

Investigating the Hormetic Role of Resolvin D2 in Atherosclerotic Cardiovascular Disease: Pathways to Biomarker Recognition for Resolvins?

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Abstract

Introduction: Resolvin D2 (RvD2), a mediator that helps resolve inflammation, plays a role in stopping the progression of atherosclerotic cardiovascular disease (ASCVD). Understanding how RvD2 levels relate to ASCVD risk could reveal its potential as both a treatment target and a biomarker.

Methods: We examined the research by Liu *et al.*, which used an analytical method that combined restricted cubic splines with multivariable Cox proportional hazard models. This approach aimed to uncover the link between plasma RvD2 levels and ASCVD risk considering linear patterns. The study also examined how serum cholesterol might influence this relationship through sensitivity analyses.

Results: Liu *et al.* discovered an inverted U-shaped relationship between plasma RvD2 levels and ASCVD risk. They found that while high levels of RvD2 are protective, moderate levels could raise the risk of ASCVD. Additionally, the study suggested that serum cholesterol might play a mediating role in this connection.

Conclusion: These results indicate that the dynamics of RvD2 levels in relation to ASCVD risk are intricate and challenge conventional views on how inflammation resolves in heart health. The study emphasizes the importance of exploring the basis for this threshold effect occurrence and how RvD2 could serve as a biomarker for ASCVD.

Further studies should explore conducting long-term research, including randomized controlled trials, to confirm the effectiveness and safety of using RvD2 as a treatment option.

Keywords: Resolvin D2, Inflammation resolution, Specialized pro-resolving mediator, Biomarkers, Atherosclerotic Cardiovascular disease, ASCVD

Perspective

Resolvin D2 (RvD2), discovered in 2002 [1], has been recognized for its potent ability to enhance innate immune cell function and protect against sepsis, with its complete stereochemistry and total organic synthesis reported in 2009 [2]. Recent insights have positioned RvD2 as a critical pro-resolution molecule in the complex interplay of cardiovascular and metabolic diseases [3]. As a specialized pro-resolving mediator (SPM), RvD2 plays an essential role in the resolution

phase of inflammation, a process vital for maintaining cardiovascular health and preventing the progression of ASCVD [4]. The anti-inflammatory and pro-resolving functions of RvD2, along with its interactions with the GPR18 receptor axis, underscore its protective effects across cardiovascular and metabolic disorders [3]. Recent studies have also highlighted the role of RvD2 in cardiovascular health, particularly in atherosclerosis. The RvD2–GPR18 axis is expressed in human coronary atherosclerosis and conveys atheroprotective effects in apolipoprotein E deficient mice [5]. RvD2 halts further

PMN recruitment and stimulates efferocytosis of apoptotic PMN by M2-like macrophages [4]. Therefore, the actions of RvD2 in small nanogram quantities lead to protection against atherosclerosis in animal disease models [6].

A recent study titled "Inverted U-Shaped Association of Plasma Resolvin D2 (RvD2) With Atherosclerotic Cardiovascular Disease and the Mediation Effects of Serum Cholesterol" by Liu *et al.* marks a significant advancement in identifying potential biomarkers for atherosclerotic cardiovascular disease (ASCVD) [7]. This study highlights the critical role of RvD2 in cardiovascular health [7]. Liu *et al.*'s identification of a U-shaped correlation between RvD2 levels and the risk of ASCVD invites further investigation due to its biological plausibility [7]. Their findings indicate that while high levels of RvD2 confer protection against ASCVD, intermediate levels may paradoxically increase the risk, thus challenging conventional understanding of the regulatory mechanisms involved in inflammation resolution [8]. These results prompt a deeper examination of the physiological mechanisms underlying a threshold effect, wherein the protective effects of RvD2 either plateau or diminish beyond a certain level [7]. The unresolved question of how the U-shaped correlation between RvD2 levels and ASCVD risk may vary over time, influenced by age, gender, lifestyle modifications, and management strategies, warrants further exploration [9]. The multifaceted origins of ASCVD, which are intertwined with risk factors such as dyslipidemia, hypertension, diabetes mellitus (DM), smoking, and obesity, highlight the complex interrelation between cholesterol levels and inflammation in the development and progression of plaque in ASCVD [4,10,11].

Understanding the correlation between RvD2 levels and ASCVD risk is therapeutically significant because it provides insights into potential biomarker applications for early detection and targeted treatment of ASCVD. The anti-inflammatory properties of RvD2, demonstrated in various studies, suggest its role in reducing the risk and progression of cardiovascular diseases [12]. The role of RvD2 in promoting plaque stabilization and preventing ASCVD, by activating endogenous resolution pathways, underscores the crucial interaction between lipid metabolism and vascular inflammation [4,10]. Furthermore, identifying RvD2 as a mediator that can enhance tissue healing and resolve inflammation highlights its potential to develop new therapeutic strategies for cardiovascular and metabolic disorders [13].

Recent advancements in understanding the roles of immune cells in cardiac repair and regeneration have underscored the significance of pro-resolving mediators, such as RvD2. A comprehensive review by Simões and Riley elucidates the orchestration of the initial inflammatory response and subsequent reparative phase by immune cells following myocardial injury [14]. Abplanalp *et al.* further contribute to this knowledge by demonstrating that heart failure

significantly alters circulating immune cells' phenotypes and gene expression profiles, particularly monocytes [15]. Their findings reveal an increased monocyte-to-T-cell ratio and specific alterations in monocyte subpopulations, indicating their potential as biomarkers or therapeutic targets in heart failure and ASCVD [15].

Moreover, Kumar *et al.* have highlighted the pivotal role of Tumor Necrosis Factor Receptor 1 (TNFR1) in modulating the balance between proapoptotic and pro-survival signals in CD4⁺ T cells during ischemic heart failure [16]. Their research indicates biphasic kinetics of CD4⁺ T-lymphocyte activation post-myocardial infarction (MI), with distinct phases contributing to wound healing in the early stages post-MI and pathological left ventricular (LV) remodeling during chronic heart failure [17].

Expanding on these findings, Zhang *et al.* have demonstrated that RvD2 resolves inflammation and enhances revascularization in ischemic tissues [18]. This dual functionality is vital for peripheral artery disease (PAD), where chronic inflammation hinders tissue perfusion and wound healing [18]. In a murine model of hind limb ischemia, RvD2 administration improved perfusion recovery, promoted arteriogenesis, reduced neutrophil accumulation, and decreased pro-inflammatory cytokine levels, such as TNF- α and GM-CSF, without increasing vascular permeability or inducing pathological angiogenesis [18]. These results underscore RvD2's therapeutic potential in resolving inflammation while fostering tissue repair and revascularization [18].

Similarly, Elajami *et al.* have shown that patients with coronary artery disease (CAD) exhibit lower levels of SPMs, such as RvD1, RvD2, and RvD3 [19]. For example, these levels can be restored *via* n-3 fatty acid supplementation with Lovaza [19]. The treatment increased levels of several SPMs, including Aspirin-triggered (AT)-RvD3 and AT-PD1, which are associated with enhanced macrophage phagocytosis of blood clots, thereby promoting clot resolution and reducing inflammation [19]. These findings highlight the therapeutic potential of SPMs in managing chronic vascular inflammation and thrombosis in CAD [19].

Viola *et al.* have made a significant contribution by demonstrating that the administration of Maresin 1 (MaR1) and RvD2 can prevent the progression of atherosclerosis in a murine model by promoting plaque stability [6]. Their study revealed that these lipid mediators reduce necrotic core size, increase fibrous cap thickness, and enhance smooth muscle cell numbers, thereby improving overall plaque stability [6]. Therapeutic administration of MaR1 and RvD2 induced a shift in macrophage phenotype from pro-inflammatory to reparative, promoting collagen production in smooth muscle cells [6]. This positive feedback loop between reparative macrophages and smooth muscle cells emphasizes the potential of MaR1 and RvD2 in resolving inflammation and stabilizing atherosclerotic plaques [6].

Additionally, Tang *et al.* have provided valuable insights into the impaired resolution of inflammation in acute ischemic stroke (AIS) complicated by diabetes mellitus (DM) [20]. Their study demonstrated that SPM secretion is significantly reduced in AIS patients with DM, impairing inflammation resolution [20]. In a mouse model of AIS with DM, therapeutic administration of RvD2 improved inflammation resolution, reduced infarct volume, and enhanced neurological function by promoting a shift in macrophage and microglia phenotypes from pro-inflammatory M1 to pro-resolving M2-like phenotype [20]. These findings suggest that targeting SPMs such as RvD2 could be a promising therapeutic strategy for managing inflammation in AIS and other DM-related cardiovascular conditions [20].

While Liu *et al.*'s research provides comprehensive insights, its methodology, which relies on baseline measurements of RvD2 and LTB4, may not fully capture the dynamic nature of their interaction over time [7]. Investigating the implications of the RvD2/LTB4 ratio on ASCVD risk could significantly broaden the scope and impact of the study [7]. The observation that LTB4 levels remain unchanged across various RvD2 levels necessitates a more detailed analysis of how these mediators interact [7]. Given its established role as an indicator of inflammation resolution efficacy [11], the RvD2/LTB4 ratio has proven valuable in evaluating carotid intima-media thickness and plaque stability in cardiovascular studies [21]. Moreover, it holds promise as a prognostic tool for ischemic stroke outcomes [21]. Expanding the investigation to include these aspects could provide deeper insights into the mechanisms governing inflammation resolution and its clinical implications.

In their research, Liu *et al.* implemented an advanced analytical approach by integrating restricted cubic splines with multivariable Cox proportional hazard models, further enriched by sensitivity analyses, to elucidate the association between plasma RvD2 concentrations and ASCVD risk [7]. Their analysis uncovered the non-linear dynamics of this relationship, with careful validation ensuring the robustness of their findings [7]. Particularly noteworthy is their application of mediation models to explore the role of serum cholesterol markers as intermediaries in the RvD2-ASCVD relationship, adding a critical layer of understanding to the analysis [7]. Such statistical diligence reveals the intricate nature of these interactions and underscores the importance of considering both direct and indirect effects when evaluating RvD2's impact on ASCVD risk [7].

This study included 2633 community-dwelling individuals aged 35–60 years from Soochow, China, who were followed for eight years, during which 284 new cases of ASCVD were identified [7]. Participants were selected based on specific criteria: those with malignancies, abnormal liver, and kidney disease, recent use of antibiotics or nonsteroidal anti-inflammatory drugs, and those with insufficient blood

samples or a history of CVD at baseline were excluded. This careful selection process ensures the relevance and reliability of the study's findings [7].

Data collection at baseline included sociodemographic and lifestyle characteristics, anthropometric measures, and blood samples for biochemical analysis [7]. Plasma RvD2 concentrations were measured using a human RvD2 ELISA kit from Cayman Chemical with a coefficient of variation $\leq 10\%$, ensuring precise quantification [7]. Continuous variables were log-transformed to address non-normality distribution issues [7].

To assess the relationship shape between plasma RvD2 concentrations and ASCVD, restricted cubic splines were conducted, and multivariable Cox proportional hazard models were used to estimate the association [7]. The models were adjusted for various covariates, including age, sex, income, physical activity, smoking status, alcohol consumption, BMI, diabetes, hypertension, dyslipidemia, and family history of CVD [7]. Several sensitivity analyses were performed to verify the robustness of the results, including adjustments for lipid-lowering drugs, high-sensitivity C-reactive protein (hs-CRP), LTB4, and multiple imputations for missing data [7].

The study reports an inverted U-shaped association between plasma RvD2 levels and ASCVD risk, with a threshold value of $\ln RvD2$ at 3.87 [7]. Below this threshold, each unit increase in RvD2 was associated with a 2.05-fold increased risk of ASCVD (95% CI, 1.13–3.74; $P=0.019$) [7]. Above the threshold, each unit increase in $\ln RvD2$ was associated with a 36% reduced risk of ASCVD (95% CI, 0.51–0.80; $P<0.001$) [7]. These precise effect estimates explain the relationship between RvD2 levels and ASCVD risk [7]. Additionally, below the threshold, each unit increase in $\ln RvD2$ was linked to a significantly increased risk of stroke (adjusted HR, 2.22; 95% CI, 1.09–4.50) and coronary heart disease (adjusted HR, 2.42; 95% CI, 1.18–4.95) [7]. Conversely, above the threshold, each unit increase in $\ln RvD2$ was associated with a significantly reduced risk of stroke (adjusted HR, 0.60; 95% CI, 0.46–0.78) and coronary heart disease (adjusted HR, 0.64; 95% CI, 0.50–0.82) [7].

The study also employed mediation analysis to examine whether the association of $\ln RvD2$ concentrations with ASCVD risk was mediated by serum cholesterol indicators, such as total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) [7]. When $\ln RvD2$ was below 3.87, HDL-C partially mediated the association (15.81%) [7]. When $\ln RvD2$ was above 3.87, the association was primarily mediated by TC (30.23%) and LDL-C (30.13%) [7]. The mediation effect was tested using bootstrap analysis with 5,000 samples, ensuring the statistical robustness of the findings [7].

The inverted U-shaped relationship between plasma RvD2 levels and ASCVD risk reflects a complex interplay of pro-resolving and inflammatory pathways in cardiovascular health

[7]. RvD2, a specialized pro-resolving mediator biosynthesized from the omega-3 fatty acid docosahexaenoic acid (DHA), plays a crucial role in the resolution phase of inflammation, essential for maintaining cardiovascular health and preventing the progression of atherosclerosis [22]. At low levels of RvD2 [7], insufficient resolution of inflammation leads to persistent inflammatory responses, contributing to endothelial dysfunction, foam cell formation, and plaque instability [23]. This chronic inflammation is exacerbated by an imbalance of pro-inflammatory cytokines, such as TNF- α , IL-6, and IL-1 β , promoting further immune cell activation and vascular damage [20]. Conversely, higher levels of RvD2 enhance the resolution of inflammation, stabilize atherosclerotic plaques, and prevent rupture by reducing neutrophil and macrophage infiltration, promoting the clearance of apoptotic cells, and inhibiting pro-inflammatory mediators [6]. The findings align with research demonstrating that the RvD2-GPR18 axis reduces atherosclerosis, necrotic core area, and pro-inflammatory macrophage marker expression while enhancing macrophage phagocytosis [5]. This underscores the potential of RvD2 as a therapeutic target in ASCVD.

Furthermore, RvD2 supports the conversion of macrophages to a reparative phenotype, aiding in collagen deposition and plaque stabilization, and promotes revascularization and tissue repair processes vital in ischemic conditions [6,18]. The U-shaped relationship may reflect a hormetic response [24], where moderate levels of RvD2 confer the most benefit, while both deficiency and excess can be harmful due to complex feedback mechanisms. The mediation analysis reveals that serum cholesterol levels influence the relationship between RvD2 and ASCVD risk. HDL-C partially mediates the protective effects at low RvD2 levels and total cholesterol and LDL-C mediating effects at higher levels [7]. This interaction underscores the role of lipid metabolism in inflammation resolution [25], highlighting the intricate balance between lipid levels and inflammatory processes in ASCVD progression [26].

While the use of sophisticated statistical methods, including bootstrap analysis and multiple imputation, significantly enhances the depth of dataset examination, definitive evidence of RvD2's efficacy and safety (whether as a biomarker or therapeutic target) demands validation through randomized controlled trials (RCTs), particularly since the data are observational [27]. As the gold standard in clinical research, RCTs provide the most conclusive evidence [11,28]. Integrating experimental data is essential in navigating the complex array of mediators involved in the resolution of inflammation. Moreover, advanced techniques such as LC-MS/MS in metabolipidomics can identify biomarkers for cardiovascular research, as demonstrated by recent successful applications [29].

Affirming RvD2 as a biomarker for ASCVD, which may reflect human resilience, calls for a comprehensive approach. This strategy should incorporate immunonutrition, underscoring

the significance of dietary omega-3 intake, especially DHA serving as a precursor for RvD2 biosynthesis [2], along with considerations for physical activity and genetic predispositions influencing the production and functionality of pro-resolving mediators [30]. Highlighting the critical need for longitudinal studies, this approach delves into the temporal variations and interactions among mediators [31]. Such research endeavors are pivotal for deepening our understanding of their role in cardiovascular disease progression and crafting effective therapeutic interventions [4].

We propose the concept of "Resolvins as disease-modifying anti-cardiovascular disease therapeutics (RDMACVDTs)" to signify a potential paradigm shift in treating cardiovascular diseases [4,12]. By fine-tuning Resolvins to achieve a balance between inflammation resolution and lipid management, akin to targeted lipid management strategies, this innovative approach could revolutionize ASCVD treatment [30,32].

In summation, while Liu *et al*'s study results open the opportunity for significant insights into inflammation resolution's role in ASCVD, it also highlights the critical need for deeper mechanistic research and a balanced approach in evaluating RvD2 and other Resolvins as potential biomarkers and/or therapeutic agent. The "Atlas of Inflammation Resolution" emerges as a tool for future research, providing a roadmap for identifying intervention targets and drug actions, thereby paving the way for novel therapeutic modalities in cardiovascular disease management [33] and potentially other diseases where excessive uncontrolled inflammation is a hallmark.

Ethics Approval and Consent to Participate

Not Applicable.

Consent for Publication

Not Applicable.

Availability of Data and Materials

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Competing Interests

The author has nothing to disclose.

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Authors' Contributions

Dr. Loukman Omarjee and Prof. Charles N. Serhan contributed to literature search, analysis, and interpretation, writing the

report, revising the intellectual content, and final approval of the version to be published.

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