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Challenges and Opportunities in the Management of Cardiovascular Diseases

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Abstract: In the 21st century, cardiovascular diseases (CVDs) constitute the leading cause of death. It is difficult for potential CVD therapies to be successful since CVDs cannot be effectively or cheaply treated with existing therapy. To formulate and transport therapeutically active molecules to treat a variety of ailments, innovative drug delivery carrier systems have emerged as an efficient method. Their applications have a potential role in routine drug discovery. Heart failure has been studied using a variety of novel treatment approaches, such as cell transplantation, gene transfer or therapy, cytokines, or other small molecules. This review briefly highlights key points in the management of CVDs.

Introduction

Cardiovascular illness or diseases (CVDs) affects the heart and blood vessels (arteries, veins, and capillaries), either alone or together (1). A cardiac disorder called angina pectoris is characterized by chest discomfort brought on by a lack of oxygen to the heart (2). A variety of factors can bring on heart disease, but the two most frequent are atherosclerosis and hypertension. Additionally, even in healthy, symptom-free individuals, aging causes a variety of physiological and morphological changes that alter cardiovascular function and raise the risk of cardiovascular disease in later years (3). Large numbers of people die each year as a result of cardiovascular disease. Cardiovascular death rates have decreased in several developed nations since the 1970s (4). Likewise, cardiovascular-related fatalities and illnesses have shot up quickly in emerging nations (5). Since atherosclerosis is a precursor to cardiovascular disease, we should take the required primary preventative measures as early as possible (6). To avoid atherosclerosis, it is necessary to focus more attention on modifying and managing risk factors, such as good food, appropriate exercise, and quitting smoking, among others.

Current Statistics on Cardiovascular Disease

Cardiovascular disease (CVD) remains the leading cause of mortality worldwide, affecting millions of individuals and disproportionately impacting developing nations, where over 80% of deaths occur. It affects both men and women almost equally, making it a critical global health issue. By 2030, the number of deaths from CVD is projected to rise to 23.3 million, primarily due to heart disease and stroke, further cementing its status as the top global cause of death (7). In 2008 alone, CVD accounted for an estimated 17.3 million deaths, making up approximately 30% of all global fatalities, with coronary heart disease and stroke contributing to 7.3 million of those deaths. More recent estimates indicate that around 9.4 million people die from CVD annually, with 45% of these deaths attributed to coronary heart disease and 51% to heart attacks. The burden of CVD continues to strain healthcare systems and economies, particularly in low- and middle-income countries where access to preventive care and treatment is limited. However, a significant portion of CVD-related deaths could be prevented through increased public awareness and proactive lifestyle changes (8). Addressing modifiable

risk factors such as obesity, unhealthy diets, tobacco use, physical inactivity, high blood pressure, elevated blood lipid levels, and diabetes can substantially reduce the incidence of CVD. Governments and healthcare organizations worldwide are working to implement public health initiatives aimed at educating communities about prevention strategies, improving access to medical care, and promoting heart-healthy behaviors. Through a combination of policy changes, healthcare interventions, and individual efforts, the global burden of CVD can be mitigated, ultimately saving millions of lives each year.

Roadmap for CVD Drug Screening

With over 30% of fatalities each year, CVDs are among the most prevalent illnesses in the world (9). Drug administration in the early stages of the illnesses and mediated techniques in the diseases after stages, later on, have been common strategies for avoiding and treating such problems (10). New treatment agents with increased effectiveness and safety are thus increasingly needed. Each new medicine candidate costs the pharmaceutical industry an average of $2 billion, and it takes over 20 years to research, get approval, and get to market. Over the past ten years, fewer novel pharmaceutical compounds have received regulatory approval, despite rising demands as well as ongoing research and development (R&D) activities. Before being allowed on the market, new medications must adhere to strict regulatory standards maintained by different international as well as national agencies, including the World Health Organization (WHO), Food Drug Administration (FDA), Health Canada, and the European Medicines Agency (EMA). Nevertheless, many such therapeutically active molecules, despite entering the later pipeline stage of discovery, cannot make it into the market due to their issues related to safety like hepatic damage, kidney damage, cardiac issues, or concerns regarding effectiveness. The two development phases of the clinical trial, Phase II and III, have been seen to have higher debilitation rates, like 80% (11, 12). Due to having severe cardio or hepatic toxicity, many drugs have also been withdrawn from the market after receiving approval (13). Early phases of development account for more than 60% of costs associated with medication development (14). This fact highlights the value of investing in precise, affordable, and secure preclinical screening methods to screen for promising molecules of the drug early into the process of development in the view of reducing Research costs, development costs, and time by substituting or streamlining ineffective development procedures of the drug.

These days, in silico modeling, or computer-aided drug design (CADD), is a very important subject centered on creating quantitative strategies to support decision-making, lower the price of drug development, and increase the likelihood of therapeutic success (15). A cheap, moral, and valuable way to swiftly test several hypotheses is using in silico modeling. Mechanistic modeling is a well-known computational medicine technique that converts biological processes into mathematical expressions, sometimes referred to as the knowledge-based method (16). For instance, a vital mechanistic model that effectively captures the interactivity between medications and networks of the disease may be created using quantitative systems pharmacology (QSP) (17). These artificial in-silico drug-disease models have drawn a lot of interest for their potential to reduce the use of animal models, produce a higher quality of results in the future, and help determine the best treatment plans for patients with CVDs with numerous risks.

Limitations and Future Outlooks

By developing a multi-functional platform that combines the etiology and pathophysiology understanding of CVD, ever-evolving engineering technologies (such as micro/nanofabrication), and CADD, the goal is to reduce the use of experimental animals in preclinical research while enhancing translation and drug discovery is made possible. The ultimate objective, for instance, would be to create innovative CVD medication candidates with high efficacy while carefully regulating toxicity and pharmacokinetics (PK). Even though several successful CADD uses in contemporary drug design, there are some limitations with these platforms. In particular, results in hypothetical computer-aided systems must be verified in natural systems, and several lead molecule recantations using CADD have failed to show the intended activities in different physiological systems (18). Before a chemical is approved as a decisive lead or medication, it must fulfil some crucial requirements and meet certain pharmacological requirements. On average, only 40% of medication or lead molecules make it through the various stages of clinical studies and are authorized for use in patients. Molecular docking, virtual screening, QSAR (Quantitative structure-activity relationship), pharmacophore modeling, and molecular dynamics are a few of CADD's computational techniques that have shortcomings (19-22). Furthermore, various methods of these computational techniques fail in the literature (23, 24), and trustworthy evidence does not explain the ADME and many toxicity evaluation tools based on experiments.

It is vital to address the continuous updates of techniques and algorithms to come out from the limitations and increase efficacy when analyzing powerful lead compounds. To create and maintain high-quality experimental molecules, it is also vital to

increase the database's dependability. Numerous pharmacophoric groups cannot pass the physiological activity test because there are not enough high-quality data sets available. Databases should provide comprehensive genomes and proteomics data, reliable sequencing data, and information on structures and their physicochemical characteristics. However, there is still room for advancement and optimization. High-throughput screening for toxicity determination for testing drugs, which enables evaluating a huge number of molecules at a cheaper cost and in a brief amount of time, is also an unmet need. Numerous pharmaceuticals have received FDA clearance in the United States, including TKI-related compounds for cancer therapies created utilizing high-throughput screening technologies. Developing a high-throughput platform for screening the drug with accurate, repeatable findings and proper physiological function for the native cardiac system is challenging because of technical constraints and the ensuing tissue maturation.

To evaluate the in-vitro cardiotoxicity of innovative medications, the FDA has asked businesses to research the suppression of the human cardiac ether-à-go-go-related (hERG) gene, which encodes a potassium ion channel in cardiac cells. Early on in the drug development process, the hERG channel can be inhibited to increase cardiotoxicity and action potential duration. Using patient-specific human-induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs), researchers may also create models for several CVDs, including left ventricular non-compaction, long QT syndrome, dilated cardiomyopathy, and hypertrophic cardiomyopathy (25).

With the use of in silico models, we can now imagine vital systems of various sizes, mimic the effects of medications and treatment approaches utilized in clinical methods and their settings, and assess the reliability of existing physiological understanding and clinical results. These computer models are significantly cost-effective for forecasting medication pharmacokinetics (PK), pharmacodynamics (PD), and patient population responses [26]. They also offer fresh perspectives on the underlying biology, which broadens our understanding of illnesses. For instance, the regulatory decision-making paradigm has been transformed to avoid the danger brought on by a newly discovered medicine, thanks to the program for forecasting ADMET qualities. Implementing these cutting-edge technologies at the beginning of the drug research process, such as the preclinical phases, may avoid drug attrition later. Similarly, bringing together regulatory authorities and academic and industry scientists to make judgments on the present platforms' standardization, regulation, and validation to assure accuracy, specificity, and repeatability might prevent late-stage drug failures. Additionally, the combination of in-vitro and in-silico CVD models that take into account a person's genomes, surroundings, and lifestyle decisions may lead to more precise in-vivo predictions, which would help CVD patients by giving them access to safer and more efficient treatments. The new drug discovery paradigm may change the preclinical methodology now in place for using animal models.

Conclusions

Drug discovery and their formulation development are promising and cutting-edge drug delivery technologies that have the potential to significantly improve the stability and non-specific side effects of both traditional and contemporary therapies. Future design and development of efficient drug delivery systems based on CADD are advancing to identify and treat CVDs.

Declarations

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Conflict of Interest

The authors declare no competing interest.

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Not applicable.

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