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EDITORIAL COMMENT

PCSK9 Inhibition

A Novel Approach to Attenuate Cardiovascular and Liver Aging*

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Aging is a complex biological process that exerts significant effects on multiple organ systems, including the cardiovascular system and liver. Cardiovascular diseases are among the leading causes of mortality and morbidity in the elderly population.[1] As individuals age, they become more susceptible to conditions like atherosclerosis, hypertension, and heart failure, contributing to the alarming rise in cardiovascular diseases among the elderly.[1] The burden of these diseases on health care systems is substantial, with cardiovascular diseases ranking among the leading causes of death and disability in elderly populations worldwide.[1]

Cardiovascular aging is a multifaceted process characterized by lipid abnormalities, atherosclerosis, and alterations in myocardial structure, such as hypertrophy and fibrosis. These changes ultimately lead to cardiac dysfunction and, in severe cases, heart failure. Mitochondrial dysfunction, increased oxidative and nitrative stress, and enhanced inflammation are among the major pathophysiological events implicated in the development and progression of age-related cardiovascular functional decline and disease.[1] Similarly to cardiovascular aging, liver aging is also characterized by inflammation and fibrosis, with nonalcoholic fatty liver disease (NAFLD) becoming more prevalent with age, further contributing to cardiovascular risk. Notably, emerging clinical and preclinical evidence suggests an important interplay between liver disease and cardiovascular dysfunction, suggesting that liver-related pathology can contribute to various cardiac disorders.[2] A key connecting factor between these aging processes is dysregulation of cholesterol metabolism.[2] Cholesterol metabolism disturbances are a common occurrence in both age-related cardiovascular and liver disorders, accentuating the importance of finding effective therapies to address these issues.

Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a key enzyme in regulating cholesterol levels by interacting with low-density lipoprotein (LDL) receptors. Its binding to LDL receptors prevents the efficient removal of low-density lipoprotein cholesterol (LDL-C) from the bloodstream, leading to elevated LDL-C levels and an increased risk of cardiovascular disease. Consequently, PCSK9 inhibition prevents its interaction with LDL receptors, and thus more LDL receptors remain available on the liver cell surface, facilitating enhanced LDL-C clearance from the bloodstream.

The effectiveness of PCSK9 inhibition has been demonstrated in clinical trials using monoclonal antibodies. These trials have shown that PCSK9 inhibition is particularly beneficial for patients with familial hypercholesterolemia or those who do not respond well to traditional statin therapies, because it significantly reduces LDL-C levels.[3] Moreover, beyond its primary role in cholesterol metabolism, PCSK9 inhibition has been found to substantially reduce cardiovascular mortality and morbidity, indicating additional beneficial effects. Despite accumulating data on PCSK9's role in cardiovascular diseases and hypercholesterolemia, there remains a significant

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knowledge gap regarding its involvement in cardiovascular and hepatic aging. The impact of PCSK9 on the aging process of the cardiovascular and hepatic systems is largely unexplored and warrants further investigation. Understanding the role of PCSK9 in the aging process could offer valuable insights into potential therapeutic interventions for age-related cardiovascular and liver disorders. Because cholesterol metabolism dysregulation is a common hallmark in aging-related diseases, exploring the role of PCSK9 in aging could have far-reaching implications for promoting healthy aging and reducing the burden of cardiovascular and hepatic disorders in the elderly population.

In their intriguing translational study in this issue of *JACC: Basic to Translational Science*, Matyas et al[4] investigated the role of PCSK9 in age-related cardiovascular dysfunction and the development of NAFLD. To comprehensively investigate this aspect, they employed a large cohort of human subjects and aging Fisher rats, a well-established preclinical model for cardiovascular and liver aging. First, they examined the association between serum PCSK9 levels, as a biomarker, and age-related cardiac dysfunction in both humans and rats. Then, they explored the effect of PCSK9 inhibition using the monoclonal antibody alirocumab on cellular mechanisms known to contribute to cardiac dysfunction and remodeling, including mitochondrial dysfunction, oxidative stress, inflammation, and fibrosis. Additionally, they assessed the effect of PCSK9 inhibition on age-related liver pathology.

The findings of the study revealed that serum PCSK9 levels increased significantly both in aged humans and rats. Importantly, the elevated serum PCSK9 levels positively correlated with diastolic and/or systolic dysfunction, which were assessed using echocardiography and pressure-volume approaches in both aging human subjects and rats. This exciting discovery opens up the possibility of PCSK9 potentially serving as a novel biomarker for age-related cardiovascular disease.

To ascertain the source of the increased serum/plasma PCSK9 levels in aging, the authors conducted a comprehensive investigation by employing myocardial/liver tissue RNA and single-cell sequencing; spatial transcriptomics in mice, rats, and/or humans; and/or enzyme-linked immunosorbent assay. These experiments revealed negligible, if any, PCSK9 expression in young and aging mouse, rat, or human hearts or cardiomyocytes. In contrast, there was high PCSK9 expression in the livers, which was further increased by age, suggesting that the liver is the primary source for elevated serum PCSK9 levels observed in aging. Consistently with the key role of PCSK9 in the liver, the U.S. Food and Drug Administration approved the small interfering RNA Leqvio (inclisiran), which inhibits PCSK9 synthesis in liver hepatocytes and which in clinical trials showed comparable efficacy to reduce LDL-C to monoclonal antibodies targeting PCSK9.[5]

The translational rat model utilized in this study allowed for comprehensive analyses of cardiac function through echocardiography and invasive pressure-volume approaches, revealing significant impairment in both systolic and diastolic function as well as vascular function in aging rats. These functional changes were found to be consistent with existing literature, and they were associated with mitochondrial dysfunction, increased oxidative stress, inflammation, and myocardial fibrosis. Additionally, the study observed age-associated development of NAFLD in rats, characterized by oxidative stress, inflammation, and fibrosis. Notably, the development of NAFLD in the liver positively correlated with the impairment of cardiovascular systolic and diastolic function, indicating the importance of interorgan (liver-heart) communication.[4]

The chronic 6-week treatment with alirocumab, a PCSK9 inhibitor, significantly ameliorated serum lipid abnormalities and improved aging-related cardiac dysfunction, as well as the primary pathophysiological processes linked to cardiovascular aging, such as mitochondrial dysfunction, oxidative stress, inflammation, and fibrosis. The authors proposed that the indirect beneficial effects of PCSK9 inhibition on the heart might be attributed to the reduction of oxidative stress, inflammation, and cholesterol levels, including ox-LDL, in the circulation. Nevertheless, direct beneficial effects of PCSK9 neutralization on the heart and liver, as well as systemic effects on inflammatory cells, cannot be ruled out. Interestingly, the study found an increase in PCSK9 levels in aging livers, and alirocumab treatment mitigated the age-associated hepatic oxidative stress, steatosis, inflammation, and fibrosis. The study's robustness is acknowledged, with wide-ranging human and rat data sets and top-of-the-art methodologies, including comprehensive hemodynamic analysis in both humans and rats. One notable aspect the study did not investigate was whether elevated PCSK9 levels contributed to the development of nonalcoholic steatohepatitis-like features in the liver or if the increased PCSK9 levels were a consequence of inflammation and oxidative stress in the hepatic tissue.

Overall, the study provides compelling initial evidence of the mechanistic link between age-related

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NAFLD development and elevated PCSK9 levels, elucidating the association with left ventricular dysfunction. Age emerged as one of the strongest predictors of plasma PCSK9 levels, whereas elevated blood PCSK9 levels independently predicted the development of LV diastolic dysfunction in elderly individuals. The animal data supported the human observations, because elevated PCSK9 levels correlated with both systolic and diastolic LV dysfunction and a characteristic aging cardiac phenotype, which was ameliorated by PCSK9 inhibition. This study offers valuable mechanistic insights into the potential beneficial effects of PCSK9 inhibition in aging, suggesting benefits beyond its impact on cholesterol metabolism. Moreover, it proposes serum PCSK9 levels as a potential biomarker for age-related cardiac dysfunction and highlights the significance of the heart-liver connection in the benefits of PCSK9 inhibition.

Based on the results of this comprehensive translational study, PCSK9 appears to play a significant role in cardiovascular aging, making it a potentially novel target for age-related cardiovascular diseases. The study also emphasizes the critical role of interorgan communication, with PCSK9 being synthesized in the liver but exerting pathological changes associated with cardiovascular aging in the cardiovascular system (and perhaps also in the liver). Further investigations are warranted to delineate the extent to which the observed beneficial effects of PCSK9 inhibition are associated with indirect effects on cholesterol normalization and reduced oxidative stress and inflammation, or direct effects on various cell types, such as cardiomyocytes, endothelial cells, fibroblasts, hepatocytes, Kupffer cells, and inflammatory cells.

In summary, this study contributes substantially to our understanding of the role of PCSK9 in cardiovascular and liver aging and underscores the potential therapeutic significance of PCSK9 inhibition in age-related cardiovascular and liver diseases.

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