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ROLE OF VITAMIN D IN CARDIOVASCULAR COMPLICATIONS OF METABOLIC-ASSOCIATED STEATOTIC LIVER DISEASE

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Metabolic-associated steatotic liver disease is a systemic disease closely related to cardiovascular pathology. One of the key pathogenetic mechanisms of cardiovascular complications in such patients is endothelial dysfunction. It is manifested by impaired vascular tone, decreased production of vasodilators (in particular, nitric oxide), increased synthesis of adhesive molecules and activation of inflammatory cascades. This contributes to the development of atherosclerosis, arterial hypertension and impaired microcirculation. Vitamin D plays an important role in maintaining endothelial homeostasis. Its deficiency is often detected in patients with liver disease and is associated with more pronounced endothelial dysfunction. Vitamin D has anti-inflammatory properties, reduces the expression of pro-inflammatory cytokines and modulates the immune response, and also has a positive effect on insulin sensitivity. Thus, correction of vitamin D levels may be a promising direction in preventing vascular complications in patients with metabolic dysfunction-associated steatotic liver disease.

Key words: metabolic-associated steatotic liver disease, endothelial dysfunction, vitamin D, nitric oxide, obesity, cardiovascular disease, diabetes mellitus.

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РОЛЬ ВІТАМІНУ D У СЕРЦЕВО-СУДИННИХ УСКЛАДНЕННЯХ МЕТАБОЛІЧНО-АСОЦІЙОВАНОЇ СТЕАТОТИЧНОЇ ХВОРОБИ ПЕЧІНКИ

Метаболічно-асоційована стеатотична хвороба печінки – це системне захворювання, тісно пов'язане з серцево-судинною патологією. Одним з ключових патогенетичних механізмів серцево-судинних ускладнень у таких пацієнтів є ендотеліальна дисфункція. Вона проявляється порушенням судинного тонусу, зниженням продукування вазодилататорів (зокрема, оксиду азоту), посиленням синтезу адгезивних молекул та активацією запальних каскадів. Це сприяє розвитку атеросклерозу, артеріальної гіпертензії та порушення мікроциркуляції. Вітамін D відіграє важливу роль у підтримці ендотеліального гомеостазу. Його дефіцит часто виявляється у пацієнтів із захворюваннями печінки та пов'язаний з більш вираженою ендотеліальною дисфункцією. Вітамін D має протизапальні властивості, знижує експресію прозапальних цитокінів та модулює імунну відповідь, а також позитивно впливає на чутливість до інсуліну. Таким чином, корекція рівня вітаміну D може бути перспективним напрямком у профілактиці судинних ускладнень у пацієнтів зі стеатотичним захворюванням печінки, пов'язаним з метаболічною дисфункцією.

Ключові слова: метаболічно-асоційована стеатотична хвороба печінки, ендотеліальна дисфункція, вітамін D, оксид азоту, ожиріння, серцево-судинні захворювання, цукровий діабет.

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We are aware of a complex and tightly regulated metabolic system that maintains vascular homeostasis – endothelium. It achieves this by regulating vascular tone, supporting the trophic needs of endothelial cells, and providing protective responses during injury [12]. When activated, the endothelium undergoes phenotypic changes, including the production and display of adhesion molecules that enable interactions between endothelial and blood cells. Endothelial cells are key participants in multiple phases of both acute and chronic inflammation, including initial vasodilation, increased vascular permeability, leukocyte adhesion and transmigration, activation, angiogenesis, and fibroplasia. The endothelium's involvement in the onset and progression of different pathological conditions is multifaceted, extending beyond vascular tone regulation and vascular wall integrity protection to its participation in atherogenesis and thrombus formation [26]. Several factors can trigger endothelial cell responses, including changes in blood flow rate (increased shear stress), platelet mediators (serotonin, thrombin, ADP), and circulating or intramural neurohormones such as acetylcholine, bradykinin, histamine, catecholamines, endothelin, and vasopressin.

Under physiological conditions, endothelial cells enhance the synthesis of various substances, including nitric oxide, prostacyclin, and endothelium-dependent hyperpolarization factor, which contribute to the relaxation of local smooth muscle structures, particularly vascular wall cells.

The structure and function of the endothelium vary across different organs, which can be explained by the specific role of each organ. The presence of pro-inflammatory cytokines and pathogenic bacteria compels the liver to increase nitric oxide synthesis, helping to protect the body's internal environment.

Additionally, toxic substances that enter the body through various routes are also neutralized [22]. Two main hypotheses regarding the development of endotheliopathy in metabolic syndrome are currently under active discussion [35]. The first hypothesis suggests that endothelial dysfunction is secondary to existing insulin resistance (IR), meaning it results from factors characteristic of IR, such as hyperglycemia, dyslipidemia, and arterial hypertension.

The purpose of the study was to analyze the pathogenetic role of vitamin D in the development of cardiovascular complications in patients with metabolic-associated steatotic liver disease and to determine its significance as a potential therapeutic factor.

In cases of hyperglycemia, protein kinase C is activated in endothelial cells, which disrupts endothelium-dependent vasodilation and increases vascular permeability to proteins. Additionally, elevated blood glucose levels trigger lipid peroxidation processes, whose byproducts suppress the vasodilatory function of the endothelium [31].

Arterial hypertension exerts sustained mechanical stress on the vascular walls, particularly in small arteries and arterioles, which leads to structural and functional alterations of the endothelium. This stress disrupts the normal architecture and alignment of endothelial cells, leading to impaired tight junction integrity and an increase in transcellular and paracellular permeability. As a result, albumin and other plasma proteins can more easily penetrate the endothelial barrier, contributing to subendothelial accumulation and inflammation. Additionally, endothelial cells subjected to prolonged hypertensive stimuli begin to synthesize and secrete higher levels of endothelin-1, a potent vasoconstrictor that not only increases vascular tone but also promotes smooth muscle cell proliferation and migration, accelerating the process of vascular remodeling. This remodeling involves changes such as intimal thickening, medial hypertrophy, and a reduction in arterial elasticity, which further perpetuates hypertension and endothelial dysfunction.

Meanwhile, lipid metabolism disorders – particularly elevated levels of low-density lipoproteins (LDL) and their oxidized forms – play a crucial role in endothelial activation. These atherogenic lipids stimulate the expression of adhesion molecules such as vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), and selectins on the luminal surface of endothelial cells. These molecules facilitate the adherence of circulating monocytes and lymphocytes to the endothelium, promoting their migration into the subendothelial space, where they differentiate into macrophages and contribute to the formation of fatty streaks. This immune cell infiltration marks the early stages of atheroma development and initiates a chronic inflammatory process within the vascular wall [43].

Thus, the combined impact of these pathological conditions – namely, increased endothelial permeability, heightened expression of adhesion molecules, reduced nitric oxide bioavailability, and impaired endothelium-dependent vasodilation – collectively drives the pathophysiological cascade that underlies the development and progression of atherosclerosis. Over time, this contributes to plaque formation, arterial stiffening, and narrowing of the vascular lumen, significantly increasing the risk of cardiovascular events such as myocardial infarction and stroke [2]. The second hypothesis proposes an inverse relationship: endothelial dysfunction is not a consequence, but rather a primary trigger of insulin resistance and related metabolic abnormalities. According to this concept, the endothelium plays a gatekeeping role in insulin delivery, as insulin must traverse the endothelial barrier to reach its receptors on target tissues such as muscle and adipose tissue. Any disturbance in transendothelial insulin transport – such as reduced NO bioavailability, increased oxidative stress, or defects in insulin receptor signaling within endothelial cells – may lead to impaired insulin action at the tissue level. This model implies that insulin resistance may arise as a downstream effect of an underlying endotheliopathy. Consequently, hypertension, hyperglycemia, and dyslipidemia could all be secondary manifestations of primary endothelial dysfunction. However, despite the growing body of evidence supporting both hypotheses, current research remains insufficient to definitively determine whether endothelial dysfunction is a primary driver or a secondary consequence of insulin resistance. Further longitudinal studies and mechanistic investigations are needed to clarify the temporal and causal relationships between these interrelated pathologies [42]. When the endothelium is intact, it releases anticoagulants that inhibit the proliferation of vascular smooth muscle, thereby maintaining stable vessel diameter. Additionally, the endothelium adsorbs various anticoagulants from blood plasma, ensuring proper blood flow, which is particularly crucial for optimizing microcirculation [43]. However, when endothelial integrity is compromised and the underlying layers become exposed, physiological aggregation and coagulation mechanisms are activated to prevent blood loss. This process leads to vasospasm and suppression of antiplatelet agent formation. While these responses serve a protective function against acute damage, prolonged endothelial injury alters the dynamics, making the endothelium a central player in the pathogenesis of multiple systemic diseases [5].

In such cases, platelets may adhere to endothelial cells, facilitating leukocyte adhesion to arterial walls. Moreover, elevated homocysteine levels are known to exert detrimental effects on endothelial cells [9]. Studies have confirmed that patients with metabolic dysfunction-associated steatotic liver disease (MASLD) exhibit higher plasma homocysteine levels compared to healthy individuals [43]. Notably, homocysteine levels are inversely correlated with plasma vitamin B12 concentrations [36]. Additionally, scientific studies have documented hepatocyte damage resulting from vitamin deficiencies, shedding light on the pathophysiological mechanisms underlying this phenomenon [7]. Hyperhomocysteinemia has also been associated with increased oxidative stress, mitochondrial dysfunction, and impaired nitric oxide bioavailability, all of which contribute to vascular injury. Deficiencies in B vitamins, particularly B6, B12, and folate, further exacerbate homocysteine accumulation, thereby amplifying endothelial dysfunction. Experimental models indicate that restoring adequate vitamin intake can mitigate hepatocellular injury and improve vascular reactivity. These findings suggest a strong interplay between micronutrient status, liver function, and cardiovascular health in MASLD patients. Therefore, early detection and correction of vitamin deficiencies may represent a valuable adjunctive strategy in preventing disease progression and associated complications [36].

In 2020, the term Metabolic Dysfunction-Associated Fatty Liver Disease (MAFLD) was introduced, later replaced in June 2023 by Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) [1]. Recent studies indicate that MASLD is an emerging risk factor for cardiovascular disease and may play a role in its pathogenesis [39]. Notably, the prevalence of MASLD continues to rise in parallel with the increasing rates of obesity and diabetes. However, it remains unclear whether hepatic steatosis is a cause or a consequence of metabolic dysfunction [39].

Cardiovascular diseases account for 48 % of total mortality in MASLD patients, whereas liver-related complications contribute to only 7 % of deaths [20]. Experts highlight those cardiovascular diseases are the primary cause of death among individuals with metabolic syndrome [42]. Additionally, patients with metabolic syndrome exhibit a significantly higher prevalence of both calcified and non-calcified coronary plaques compared to healthy individuals, regardless of the overall prevalence of metabolic syndrome. These plaque characteristics are strongly associated with an increased risk of future cardiovascular events, highlighting their clinical relevance. Moreover, advanced imaging studies suggest that non-calcified plaques in particular may represent a more unstable phenotype, predisposing patients to acute coronary syndromes [43].

A meta-analysis conducted by Italian researchers examined 16 unique prospective and retrospective studies involving 34,043 adults, of whom 36.3 % had MASLD. During an average follow-up period of 6.9 years, approximately 2,600 cardiovascular disease-related deaths were recorded, accounting for over 70% of all CVD deaths. The findings suggest that individuals with MASLD have a higher risk of cardiovascular events compared to those without the condition. However, due to the observational nature of these studies, causal relationships cannot be established definitively [42].

Furthermore, a meta-analysis by Chinese researchers found that MASLD patients with obesity (as defined by ethnicity-specific BMI criteria) may have a worse long-term prognosis. However, their findings suggest that obesity is not an independent factor in the progression of MASH or advanced fibrosis in MASLD patients. Instead, MASH should be considered a potential pharmacological target, independent of obesity. This perspective underscores the need to differentiate between obesity-related metabolic stress and the intrinsic inflammatory mechanisms driving MASH. Recent evidence indicates that hepatocellular injury, oxidative stress, and immune-mediated pathways may play a more decisive role in fibrosis progression than adiposity alone. Consequently, therapeutic strategies should prioritize the modulation of hepatic inflammation and fibrogenesis rather than focusing solely on weight reduction. Future randomized controlled trials are warranted to clarify the efficacy of targeted pharmacological interventions in improving outcomes for MASLD patients irrespective of obesity status [3, 15].

Patients with MASLD exhibit an accumulation of epicardial adipose tissue [27], which serves as a source of pro-inflammatory cytokines and increases the risk of cardiovascular diseases [25]. Furthermore, MASLD is strongly associated with a heightened risk of aortic valve sclerosis, an independent marker of atherosclerosis [6].

When analyzing the relationship between the endothelial dysfunction marker ET-1 and the concentration of high-sensitivity C-reactive protein (hs-CRP), a direct moderate correlation was identified ($r=0.58$, $p=0.0000$) [28]. Literature evidence suggests that the intensity of CRP secretion is closely linked to lipid metabolism and insulin resistance, both of which contribute to the development of atherosclerosis and atherothrombosis due to endothelial dysfunction. However, the pathogenetic mechanisms underlying these processes remain insufficiently studied.

According to current understanding, vWF is recognized as a marker of the acute phase of inflammatory reactions and thrombosis, primarily interacting with collagen and subendothelial microfibrils. Elevated levels of ET-1 and increased vWF activity in blood plasma indicate endothelial dysfunction, characterized by impaired vasoconstrictive and thrombogenic functions in patients with MASLD [34]. A correlation between the severity of endothelial dysfunction and the progression of liver fibrosis in MASLD has been identified [19]. The pathogenesis of MASLD-related fibrosis involves multiple mechanisms. Initially, hepatic and systemic blood flow is disrupted, which naturally leads to the activation of the sympathoadrenal system. This process is accompanied by alterations in the balance of humoral-metabolic factors, as well as the activation of the renin-angiotensin-aldosterone system, whose role in fibrogenesis has been well established. As liver fibrosis progresses, structural remodeling occurs with the deposition of extracellular matrix components, primarily in the subendothelial space of Disse and the perivenular zone of the acini. This results in the formation of a subendothelial basement membrane, creating a barrier between hepatocytes and hepatic sinusoids. In individuals with metabolic syndrome, extracellular matrix degradation decreases while its synthesis increases, ultimately contributing to the development of fibrosis and cirrhosis [4].

Interestingly, the expression of endothelial damage and dysfunction markers is directly linked to the severity of liver damage, as demonstrated in multiple studies [16, 33]. Histological analysis of liver tissues in MASLD reveals alterations in sinusoidal fenestration and collagenization of Disse's space. These changes contribute to increased intrahepatic vascular resistance, which inevitably disrupts hepatic blood flow and may lead to liver tissue necrosis due to ischemia. Consequently, necrosis triggers fibrotic processes. Metabolic dysfunction-associated steatotic liver disease is also linked to a heightened risk of future cardiovascular events [32].

Hypoadiponectinemia may serve as an early indicator of not only hepatic steatosis but also an increased risk of cardiovascular events [30]. Patients with metabolic dysfunction-associated steatohepatitis (MASH) have a significantly higher risk of cardiovascular disease compared to those with simple steatosis, underscoring the role of chronic inflammation in atherosclerosis pathogenesis [40]. Experimental studies have shown that nitric oxide synthase plays a protective role in liver cells against destructive factors. Research on the roles of inducible and endothelial nitric oxide synthase in liver damage due to ischemia suggests that increased nitric oxide synthesis may be crucial for shielding liver cells from toxic damage [13]. Proper blood flow in the microcirculatory system requires vasodilatory and anticoagulant molecules [29]. However, an excessive amount of endothelium-derived substances can have adverse effects. Notably, an overproduction of nitric oxide leads to endothelial dysfunction and impairs myocardial contractility by reducing endothelial NO secretion [18].

The relationship between inflammation and endothelial dysfunction is mediated by nitric oxide, a potent vasodilator with anti-inflammatory properties. Nitric oxide plays a fundamental role in regulating vascular tone, as it is produced by endothelial cells. Consequently, endothelial dysfunction is characterized by reduced nitric oxide production and decreased sensitivity to its effects [11]. Given the endothelium's multifaceted functions, dysfunction leads to impaired regulation, increasing susceptibility to inflammation, thrombosis, and vascular rigidity. Due to nitric oxide's diverse biological effects, endothelial dysfunction is a key component in the pathogenesis of numerous pathophysiological conditions. For centuries, hydrogen sulfide (H_2S) has been regarded as a toxic gas that inhibits mitochondrial respiration. However, scientific advancements have identified H_2S as the third gaseous signaling molecule in humans and other mammals, playing a crucial role in various physiological processes, including inflammation and vascular tone regulation. Consequently, its potential applications in shock conditions and ischemia have gained attention. A novel research direction explores its role in liver diseases, such as metabolic dysfunction-associated steatotic liver disease [37]. Recent discoveries indicate that hydrogen sulfide regulates essential physiological functions, including vascular relaxation, neuromodulation, and inflammatory responses [43]. Furthermore, studies have demonstrated that the endogenous synthesis of hydrogen sulfide is disrupted in liver cirrhosis [38].

Vitamin D plays a crucial and multifaceted role in maintaining endothelial homeostasis, influencing both the structural and functional integrity of the vascular endothelium. It participates in a wide array of biological processes that collectively ensure vascular health and systemic metabolic balance. Vitamin D receptors (VDR) are widely expressed in various cell types, including endothelial cells, vascular smooth muscle cells, and cardiomyocytes. Upon activation by its ligand, these receptors initiate genomic and non-genomic signaling pathways that can modulate the expression of anti-inflammatory cytokines, suppress oxidative stress, and reduce vascular inflammation. Specifically, VDR activation in endothelial cells has been shown to reduce oxidative stress, improve nitric oxide (NO) bioavailability, and inhibit platelet aggregation, thereby promoting vasodilation and limiting thrombogenic potential [10].

A comprehensive meta-analysis involving more than 426,000 patients demonstrated that vitamin D deficiency is independently associated with an increased risk of major adverse cardiovascular events, including myocardial infarction, stroke, and cardiovascular mortality [14]. This highlights the systemic impact of vitamin D on cardiovascular health. Deficiency in vitamin D correlates with various adverse vascular outcomes, not only due to its direct role in endothelial regulation but also through its influence on glucose metabolism, lipid profile, and systemic inflammation. Several longitudinal studies further suggest that inadequate vitamin D levels may accelerate the progression of atherosclerosis and impair vascular compliance. Experimental data also indicate that vitamin D exerts protective effects on the renin–angiotensin–aldosterone system, thereby contributing to blood pressure regulation. Moreover, low vitamin D status has been linked to increased arterial stiffness and heightened thrombotic risk, both of which exacerbate cardiovascular vulnerability. Taken together, these findings emphasize the importance of maintaining adequate vitamin D levels as part of comprehensive cardiovascular risk reduction strategies [14].

In individuals diagnosed with metabolic dysfunction-associated steatotic liver disease (MASLD), previously referred to as NAFLD, vitamin D deficiency is significantly more prevalent compared to the general population. This deficiency in MASLD patients is associated with increased levels of systemic inflammation, impaired insulin sensitivity, enhanced oxidative stress, and worsening of endothelial dysfunction [21]. These interlinked processes exacerbate disease progression by further impairing hepatic and vascular function. Moreover, low serum levels of vitamin D are strongly associated with greater arterial stiffness, atherosclerotic progression, elevated blood pressure, and disturbed microvascular function. These alterations collectively increase the risk of cardiovascular complications in MASLD patients, placing them in a high-risk category for long-term adverse events.

A randomized clinical trial revealed that vitamin D supplementation in patients with MASLD significantly reduced circulating levels of fibrogenic factors, such as transforming growth factor-beta (TGF-β), and downregulated the expression of fibrosis-related microRNAs, suggesting a potential antifibrotic and hepatoprotective effect of vitamin D [17]. These results suggest that vitamin D may play a therapeutic role not only in improving vascular health but also in slowing the progression of liver fibrosis, a key determinant of prognosis in MASLD.

Furthermore, interventional studies have suggested that regular daily supplementation with vitamin D may improve endothelial biomarkers – such as flow-mediated dilation, vascular cell adhesion molecule-1 (VCAM-1), and E-selectin – and positively influence vascular outcomes, particularly in populations with type 2 diabetes, insulin resistance, or existing cardiovascular disease [23]. Improvements in these biomarkers reflect better endothelial function, reduced inflammation, and a more stable vascular environment, supporting the preventive and therapeutic potential of vitamin D.

A recent literature review highlights the association between vitamin D deficiency and endothelial dysfunction, especially in the context of COVID-19, where endothelial injury, hyperinflammation, and thrombotic events are common. Vitamin D's anti-inflammatory and antithrombotic properties are considered beneficial in mitigating these risks, further supporting its importance in maintaining endothelial health during systemic illness [41]. These findings underline vitamin D's role beyond calcium-phosphate homeostasis, positioning it as an immunomodulatory and vasoprotective agent with potential applications across a broad spectrum of metabolic and inflammatory diseases. Clinical observations indicate that vitamin D deficiency correlates with increased severity and mortality in patients hospitalized with COVID-19, emphasizing its prognostic significance. Experimental studies further suggest that adequate vitamin D status enhances endothelial nitric oxide synthase activity, thereby improving vascular tone and perfusion. Moreover, vitamin D modulates the expression of adhesion molecules, reducing leukocyte recruitment and subsequent endothelial damage. These mechanisms collectively highlight its capacity to attenuate the cascade of vascular inflammation and thrombosis. Consequently, supplementation strategies aimed at correcting vitamin D deficiency may serve as a cost-effective adjunct in reducing cardiovascular and systemic complications during infectious and inflammatory states [10].

Thus, vitamin D is increasingly recognized not only as a regulator of calcium metabolism but also as a potential therapeutic agent for mitigating cardiovascular and hepatic complications in patients with MASLD [8]. Emerging evidence supports its inclusion in comprehensive treatment approaches, particularly in high-risk individuals with concurrent metabolic dysfunction and cardiovascular risk factors.

In parallel, these findings also underscore the critical role of hydrogen sulfide (H_2S) in MASLD, another gas transmitter with vasodilatory and cytoprotective properties. H_2S modulates endothelial nitric oxide synthase (eNOS) activity, which is essential for vascular tone regulation and oxygen delivery to tissues [24]. Disruptions in the interplay between vitamin D, NO, and H_2S pathways may further compromise endothelial function, providing new targets for future therapeutic strategies aimed at improving outcomes in MASLD.

Conclusion

The presented data suggest that endothelial dysfunction is a key pathogenetic mechanism in the development of various pathological conditions, including metabolic syndrome. Currently, this process is recognized as one of the early stages of atherosclerosis, and the presence of endothelial dysfunction is closely associated with the level of cardiovascular risk. It is widely accepted that both insulin resistance and endothelial dysfunction contribute to the progression of metabolic dysfunction-associated steatotic liver disease.

At present, endothelial dysfunction is considered a crucial factor linking insulin resistance, atherogenesis, and arterial hypertension in metabolic dysfunction-associated steatotic liver disease. The number of novel methods for the early diagnosis of endothelial dysfunction is steadily increasing. A review of recent studies highlights that systemic inflammation and endothelial dysfunction, along with their severity, are significant predictors of cardiovascular events. Additionally, there is growing evidence suggesting that endothelial dysfunction may play a role in the pathogenesis of type 2 diabetes mellitus. Given that all pathogenetic components of metabolic dysfunction-associated steatotic liver disease can negatively impact the endothelium, endothelial dysfunction is frequently observed in patients with metabolic dysfunction-associated steatotic liver disease and serves as a predictor of an increased risk of cardiovascular disease and type 2 diabetes mellitus.

Numerous studies demonstrate that vitamin D deficiency is independently associated with impaired endothelial function, underscoring the importance of maintaining sufficient vitamin D status in this high-risk population. Through its anti-inflammatory and metabolic effects, restoring adequate vitamin D levels may improve vascular function and positively influence the overall course of metabolic dysfunction-associated steatotic liver disease.

Consequently, vitamin D is increasingly considered a potential therapeutic agent for preventing cardiovascular complications in this patient population. Therefore, further research on the clinical and pathogenetic aspects of metabolic dysfunction-associated steatotic liver disease, particularly endothelial dysfunction as a key element in its pathogenesis, is essential. Expanding knowledge in this area could enhance diagnostic, therapeutic, and preventive strategies, ultimately reducing the risk of cardiovascular complications in this patient population.

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