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Integrating strategies for the treatment of ischemic heart disease based on clinical instrumental and molecular genetic analysis (Literature review)

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Annotation

Recent progress in the comprehension and management of heart diseases, specifically those related to atherosclerosis, is highlighted. The importance of employing genetic insights alongside advancements in biotechnology and pharmacology is underscored to create tailored treatment options for individuals suffering from severe forms of conditions such as Familial Hypercholesterolemia, who do not respond effectively to conventional lipid-lowering interventions.

Limitations of current tools used for assessing cardiovascular risk, particularly in secondary prevention settings, are discussed. There is a critical need to enhance understanding of patient variability and the impact of lifestyle and environmental factors on health outcomes. Additionally, how gut microbiota and dietary practices contribute to inflammatory processes associated with atherosclerosis is examined, emphasizing the necessity for a comprehensive approach to understanding disease mechanisms.

Furthermore, the analysis elaborates on discoveries from large-scale genetic studies that illuminate the complex genetic landscape of coronary artery issues and the significant influence of specific genetic variations. Integrated approaches across multiple biological layers are advocated to discover functional pathways connected to coronary conditions, while also identifying potential biomarkers relevant to acute myocardial infarction and subsequent heart failure.

The relationship between oral health issues, such as gum disease, and cardiovascular problems is explored, with suggestions for using modern statistical methods to establish causality. Lastly, the significance of adopting innovative imaging methods and blood markers is emphasized to enhance diagnostic and prognostic capabilities in relation to coronary artery disease and similar conditions. This synthesis reflects a dynamic shift in research focused on improving prevention, diagnosis, and therapeutic strategies for ischemic heart disease.

Key words: cardiovascular disease, atherosclerosis, risk assessment, genetic information, secondary prevention, Familial Hypercholesterolemia, acute myocardial infarction, biomarkers, multiomics, Mendelian randomization, coronary artery disease, ischemic heart disease, stroke, heart failure, network pharmacology, metabolomics, Traditional Chinese Medicine, inflammatory diseases, periodontitis, epidemiological studies, gene expression profiling, machine learning, health outcomes, ischemic stroke, variability, personal health, lifestyle factors, health burden, clinical practice, predictive biomarkers.

The most common forms of cardiovascular disease, presenting with atherosclerosis as the etiopathological factor (ACVD) (e.g., secondary prevention patients complicated by metabolic alterations, severe heterozygous forms of Familial Hypercholesterolemia (FH) or, even more severe, homozygous FH) were untreatable using classical lipid-lowering treatments, before the use of genetic information and tremendous the advances in both biotechnological and pharmaceutical research.

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These advances, that have occurred in recent years, both heralded new therapeutic horizons and contributed further knowledge on the pathophysiological bases of such diseases, making it possible to identify markers at every stage of a molecular or cellular pattern, that can help to cluster patients who require the earliest and most aggressive forms of intervention. The latter is of immediate interest since, persisting through to today, the multitude of tools currently available in the clinics for risk assessment and the prevention of fatal and non-fatal cardiovascular events are often inaccurate. When addressing the issue of secondary cardiovascular prevention, for example, despite numerous attempts, a tool for a more precise risk assessment in terms of cardiovascular complications has not yet been implemented in clinical practice. Within this group of patients, there may be the potential for heterogeneity in the recurrence of cardiovascular events, which represents a particular concern. This can be viewed as a causative factor for subsequent studies focusing on the patient's position in secondary ACVD prevention. ACVDs, for all degrees of risk and at every stage, are diseases encompassing a multitude of complex, hardwired biological systems. Thus, in attempts to find a solution for a more accurate risk assessment, numerous factors should be taken into account and blended together, including not only the clinical phenotype of patients, laboratory and instrumental findings but also the impact of external environmental factors that characterize the daily life of a person. For example, the classical "metabolic-centric" vision of unhealthy dietary habits in the development of atherosclerosis and the related ACVD risk has been recently implemented in an immune-inflammatory context and is able to induce long-lasting changes in the gene expression and activation of entire molecular systems of the host. In fact, low quality in dietary habits (e.g., elevated consumption of industrially processed foods in place of fibers and vegetables), which reflects the environmental and socioeconomic status of the subjects, induces a long-term somatic leukemogenic expansion of the hematopoietic stem cells, and has been associated with ACVD. An analysis of gut microbiota composition conducted through the use of metagenomic sequencing, recently revealed that the variety of specific bacterial species, associated and implicated with subclinical atherosclerosis and its clinical manifestation, predisposes individual metabolic and inflammatory responses to foods [1].

The human genome is complex and regulated at multiple levels. Although findings from a genome-wide association study (GWAS) indicate that a single nucleotide polymorphism (SNP) is associated with a phenotype, a GWAS study cannot provide insight into the molecular mechanism whereby an SNP exerts its effect. Functional studies in the laboratory then are required to identify the underlying genes. Such studies often require collecting additional biomedical data on the study participants, which are not always possible because of privacy concerns and other logistical considerations. Parallel to the GWAS studies, in the past years, numerous studies have also been carried out to systematically investigate the role of SNPs at different molecular levels (transcriptome, proteome, epigenome...) and across our tissues. Therefore, a set of SNPs that significantly and independently contribute to a molecular biomarker (probe) can be used as an instrument to infer a causal effect between the probe and a phenotype using Mendelian randomization (MR) analysis. The past decade of research has provided a broader understanding of the genetic architecture of coronary artery disease (CAD) and demonstrates that it largely derives from the cumulative effect of common SNPs throughout the genome each of small effect size rather than rare variants with large effects on CAD risk. Despite this success, there has been limited progress in understanding the function of the

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novel loci, the majority of which are in noncoding regions of the genome. In the current study, we thought by integrating the GWAS summary statistics for CAD with GWAS findings from omic studies, we may be able to find functional mechanisms whereby a CAD locus exerts its effect and find molecular probes causally associated with CAD risk. For this purpose, we devised a multiomics data analysis plan (Figure I in the Data Supplement) based on MR and utilized it to search for molecular probes causally associated with the risk of CAD [2].

Acute myocardial infarction (AMI) is a consequence of rupture or erosion of a vulnerable, lipid-laden, chronic atherosclerotic coronary plaque, resulting in acute interruption of myocardial blood flow and ischemic myocardial necrosis, which remains a common cardiac emergency incidence with substantial morbidity and mortality worldwide. Concurrently, low and middle-income countries now cover more than 80% of deaths from cardiovascular disease worldwide, which contributes to the societal burden, as assessed by impaired disability-adjusted life-years. The current diagnostic evaluation for the presence of AMI relies on troponin or creatine kinase MB-fraction assays in addition to an electrocardiogram (ECG), which detects necrotic cardiomyocytes. However, it has been recognized for decades that most atherosclerotic lesions underlying AMIareonlypartial luminal narrowing prior to acute plaque rupture and not obstructing the coronary blood flow. Consequently, the inability to accurately and temporally predict the occurrence of AMI impairs our capability to further improve patient outcomes. Acute myocardial infarction has traditionally been classified on the basis of the presence or absence of ST-segment elevation (STEMIornon-STEMI) on the ECG.It is pertinent to note that a totally occlusive thrombus typically leads to STEMI and develops transmural or Q-wave MI, whereas most patients with non-STEMI have a partial occlusion or occlusion in the presence of collateral circulation, develop subendocardial, non-transmural, or non-Q-wave MI. However, STEMI is not only in both elderly and non-elderly (age < 65 years) patients, but survivors of acute STEMI are prone to develop progressive ventricular remodeling and dysfunction that leads to heart failure (HF). While advances in the contemporary management of STEMI have improved rates of short-term survival, the subsequent progression of HF is emerging as a prominent cause of long-term outcomes, despite the sustained potency of the infarct-related artery, by the successful percutaneous coronary intervention (PCI). Moreover, recommended HF-associated biomarkers, including B-type natriuretic peptide (BNP) and N-terminal probrain natriuretic peptide (NT-proBNP), lack specificity that they can also exhibit elevated levels in patients with congestive HF, renal failure, primary aldosteronism, and thyroid disease. There are, therefore, novel robust biomarkers with predictive potentiality for screening the chronic ischemic preconditioning and the occurrence of STEMI, and also the development of post-STEMI HF remains a crucial target for scientific advancement in cardiovascular diseases. Next-generation sequencing (NGS) technology is the driving force for genome-wide gene expression profiling, and transcriptome analysis via indispensable bioinformatics approaches has been extensively used for obtaining novel insights into mechanisms underlying the development of diseases and identifying the potential biomarkers. In the present study, we performed an integrated gene expression profiling analysis and applied a machine-learning algorithm to investigate the shared molecular patterns and identify prognostic/diagnostic differentially expressed genes (DEGs) associated with STEMI and post-STEMI HF, and detectable in the peripheral blood of patients, which may contribute to the early warning and optimized risk stratification of AMI [3].

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Coronary heart disease (CHD) is characterized by insidious onset, rapid onset, and easy progression to fatal types, such as acute myocardial infarction and heart failure. It is one of the most common ischemic heart diseases and the main reason for cardiovascular death. Since 2000, the number of deaths caused by ischemic heart disease has increased annually, contributing to 16% of the total deaths worldwide, thus becoming the world's largest killer for both men and women. At present, the main treatment methods for CHD include drug therapy, interventional therapy (endovascular balloon dilatation and stent implantation), and surgery (coronary artery bypass grafting). The aim of these treatments is to rescue ischemic myocardial tissue and cells by restoring blood supply to the ischemic area in a timely manner. However, the current methods have limited efficacy, and some of them even produce significant side effects. Therefore, targeted intervention programs should be formulated without delay to improve patients' quality of life. Some Chinese herbs have the advantage of low price, low toxicity, and synergistic effect, and are generally included in Traditional Chinese medicine (TCM) which is a very popular, complementary, and alternative medical practice. The Chinese herbal formula Xuefu Zhuyu (XFZY) is a boiled water extract of 11 herbs. It was first recorded >200 years ago in the book "Correction of Errors in Medical Classics" but remains very popular in China. During the past years, substantial research studies verified the effectiveness of XFZY in the treatment of CHD. However, because XFZY is composed of 11 Chinese herbs, its drug composition and metabolism are complex, thus rendering its pharmacological research challenging. Metabolomics is a high-throughput technology for the identification of disease biomarkers and the exploration of complex effect relationships between living systems and drugs. By analyzing the metabolite profile, metabolomics dynamically track and analyze metabolites in the metabolic cycle. With the help of multivariate statistical analysis methods, metabolomics instantly and sensitively reflect the functions of organisms caused by internal and external factors, such as genes and the surrounding environment. Furthermore, potential changes in state pro vide information to clinical practice. Because of these advantages, a growing number of researchers utilize metabolomics to reveal the pharmacological mechanism of TCM prescription. Network pharmacology, which constructs a "component-target-pathway" multi-layered network, vividly reflects the characteristics of TCM, and intuitively clarifies the mechanism of drug compatibility. Network pharmacology significantly contributes to revealing the intrinsic therapeutic mechanisms of Chinese medicine and its related compounds, and also provides more options for investigating and understanding the mechanism of TCM action. Recently, some researchers combined metabolomics and network pharmacology, and significant progress has been made toward understanding the action mechanism of TCM. In this work, we applied the combined method of network pharmacology and metabolomics to investigate the action mechanism of XFZY in the therapy of CHD and to predict its effective components, key targets, and related pathways [4].

Cardiovascular disease (CVD) is a common and complex disease, especially in middle-aged people over 50 years old; its morbidity, disability, and mortality rates are relatively high, posing a serious threat to human health. Every year, the number of people dying from CVD is as high as 17 million, ranking first among all causes of death. Ischemic heart disease, stroke, heart failure (HF), cardiomyopathy, and atrial fibrillation (AF) account for more than 95% of cardiovascular disease-related deaths. CVD is caused by heredity, environment, and their interactions; conventional risk factors for CVD are mainly lifestyle risk factors, including smoking, lipid metabolism disorders, hypertension, and altered glucose metabolism, all of which can be improved by lifestyle improvements. Currently, genetic studies have found a variety of CVD susceptibility genes. As

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knowledge of cardiovascular disease continues to increase, several chronic infectious, inflammatory, and immune diseases—such as periodontitis—are being found to be related to a significantly increased risk of adverse cardiovascular events. Periodontitis is one of the most common inflammatory diseases worldwide, with an incidence rate of 20–50%. Periodontitis is common in adults and is the sixth most prevalent disease globally, characterized by the gradual disintegration of the tooth-supporting apparatus. The World Health Organization reports that periodontitis is the leading cause of tooth loss in adults. Dental caries and periodontitis are prevalent in adults, especially in individuals who are older, leading to momentous health and financial burdens. Epidemiological studies have indicated that severe loss of support structure and tooth loss caused by advanced periodontitis affect ~15% of the world's population, mainly affecting adults, and morbidity increases with age in all populations. Familial and twin studies have emphasized the role of genetics in chronic periodontitis. There is now substantial evidence supporting an independent association between severe periodontitis and CVDs. Periodontal disease (PD) may lead to an overall burden of inflammation in the body and can play a role in the pathogenesis of CVDs. Evidence-based studies have revealed that dental diseases—such as periodontitis, dental caries, and tooth loss—increase the risk of diabetes mellitus, atherosclerosis (AS), stroke, coronary artery disease (CAD), HF, and AF. Research has shown that patients with moderate to severe periodontitis have a higher risk of an initial cerebrovascular event than patients without periodontitis or with mild periodontitis; people suffering from periodontitis have more than twice the risk of stroke than periodontally healthy people. Several studies have also reported a positive relationship between periodontitis and HF. A large-scale study from Asia based on the Taiwan National Health Insurance Research database suggests that the incidence of AF in patients with periodontal disease is significantly higher than that in patients without periodontal disease. Recently, large-cohort studies have indicated that both new-onset and prevalent periodontitis are related to increased CAD risk, and in patients with stable CAD, there are graded associations between tooth loss, stroke, and cardiovascular and all-cause death. However, the causality between PDs and CVD remains unclear, since observational studies are impeded by reverse causal bias and residual confusion. Due to the nature of the study design, the existence of potentially significant confounding effects may bias the results of observational studies. Mendelian randomization (MR) is a kind of data analysis method that is mainly used in epidemiological etiology inference. Alleles are randomly assigned to progeny gametes during gamete formation based on the Mendelian independent distribution law. Therefore, the associations between genes and diseases are not influenced by common confounding factors such as postnatal environment, socioeco nomic status, or behavioral factors, and the causal timing is reasonable, making the effect estimates closer to the real situation [5].

Stroke is a heterogeneous and complex disease composed of 3 main types: ischemic stroke, intracerebral hemorrhage, and subarachnoid hemorrhage. Within the phenotype of ischemic stroke, various subtypes appear to differ in degree of heritability. Here, we focus on ischemic stroke and its subtypes. GWASs have provided the strongest evidence for loci associated with the common form of ischemic stroke (Table 2). To date, all such loci have had 2 characteristics. First, most of the loci have been discovered in other mechanistically related conditions such as atrial fibrillation, CAD, and coagulation, with subsequent confirmation of associations with ischemic stroke. This is not unexpected, given the pathogenic associations between stroke and these other traits, and because the GWASs of these other conditions have far greater sample sizes and statistical power compared with the GWASs of ischemic stroke. Second, the associations are specific to subtypes of ischemic stroke.

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For example, a locus on chromosome 4q25 adjacent to the transcription factor PITX2 (codes for pituitary homeobox 2), found to be associated with atrial fibrillation, was subsequently found to be associated with cardioembolic stroke.52 Additionally, a locus on chromosome 16q22 involving ZFHX3 (the zinc finger homeobox protein 3) has been associated with both atrial fibrillation and cardioembolic stroke.53 Similarly, a pooled analysis demonstrated that 6 SNPs in the chromosome 9p21 locus, first identified through a heart disease GWAS,26 are associated with atherosclerotic stroke independently of demographic variables, CAD, MI, and other vascular risk factors.54 The 9p21 locus seems to affect stroke risk independently of the risk of MI. Genetic variants identified through GWASs of coagulation/fibrin phenotypes were subsequently examined for association with ischemic stroke. The rs505922 in the ABO gene was found to have a replicated association with large-vessel and cardioembolic stroke.28,55 GWASs have yet to identify a locus that imparts risk by modifying tissue sensitivity to ischemic injury. A genetic variant that imparts sensitivity of the brain parenchyma to focal ischemia might be expected to have an association across ischemic stroke subtypes while lacking an association with conventional atherosclerotic risk factors for stroke such as atrial fibrillation and hypertension (parenchymal hypothesis) [6].

Cardiovascular diseases (CVDs) are the primary cause of mortality worldwide with 17.3 million deaths per year, and an estimation of 23.6 mil lion in 2030, placing it as a relevant issue for the public health system. Coronary heart disease (CHD) is the largest contributor of CVDs and the mortality rate is due in prevalence to atherosclerosis, a chronic inflammatory condition of the arterial wall. Unfortunately, myocardial infarction (MI) is still a first common manifestation of CHD and, in about 50% of patients, angina pectoris is the first symptom of the pathology. For this reason, an accurate and prompt diagnosis in CHD patients could improve prognosis and/or quality of life and allow timely and adequate therapeutic treatments (percutaneous or surgical myocardial revascularization, pharmacological therapy). Furthermore, efforts should be focused on primary prevention or early detection of subjects suffering from coronary atherosclerosis, in order to implement therapeutic strategies, so reduce morbidity, health expenditure, and mortality. The risk of clinical manifestations of CHD is currently estimated according to multifactorial integrated prediction models developed on the basis of population studies that have allowed to evaluate the likelihood of cardiac events, even though some of them have a poor predictive value. Imaging techniques have deeply increased early detection of CHD, although the invasive approach restricts their feasibility mainly to symptomatic patients. Among them, for their higher spatial resolution, intravascular ultrasound (IVUS), X-ray angiography (XRA), and computed tomography coronary angiography (CTCA) provide a direct evaluation and quantification of coronary artery alteration, while cardiac magnetic resonance (CMR) and nuclear medicine techniques (single photon computed tomography (SPECT), and positron emission tomography (PET)) provide indirect information of CHD, estimating myocardial perfusion and metabolism abnormalities that are consequent to coronary artery disease. In addition, serum/plasma biomarkers can be mini-invaextracted in asymptomatic patients in order to analyze at different levels (e.g., cellular, biochemical, epigenetic, and/or transcriptional) atherosclerosis and CHD development. This review underlines the role of different imaging modalities in the setting of coronary atherosclerosis and describes novel blood-based markers that could improve diagnosis and have a better predictive value in CHD [7].

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