Innovative approaches to cardiovascular disease prevention based on biological research, including gene therapy and stem cells

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Abstract. This article discusses innovative biologic-based approaches to cardiovascular disease prevention, including gene therapy and stem cell therapy. Gene therapy offers promise for targeting genetic factors that contribute to cardiovascular disease, while stem cell therapy holds promise for tissue regeneration and repair. The article highlights the role of these advanced approaches in promoting cardiovascular health and preventing disease progression. The importance of ongoing biological research in developing effective measures to prevent cardiovascular disease is also discussed.

1 Introduction

Biologic therapy, involving substances derived from living organisms or lab-produced analogues, has expanded its therapeutic applications beyond cancer and rheumatologic conditions to include cardiovascular disease (CVD). While its use has raised concerns about adverse cardiovascular effects like heart failure (HF), it has also shown promise in positively impacting CVD. Notably, the relationship between inflammation and CVD has led to interest in blocking inflammatory cytokines as a treatment approach. Atherosclerosis, a key CVD pathology, involves the accumulation of oxidized lipids and inflammatory cells in arterial walls, leading to plaque formation and, potentially, rupture, thrombosis, and myocardial infarction. Ischemic cardiomyopathy, resulting from myocardial ischemia and inflammation, can progress to HF. Autoimmune disease populations, characterized by systemic inflammation, exhibit increased CVD risk, suggesting inflammation as a potential contributor to CVD development. Studies evaluating biologic therapies in rheumatologic populations have shown positive cardiac risk reduction outcomes, but generalizing these findings to the broader population requires further investigation.

Strategies for delivering genes to the vasculature need to account for the variety of cell types involved, such as vascular smooth muscle cells, endothelial cells, myocardium, and those involved in lipid metabolism. Therefore, vector systems and delivery methods must be tailored for each application. The four primary methods for introducing therapeutic genes

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into the vasculature are ex vivo gene transfer to vessel segments, cell-based delivery, systemic delivery, and local delivery approaches. Ex vivo gene therapy, in particular, is preferred in cases where it is feasible, as it allows for safe and efficient delivery of therapeutic genes directly to the target tissue. For example, during coronary artery bypass surgery, veins can be genetically modified outside the body before grafting, minimizing systemic release of the vector and reducing the risk of unwanted immune responses.

Cardiovascular disease (CVD) remains a significant contributor to mortality in the United States, accounting for approximately one-third of all deaths [1]. Rural populations face distinct disparities in CVD-related health outcomes compared to urban areas, exhibiting lower adherence to physical activity guidelines and higher prevalence rates of smoking, obesity, and type 2 diabetes. Rural women, in particular, confront additional risk factors stemming from socioeconomic factors such as income, education, age, and access to healthcare [2]. Environmental factors in rural settings, such as limited opportunities for physical activity, access to nutritious foods, and healthcare resources, further compound these risk factors. Consequently, addressing cardiovascular health among women in rural and medically underserved areas is paramount for effective CVD prevention initiatives.

Health policymakers are confronted with challenging decisions regarding the allocation of resources between targeted CVD prevention efforts, other public health initiatives, and clinical healthcare [3]. Economic evaluation methods serve as valuable tools for guiding the allocation of scarce societal resources towards endeavors that yield the greatest improvements in health outcomes. While prevention investments may initially increase healthcare costs, they often yield substantial returns on investment by reducing the need for future clinical healthcare expenditures.

Community-based prevention programs targeting CVD, type 2 diabetes, and obesity have demonstrated cost-effectiveness. Given the health disparities faced by midlife and older rural women and the scarcity of healthy lifestyle resources in rural areas, CVD prevention programs tailored to this population are critical. However, there is a dearth of cost-effectiveness analyses for community-based healthy lifestyle interventions specifically tailored to rural areas. Previous studies have been limited by factors such as small sample sizes, inclusion of both urban and rural participants, and lack of focus on midlife and older rural women.

2 Research methodology

Monoclonal antibodies emerged as a viable therapeutic option in the 1970s with the development of hybridoma technology. This method involves injecting a mammal, typically a mouse, with an antigen to stimulate the production of antigen-specific B-cell antibodies. These B-cells are then isolated and immortalized by hybridizing them with myeloma cells. The four primary types of monoclonal antibodies are murine, chimeric, humanized, and fully human. Murine antibodies faced challenges due to insufficient activation of host effector functions and the production of neutralizing human anti-mouse antibodies. To overcome this, murine antibody structures were modified with human domains, resulting in chimeric antibodies that are approximately 60% human. Humanized antibodies, which are nearly 95% human, involve engrafting a murine hypervariable region onto a human antibody. Subsequently, fully human monoclonal antibodies have been developed using advanced techniques. Humanized antibodies offer greater efficacy and reduced immunogenicity but are generally more expensive to produce. In 1918, Eduard Glanzmann identified a bleeding disorder characterized by platelet quality rather than quantity. Glanzmann's thrombasthenia was later attributed to a deficiency in the transmembrane platelet receptor GP IIb/IIIa, crucial for platelet aggregation. Decades later, a chimeric monoclonal antibody (abciximab) targeting GPIIb/IIIa was developed for cardiovascular disease (CVD) treatment. Clinical

trials in the 1990s confirmed abciximab's effectiveness as an adjunct therapy for myocardial infarction (MI), and it remains in use for this purpose. Subsequent research led to the discovery of small molecule GP IIb/IIIa inhibitors, offering rapid platelet aggregation inhibition with shorter half-lives than abciximab. Derived from natural sources, such as venom proteins from snakes, these inhibitors include tirofiban and eptifibatide. Recent meta-analyses of randomized controlled trials have validated the efficacy of GP IIb/IIIa inhibitors in percutaneous coronary intervention, despite increased bleeding risks. Overall, these inhibitors demonstrate a favorable impact on reducing major adverse cardiovascular events post-intervention.

3 Results and Discussions

Identifying the most suitable gene to treat complex cardiovascular disorders poses a significant challenge. For conditions like hypertension and atherosclerosis, it is probable that a combination of therapeutic genes, rather than a single gene, will yield the most effective treatment. To advance gene therapy in cardiovascular medicine, it is essential to pinpoint and develop effective therapeutic genes and appropriate vectors. Initial clinical trials have shown promising results, suggesting that intravascular or intramuscular administration of vascular gene transfer is not only safe but may also offer therapeutic benefits.

The cost analysis (CA) and one set of cost-effectiveness analyses (CEAs) were approached from the payer perspective, focusing on the costs borne by the intervention's sponsor or payer [6]. This perspective honed in on the direct costs linked to program administration and implementation, offering vital insights for local health policymakers contemplating the rollout of the Strong Hearts, Healthy Communities (SHHC) program.

Following recommendations from the Second Panel on Cost-Effectiveness in Health and Medicine, we also conducted Reference Case CEAs from broader viewpoints. These Reference Case CEAs embraced societal and healthcare sector perspectives, encompassing all significant health outcomes and associated costs of the intervention.

Another CEA utilized the ten-year risk for atherosclerotic cardiovascular disease (ASCVD) to gauge the cost per quality-adjusted life year (QALY) saved. ASCVD risk was assessed using the Pooled Cohort Equations, factoring in elements like age, cholesterol levels, blood pressure, diabetes, and smoking status.

Regarding costs, for the CA and CEAs from the payer perspective, we identified resources directly utilized in program administration and gathered tangible cost measures. These resources encompassed labor, facilities, food, equipment, curriculum printing, and other incidental expenses [7].

For the Reference Case CEAs from the societal perspective, we not only measured direct program resource costs but also included the opportunity costs of all resources used as a result of the intervention [8]. Participant costs, such as time spent participating in the program, were considered from surveys and valued based on relevant wage rates.

For CEAs from the healthcare sector perspective, we used estimates of the medical costs associated with cardiovascular disease events, sourced from a study using administrative claims data from a large U.S. health plan.

The cost analysis (CA) assessed the total and per participant costs of administering and implementing the SHHC and CON interventions. The cost-effectiveness analyses (CEAs) calculated incremental cost-effectiveness ratios (ICERs), comparing the incremental costs to the incremental effectiveness of the interventions.

In the intermediate health outcomes CEAs, incremental costs were determined by subtracting the per participant costs in the CON from those in the SHHC intervention. The incremental effectiveness estimates were derived from the multivariate analysis comparing the impact of the SHHC intervention to the CON on weight, BMI, CRP [9]. For the QALY

CEA, incremental costs and effectiveness were compared between the SHHC intervention and a no-intervention scenario for a hypothetical cohort of 2.2 million women. Predictions were based on pre-post within-group multivariate analysis of the SHHC intervention's impact on ASCVD risk. Probabilistic sensitivity analysis was conducted to assess parameter uncertainty, with Monte Carlo simulations generating 1000 observations of incremental costs, effects, and ICERs.

Cost-effectiveness acceptability curves were utilized in the QALY CEA to depict the probability of the SHHC intervention being acceptable for various willingness-to-pay thresholds. Analyses were performed using Stata 15 software [10].

This study represents the first comprehensive assessment of the economic effectiveness of a multilevel community-based CVD prevention program tailored for midlife and older women in rural, medically underserved areas, employing both cost analysis (CA) and cost-effectiveness analyses (CEAs). Prior interventions in rural areas lacked comparison groups, had limited sample sizes, and often overlooked participant time costs.

Limitations include the complexity of the multilevel intervention, which necessitated additional staff and participant time, with certain social and community components not fully quantified [10]. Primary outcomes were measured at six months, suggesting a need for longer-term data collection to assess sustained impacts. Additionally, not all intervention benefits were converted into quality-adjusted life years (QALYs), potentially underestimating program benefits.

Assumptions regarding the duration of intervention benefits and the causal effect of ASCVD risk reduction may not fully capture the program's long-term impact. Moreover, the use of a 10-year time horizon may not capture the full benefits and costs associated with ASCVD risk reduction. Lack of cost information for ASCVD events in the study population and sensitivity of ICERs to medical costs further underscore the study's limitations.

Recommendations for improving SHHC's cost-effectiveness include optimizing intervention components to enhance impacts on weigh and ASCVD risk, potentially by streamlining staffing and reducing participant-related costs. Encouraging participation with friends or family members could also enhance program reach and effectiveness.

4 Conclusions

In the era of post-genomics, a significant challenge lies in distilling meaningful insights from vast datasets generated by high-throughput techniques such as microarray and deep sequencing. Systems biology emerges as a crucial discipline, facilitating the interpretation of biological data by developing quantitative mathematical models to uncover the intricate interactions among genes or proteins. Given the intricate nature of cardiovascular diseases, systems biology offers a promising approach for enhanced understanding. By dissecting different components like heart failure and coronary artery disease into modular structures, each comprising multiple genes and their nonlinear interactions, a more comprehensive understanding can be achieved. Population genetics, exemplified by Genome-Wide Association Studies (GWAS), has identified numerous chromosomal loci influencing cardiovascular disease risk. Integration of GWAS variation data with multi-omics data and gene network analysis enables the identification of susceptible pathways and key genotypic determinants. In this context, the identification of hub genes within networks serves as pivotal research in cardiovascular systems biology, potentially serving as biomarkers for early detection or therapeutic targets. Additionally, considering comorbidities as exacerbating factors in cardiovascular disease risk, a systems biology approach can analyze their associations to prevent severe vascular events. Common comorbidities like diabetes and kidney disease can be scrutinized to identify specific biomarkers for early diagnosis, facilitating proactive management and potentially extending patient survival.

References

1. Kh.M. Bataev, E.A. Akhmadova, Prevention and treatment of chronic cardiovascular failure, **7**, 64-66 (2011)
2. O. Bogaevsaya, A. Ibragimova, H. Bataev, Secondary prevention of cardiovascular diseases in patients who have suffered myocardial infarction: pharmacoepidemiological studies, 353-361 (2020)
3. V.V. Tupitsin, Z.A. Godina, Kh.M. Bataev, Features of the structure of risk factors for cardiovascular pathology in men under 60 years of age with myocardial infarction and chronic inflammatory pulmonary diseases, **22(7)**, 21-25 (2020)
4. I. Podkolzina, A. Tenishchev, Z. Gornostaeva, H. Tekeeva, O. Tandelova, Assessment of Threats to Environmental Security and Climate Change. BIO Web of Conferences, **63**, 04002 (2023)
5. I. Podkolzina, A. Tenishchev, Z. Gornostaeva, H. Tekeeva, O. Tandelova, Ecological and Food Security in the Conditions of the Geopolitical Situation in the Worldglobal Digital Transformation Trends in Real Sectors of the Economy. SHS Web of Conferences, **172**, 02041 (2023)
6. L. Agarkova, T. Gurnovich, S. Shmatko, I. Podkolzina, V. Filonich, Priority directions of development of the cluster of innovative education in the regional agro-industrial complex. International Journal of Monetary Economics and Finance, **6(2)**, 718 (2016)
7. A.S. Salamova, O. Dzhioeva, Green transformation of the global economy in the context of sustainable development, 152-159 (2023)
8. R.A. Gakaev, The world's forests are a stabilizing element of the climate system, **76**, 06003 (2023)
9. D.T. Dzhatdoeva, Study of the composition of medicinal plants in the prevention of infectious diseases based on biochemical mechanisms. Bulletin of the Kursk State Agricultural Academy, **9**, 88-93 (2022)
10. S.G. Shmatko, L.V. Agarkova, T.G. Gurnovich, I.M. Podkolzina, Problems of increasing the quality of raw material for wine in the stavropol region, **7(2)**, 725-730 (2016)