family members. Genetic testing allows health care practitioners to identify relatives who may also carry the same mutation and are at risk of developing FH. Early detection and intervention in at-risk family members can significantly reduce the likelihood of cardiovascular events.

Monoclonal Antibodies and Biological Therapies: [24]

Monoclonal antibodies and biological therapies are gaining traction in cardiovascular precision medicine. These therapies are designed to selectively bind to specific molecular targets involved in disease progression. For instance, monoclonal antibodies that restrain proprotein-convertase subtilisin/ kexin-type 9 (PCSK-9) have shown success in lowering cholesterol-levels in patients with Familial-hypercholesterolemia. Monoclonal antibodies are a class of biological therapies that have gained significant attention in the field of cardiovascular disease treatment. These antibodies are designed to target specific molecules involved in disease pathways, offering a targeted and precise approach to therapy. In precision medicine, monoclonal antibodies are being harnessed to address various cardiovascular conditions by tailoring treatment to individual patient characteristics. The applications of Monoclonal antibodies in cardiovascular disease are as follows:

a) Cholesterol Management: Monoclonal antibodies targeting proprotein-convertase subtilisin/ kexin-type 9 have emerged as a breakthrough in cholesterol management. PCSK-9 inhibitors, such as Evolocumab and Alirocumab, bind to PCSK-9 and upgrade the liver's capability to strip off LDL-cholesterol from the blood-plasma. Precision medicine plays a role in identifying patients among FH or those who does not counter well to

traditional statin therapy. Genetic testing helps select patients who can benefit the most from these therapies. [24]

b) ***Inflammation and Atherosclerosis:*** Biological therapies, including monoclonal antibodies, are being explored to target inflammation pathways involved in atherosclerosis. Interleukin-1 beta (IL-1β) inhibitors, like Canakinumab, have shown promise in reducing cardiovascular events by targeting inflammation. Precision medicine aims to identify patients with elevated inflammation markers who could benefit from these therapies. [25]

c) ***Heart Failure:*** Monoclonal antibodies targeting the neprilysin pathway, such as Sacubitril/ Valsartan, have been approved for the management of heart-failure with demoted ejection fraction. Precision medicine aids in patient selection, ensuring that those with appropriate clinical characteristics benefit from these therapies. [26]

1. Gene Therapy:

Gene-therapy has arisen as a promising vision for targeted interventions. By delivering functional genes or altering gene expression, gene therapy aims to correct genetic defects underlying cardiovascular diseases. In the context of heart failure, gene therapy trials are exploring approaches to enhance cardiac function by modulating specific genes. For the medical management of hereditary and acquired heart disease, gene therapy is a potential approach. Pre-clinical gene-therapy investigations in trivial and portly animal prototypes were encouraged as a result of the discovery of the molecular pathways implicated in the patho-physiology of heart-failure and further related cardiac-illnesses. However, the early clinical outcomes showed just a slight or nonexistent improvements in the clinical objectives. The overall modest clinical benefits were attributed to the existence of neutralizing antibodies and cellular immune rejoinders focused alongside the viral vector or the gene-adapted cells, the inadequate extent of gene expression, as well as the restricted gene-transduction efficiency. However, recent developments in gene delivery techniques with a deeper comprehension of the triggering biology have stoked devotion in gene therapy for heart-failure once more. [27]

a) ***Non-viral vectors for CVD:*** Gene therapy aims to either insert a therapeutic gene or substitute a damaged gene within a patient's cells along with tissues. The creation of the gene delivery vector is essential for the effectiveness of treatment involving genes. Notwithstanding the early hoopla around the trials and the first optimistic results generated by non-viral vectors, the majority of current investigations have demonstrated that this strategy is often not particularly effective for treating CVD using gene therapy. While the plasmid is quickly removed from the systemic-circulation, many methods have been devised to augment its whole effectiveness, such through the utilization of liposome-DNA-complexes which foster plasmid permanency. Plasmids are shielded from nuclease digestion and made easier for cells to absorb thanks to polymer-based-DNA complexes grounded on poly-L-lysine (PLL) as well as poly-ethyleneimine (PEI) compounds. [27, 28]

b) ***Viral vectors for CVD:*** Viral vectors are made up of genetic information encased in a protein- or lipid-based envelope that engages with certain receptors found on cell surfaces to help the therapeutic gene bind, internalize, and enter the target cell. Viral vectors offer the potential for long-term gene expression and are superior to non-viral vectors.

i. ***Adenoviral vectors:*** Adenoviral carriers are non-enveloped, non-integrating double-stranded genetic vector which connect to the coxsackie-adenovirus receptor and are mostly internalized through clathrin-mediated endocytosis. That is a helpful approach for administering short-term pro-angiogenic treatments for limb ischaemia, peripheral artery occlusive disease, and ischemic heart illnesses. Single key drawback of Adenoviral vectors links to their capability to persuade soreness, which negotiate their effectiveness and welfare within the trials.

ii. ***AAV:*** Single-stranded DNA vectors called adeno-associated-viral vectors (AAV) have a good safety record and may successfully achieve permanent transgene expression in a variety of target organs, notably the cardiac muscle. As they hassle extensively less soreness assessed with Ad-vectors, they have earned a heap of advantage for cardiac-gene therapy involving treatments. More than one hundred serotypes of the wild-type Adeno-associated-viral vectors have been reported. The molecular makeup of the capsid protein determines the tissue tropism of many. AAV-1, AAV-6, AAV-8, along with AAV-9 have been established as the utmost cardiotropic serotypes afterwards systemic delivery. AAV-9 was found as the utmost capable serotype for cardiac-gene delivery in mice. [27, 29]

iii. ***Lentiviral vectors:*** Recombinant viral vectors that have been specially engineered are effective vehicles for delivering genetic material to cells in mammals. Lentiviral vectors which are gaining special attention for fundamental investigation and preclinical investigations in the cardio-vascular sector because of their remarkable effectiveness at infecting both dividing and non-dividing cells. The AIDS-virus virion is the principal source of lentiviral vectors. Via dividing the HIV-genome's cis- as well as trans-acting regions, they are made to be replication-defective. This reduces the possibility of creating recombination which are replication-competent and creates viral particles that are unable to replicate in the recipient after delivering their genetic material.

By employing fluorescent reporter genes or protein molecules that confer particular drug obstruction, lentiviral vectors may be employed to monitor cardiac cells while differentiation, reveal cardiac cells in vivo, and purify cardiac-specific groups of cells while differentiation. Lentiviral vectors can also be utilized for transmitting certain genes that trigger cardiac differentiation or for gene transfer/ correction tactics for therapeutic purposes. [30, 31]

CONCLUSION

Precision medicine presents a paradigm shift in the management of cardiovascular disease, harnessing genetic, molecular, and clinical insights to tailor interventions. Clinical trials evaluating personalized treatment approaches underscore the proficiency of precision medicine to revolutionize cardiovascular care. Principles of precision medicine in cardiovascular disease revolve around the recognition of individual variability, genetic influences, biomarker insights, patient-specific factors, and personalized treatment strategies. By applying these principles, healthcare practitioners can move beyond a generalized approach to treatment, thereby enhancing patient effects, reducing side-effects, also optimizes the allocation of healthcare supplies. Biomarkers and genetic profiling serve as cornerstones of precision medicine's personalized approach to cardiovascular disease management. These tools enable health care practitioners to identify individuals at risk, tailor treatments for optimal responses, and monitor disease progression non-invasively. While challenges exist, advancements in "OMICS" technologies and the potential to enhance patient outcomes make biomarker and genetic profiling integral components of the future of cardiovascular medicine. Targeted therapies in cardiovascular disease represent a pivotal advancement in cardiovascular precision medicine, ushering in an era of treatment customization based on individual patient characteristics. By leveraging genetic insights and molecular knowledge, these therapies optimize treatment outcomes while minimizing adverse effects. While challenges persist, the promise of improved patient care, reduced treatment burden, and enhanced therapeutic efficacy makes targeted therapies a cornerstone of future cardiovascular disease management.

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