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The Interplay of Atherothrombotic Factors and the Evolving Landscape of Atherosclerotic Cardiovascular Disease: Comprehensive Insights from Recent Studies

ABSTRACT

The aim of the current work is to present a thorough recapitulation of the emerging understanding of atherosclerotic cardiovascular disease and recommending avenues for future studies.

Cardiovascular diseases (CVDs) remain a leading cause of global morbidity and mortality, influenced by a complex interplay of genetic, environmental, and atherothrombotic factors. Atherosclerosis, a multifaceted and dynamic process, is at the core of many CVDs.

Recent studies have shed light on the multilayered nature of atherosclerosis and cardiovascular risk, emphasizing the need for a nuanced understanding of these diseases across different populations and disease mechanisms.

This review synthesizes findings from 6 pivotal studies, shedding light on the intricate mechanisms underlying atherosclerotic cardiovascular events, the evolving understanding of atherosclerosis, and the potential pathways to attempt implementation in clinical practice. Insights into atherothrombotic factors, the role of macrophages, and the implications of aortic enlargement and coronary artery calcification underscore the complexity of CVD pathogenesis and highlight the need for comprehensive strategies in diagnosis, treatment, and prevention.

Keywords: Atherosclerosis, cardiovascular events, coronary heart disease, fibrinolytic factors, imaging, pathophysiology, precision medicine, thrombotic factors

REVIEW

INTRODUCTION

Atherosclerotic cardiovascular disease (ASCVD) remains a leading cause of morbidity and mortality worldwide, with atherosclerosis being a primary pathological process underlying the majority of cardiovascular diseases (CVDs). Atherosclerosis, a complex and multifactorial disease, underpins many CVDs, including coronary artery disease, stroke, and peripheral artery disease. Its development is influenced by a complex interplay of genetic, metabolic, and environmental factors. Recent research has provided new insights into the pathophysiology of atherosclerosis and expanded our understanding of these processes, offering new perspectives on prevention, diagnosis, and management.

The traditional view of atherosclerosis as merely driven by lipid accumulation within arterial walls has evolved into a more complex understanding of its inflammatory nature and the role of various atherothrombotic factors. This review article integrates findings from 6 pivotal studies to elucidate current perspectives on atherosclerosis and its contribution to cardiovascular events, focusing on atherothrombotic factors, the role of macrophages, and vascular changes like aortic enlargement and coronary artery calcification.

Furthermore, no artificial intelligence (AI)-assisted technologies were used in our article. All the figures attached were created from the original figure containing the original data independently by a Certified Medical Illustrator, to significantly enhance our analysis and presentation.

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The Evolving Perception of Atherosclerosis

Peter Libby's review in the European Heart Journal critically evaluates the changing paradigms on atherosclerosis, pointing out the gaps in current knowledge and the need for further research, as well as providing an insightful commentary on the changing perspectives regarding atherosclerosis over time.[1] Our understanding has shifted from viewing atherosclerosis as a simple buildup of plaque to recognizing it as a dynamic and inflammatory process. This emphasizes that our understanding of the disease is continually evolving, influenced by new scientific discoveries. It also foregrounds the disease's dynamic nature, the role of inflammation, and the potential of emerging technologies in uncovering new therapeutic targets. By advancing our understanding of atherosclerosis, the need for ongoing research is emphasized in order to unravel the complex mechanisms underlying atherosclerosis and to develop more effective interventions. One of the important insights from this work is that we are dealing with 2 types of pathogenetic pathways leading to acute atherothrombotic events which ultimately trigger acute myocardial infarctions (MIs): one is the classical plaque rupture occurring on top of a lipid-rich coronary artery plaque that contains a multitude of immunocompetent cells, lipid debris, and all covered by a thin fibrotic cap. When this occurs, the main effect is an acute thrombotic event, often a total occlusion, leading typically to an ST-elevation myocardial infraction (STEMI).

In contrast to this mechanism, the researchers have identified a distinctly different pathophysiologic pathway, based on the build-up of plaque mainly consisting of a fibroatheroma rather than a lipid-rich core. The fibroatheromatous type of plaque will contain many more fibroblasts and other elements of connective tissue than lipids and macrophages, leading to a different type of dynamic when the plaque undergoes erosion (rather than rupture). This pathophysiology tends to generate smaller intravasal thrombi, typically leading to Non-STEMIs. A depiction of these contrasting mechanisms is provided in Figure 1.

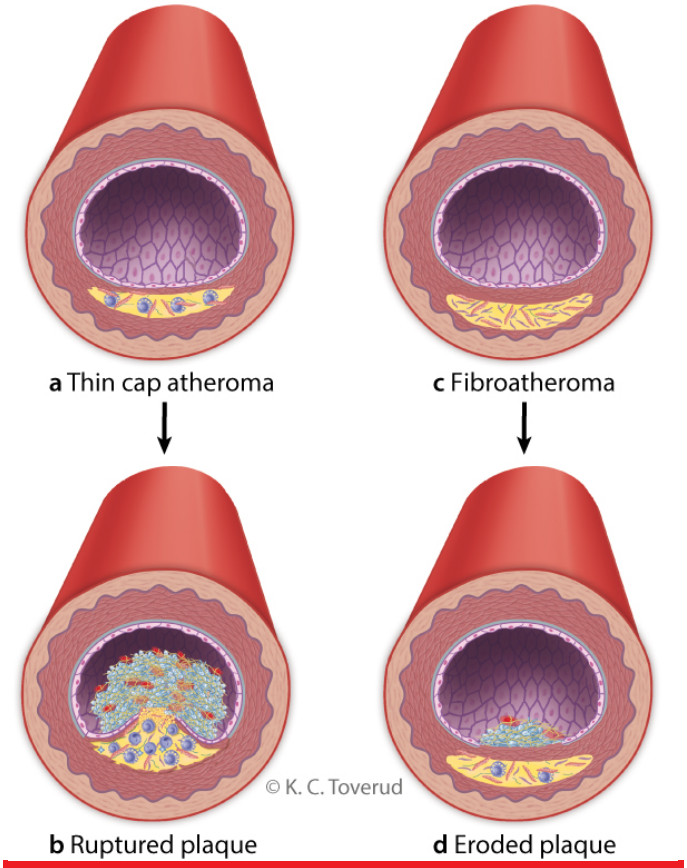

Figure 1. Typical pathways of coronary artery plaques with an evolution over time in the setting of a classical atheromatous plaque with a substantial lipid-rich core and a multitude of immunocompetent cells (left panel), and a different type of plaque, named fibromatous plaque, with a predominance of fibrous elements and fibroblasts (right panel). The development over time is depicted from (A) to (B) on the left panel, and from (C) to (D) on the right panel, respectively. Importantly, the acute build-up of intravascular thrombi is different according to the 2 pathways: the acutely ruptured plaque typically triggers a complete intravascular thrombus, leading to a STEMI (left panel). On the other hand, the eroded fibromatous plaque typically triggers a flat intravascular thrombosis, leading to a Non-STEMI (right panel). *Graph independently created from the original figure containing the original data.*[1].

HIGHLIGHTS

- Our review highlights the evolving understanding of atherosclerosis from a simple lipid plaque buildup to a complex inflammatory process. The crucial role of macrophages in cardiovascular inflammation is also pointed out, offering new avenues for targeted interventions and better management of atherosclerotic cardiovascular disease.
- Pivotal studies underscore atherothrombotic factors' significance in predicting cardiovascular events, suggesting that both thrombotic and fibrinolytic factors should be considered for a comprehensive risk assessment.
- Research shows a notable correlation between aortic enlargement and coronary artery calcification, indicating their potential as markers for cardiovascular risk stratification and guiding early intervention strategies. Additionally, the underestimated role of supra-cardiac atherosclerosis in ischemic strokes is highlighted, advocating for comprehensive atherosclerotic evaluation to improve stroke prevention and management.

DNA Damage, Extranuclear Sensors, and Atherosclerosis

Santovito and Steffens[2] discussed the role of DNA damage and extranuclear DNA sensors in the development of atherosclerosis, proposing a novel perspective on how these factors contribute to the inflammatory milieu of atherosclerotic plaques. The article centers on 2 specific DNA sensors, AIM2 and the cGAS-STING pathways, which identify cytoplasmic DNA and activate immune responses. It

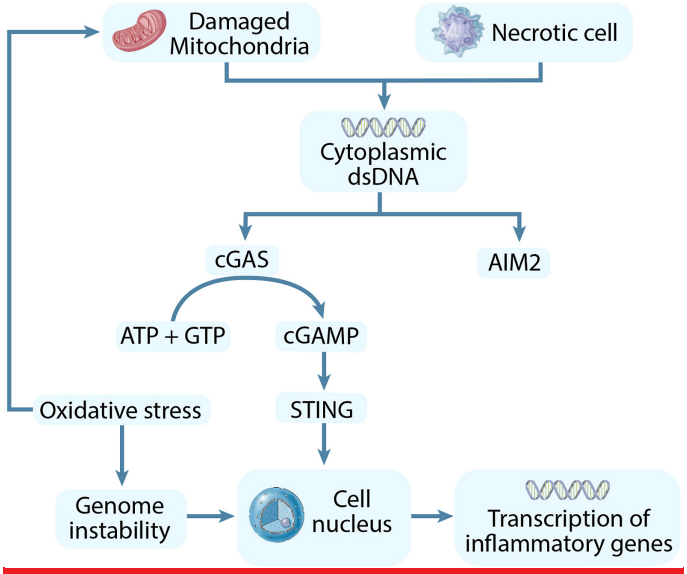

Figure 2. Cytoplasmic DNA sensing pathways are depicted. Double-stranded DNA in the cytosol of cells stems from damaged mitochondria and from debris from external necrotic cells that are internalized. This DNA triggers a cascade of deleterious intracellular pathways, leading to the entry of genomic particles into the cell nucleus. Inside the cell nucleus, deleterious new genetic transcription may occur, leading to a further buildup of intracellular inflammation, and thus contributing to the atherosclerotic processes. *Graph independently created from the original figure.*[2].

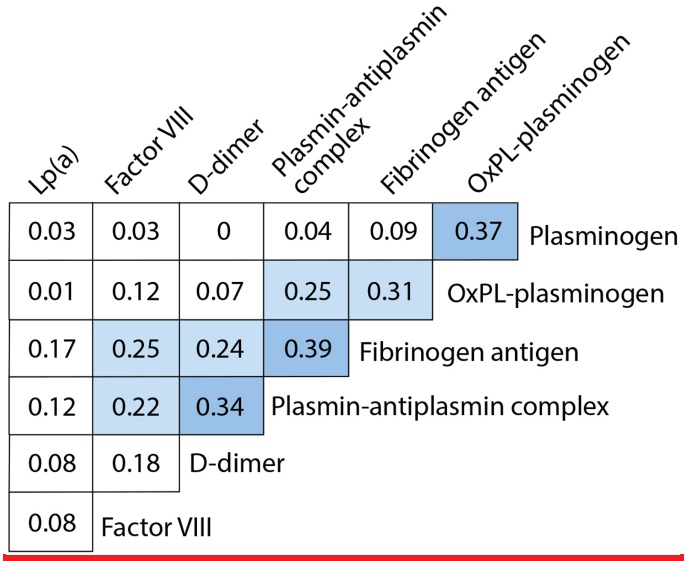

Figure 3. The association between a number of well-known and less-known variables of biomarkers of ASCVD. Upper line: thrombotic factors. Right-sided line: fibrinolytic factors. Each of the biomarkers features a correlation coefficient which allows a ranking of the severity of its involvement in the pathophysiology of ASCVD. The darker the blue filling in the box, the stronger the association. *Graph independently created from the original figure containing the original data.*[3].

explores how these pathways potentially contribute to the advancement of atherosclerosis, with indications suggesting their participation in the formation of atherosclerotic plaques.

The research detailed in the article delves into the role of the cGAS-STING pathway in a murine model of atherosclerosis. It demonstrates that mice lacking the STING gene exhibit smaller plaques with less inflammation compared to control mice. Moreover, inhibiting the STING pathway reduces inflammatory reactions and plaque formation in mice.

This emerging area of research opens new avenues for understanding the molecular pathogenesis of atherosclerosis and identifying potential targets for therapeutic intervention (Figure 2).

Atherothrombotic Factors and ASCVD Events

DeFilippis et al[3] conducted a comprehensive analysis within the Multi-Ethnic Study of Atherosclerosis (MESA) cohort to explore the association between atherothrombotic factors and ASCVD events. The study underscored the importance of managing the well-known traditional risk factors but shed additional light on potential biomarkers that can be deployed for predicting ASCVD risk with a higher degree of prognostic accuracy. It further highlighted the importance of ethnicity-specific risk factors in cardiovascular risk assessment and management strategies, indicating the study's focus on how these associations vary across different racial and ethnic groups.

Figure 3 has been redrawn from this article and showcases the results of significant, yet modest correlations between several well-known and relatively unknown atherothrombotic biomarkers. The upper denominations represent thrombotic factors, while the right-sided biomarkers represent fibrinolytic factors.

Based on these findings, the authors were able to distinguish specific factors—either thrombotic ones or fibrinolytic ones—that significantly contribute to the risk of cardiovascular events, emphasizing the complexity of atherosclerotic disease mechanisms beyond the traditional lipid-centric view. The analysis highlighted that studying ASCVD risk factors together contributes to an increased association with ASCVD events beyond and above what can be observed from either factor alone. The authors followed a cohort of patients over 15.25 years and showed how strong a discrimination that can be achieved using their algorithm (Figure 4). Estimated survival curves are depicted by quartiles of thrombotic factors and fibrinolytic factors, respectively, and survival was greatest in the combination of thrombotic factor: lowest quartile together with s fibrinolytic factor: highest quartile, with a Kaplan–Meier estimated survival of 92.0% (95% CI: 87.2%-97.2%) at 15.25 years (Figure 4).

This study underscores the importance of a multifactorial approach, considering both conventional and novel risk factors to predict ASCVD events, in assessing cardiovascular risk and the potential for targeted interventions.[3] This represents an obvious step toward more personalized medicine / precision medicine.

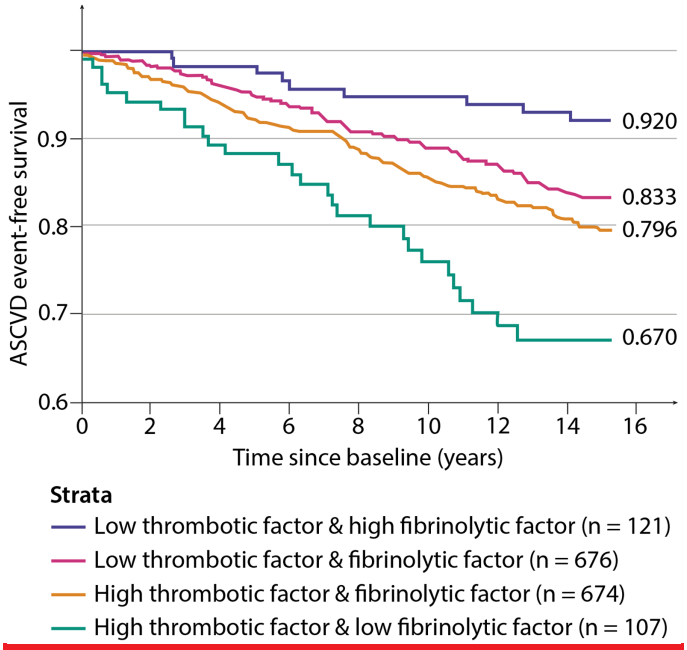

Figure 4. Kaplan–Meier curves for a cohort of patients divided into biomarkers representing either low or high thrombotic factors, or biomarkers representing low or high fibrinolytic factors. Numbers in brackets are the number of patients followed in each category. *Graph independently created from the original figure containing the original data.*[3].

Vascular Changes and Their Implications

The study on aortic enlargement and coronary artery calcification, detailed in the *European Heart Journal - Cardiovascular Imaging*, explores their association in a general population cohort.[4] Their findings indicate a significant correlation between these vascular changes and cardiovascular risk, suggesting that aortic enlargement could serve as a marker for coronary artery disease and potentially guide risk stratification, early detection of individuals at high risk for cardiovascular events, and management strategies. This represents yet another step towards refinement in the sense of precision medicine. The research identified a correlation between the size of aortic diameters across different aortic sections and elevated coronary artery calcium scores (CACS), suggesting a relationship between the expansion of the aorta and coronary artery calcification. This association persisted even after adjusting for various risk factors, with individuals having a CACS greater than 400 exhibiting notably larger aortic diameters compared to those with no coronary calcification. This study portrayed that including CACS in the evaluation process for determining the risk of aortic enlargement could be beneficial for the stratification of therapeutic interventions in a broad range of patients at CV risk (Figure 5).[4]

Supra-Cardiac Atherosclerosis and Stroke

Ntaios et al's[5] research, published in the European Heart Journal, focused on the often-underestimated role of supra-cardiac atherosclerosis in patients with embolic stroke of undetermined source (ESUS). The data highlighted

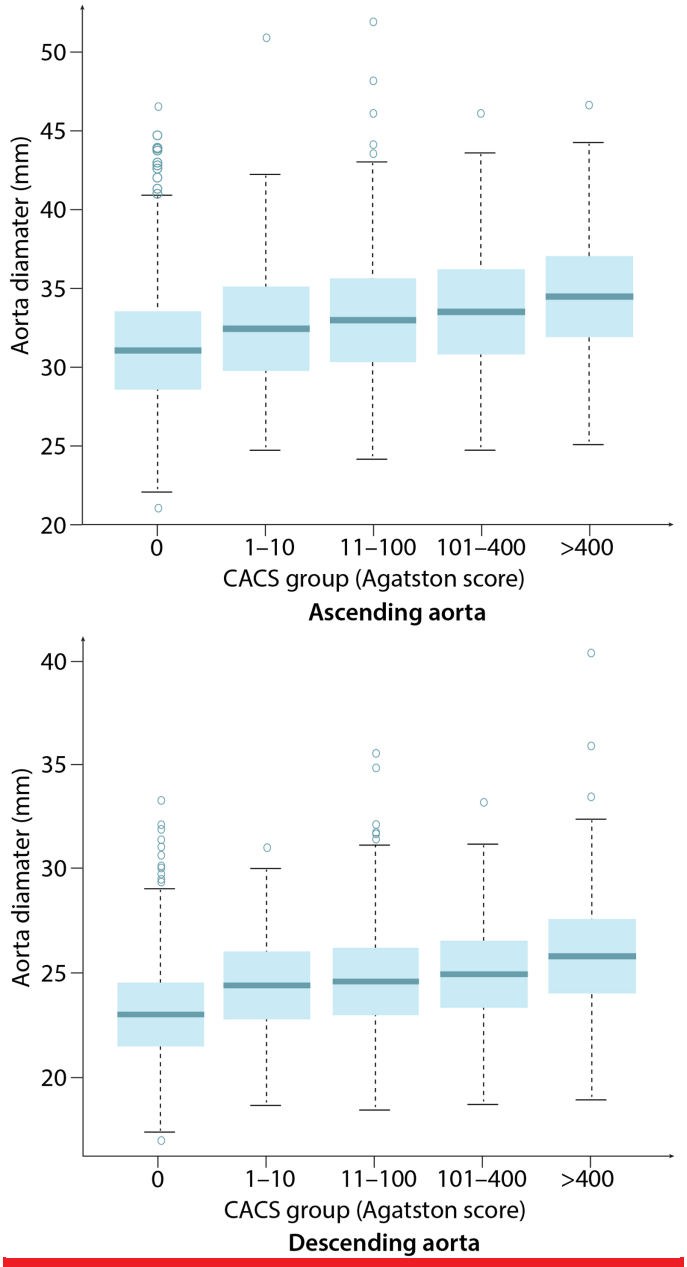

Figure 5. Patients were stratified according to their aortic diameter (y-axis) and the correlation was established to their coronary artery calcium score (Agatston score) on the x-axis. The moderate yet consistent correlation becomes obvious across all degrees of aortic diameter. *Graph independently created from the original figure containing the original data.*[4].

the role of atherosclerosis beyond its mere confinement to the heart, namely the systemic manifestations such as in the aorta, suggesting that a comprehensive evaluation of atherosclerotic disease, including supra-cardiac regions, is essential in the management and prevention of ischemic strokes. By advocating for advanced imaging techniques for better detection and characterization of atherosclerotic plaques, this study calls for a broader approach to evaluating stroke etiology and tailoring secondary prevention

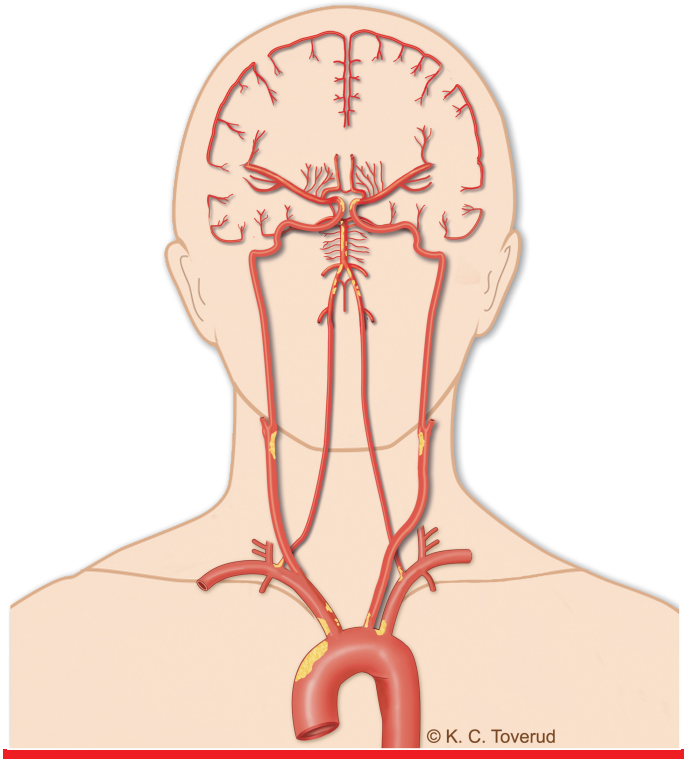

Figure 6. An anatomic depiction of the major supra-cardiac vascular structures, including the ascending aorta and the aortic arch, the carotids, the vertebral arteries (with both cervical and intracranial segments), and the *circulus Willisii*. The yellow marks within the vascular structures represent atherosclerotic deposits, all of which can be responsible for contributing to ischemic strokes. *Graph independently created from the original figure.*[5].

strategies according to these findings. The typical locations of atherosclerotic plaque manifestations are depicted in Figure 6.

Macrophages in Cardiovascular Inflammation

Parry et al[6] reviewed the state-of-the-art imaging techniques for visualizing macrophages and studying their role in cardiovascular inflammation. This comprehensive review not only underscores the prominent role of macrophages in the evolution of atherosclerosis evolution, but also highlights the potential of advanced imaging techniques in elucidating the mechanisms of ASCVD progression, managing it, and facilitating the development of targeted interventions.

The article presents a compilation of studies investigating the clinical significance of macrophages in various coronary syndromes. Each study outlines its aim, sample size, methods used, and the results obtained. These results typically include correlations between macrophage density and specific clinical presentations, such as acute coronary syndrome (ACS) or stable angina pectoris (AP), as well as associations with plaque vulnerability and other relevant parameters. The studies employ various imaging techniques, such as optical coherence tomography (OCT) and positron emission tomography (PET), to assess macrophage density and its implications for coronary artery disease progression. The modern imaging techniques deployed in the summarized studies open avenues to a significantly deeper understanding of the role of macrophages in atherosclerotic disease manifestations.

DISCUSSION

Integration of Findings

The studies compiled and reviewed in this article collectively underscore the complexity of atherosclerosis and cardiovascular diseases and enhance our understanding of atherosclerosis from multiple angles, including its risk factors, pathophysiology, and implications for clinical practice. The influence of atherothrombotic factors, the importance of aortic and coronary pathology, and the underappreciated role of supra-cardiac atherosclerosis in stroke are accentuated, demonstrating the critical need for continued research, interdisciplinary collaboration, and the incorporation of futuristic technologies in the field. DeFilippis et al[3] and Ballegaard et al[4] contribute to the understanding of atherothrombotic factors and structural changes in the aorta and their relationship to cardiovascular events. Libby's[1] commentary and Ntaios et al's[5] research underscore the dynamic complexion of atherosclerotic research and the importance of considering less traditional risk areas, such as supra-cardiac atherosclerosis. The disparities in disease impact across ethnicities and individual profiles further emphasize the necessity for personalized medicine approaches in cardiovascular care.

Clinical Implications

The reviewed literature suggests that a comprehensive approach to evaluating atherosclerotic risk, considering both traditional and emerging factors, can enhance prevention and management strategies. The identification of biomarkers and structural and vascular changes associated with increased risk of CVD highlights the potential for early intervention and individualized medicine.

Future Directions

Future research should focus on longitudinal studies to confirm the causal relationships between identified risk factors and cardiovascular events. Diving into the emerging research area of the molecular pathogenesis of atherosclerosis will possibly provide important insight. Additionally, not only is there a need for the development of non-invasive, cost-effective screening tools for the early detection of atherosclerotic changes, but also for preventive measures of ASCVD. Investigating the genetic and molecular bases of atherosclerosis will further our understanding of disease mechanisms and potential targets for therapeutic intervention.

CONCLUSION

The studies reviewed herein conjointly advance our understanding of the complex mechanisms driving ASCVD. They highlight the importance of a multifaceted approach to cardiovascular risk assessment and management, incorporating insights into atherothrombotic factors, inflammatory

processes, and vascular changes, and illuminating the complex and multifactorial nature of ASCVD, involving genetic, environmental, and molecular dynamics.

The ongoing evolution of our comprehension of these disorders emphasizes the critical need for continued research. Thus, future research should continue to explore these complex interactions, with an emphasis on translating these insights into therapeutic targets. The aim is to apply these comprehensive learnings to practical healthcare solutions, thereby enhancing patient outcomes in the face of cardiovascular diseases. As our knowledge evolves, so too will our strategies. By offering new perspectives on ASCVD's advancement and paving the way for innovative research and clinical methodologies, this body of work signals a pivotal shift towards more tailored and efficacious strategies in preventing, diagnosing, and treating ASCVD, moving towards more personalized and effective approaches to combat this disease.

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REFERENCES

1. Libby P. The changing nature of atherosclerosis: what we thought we knew, what we think we know, and what we have to learn. *Eur Heart J*. 2021;42(47):4781-4782. [CrossRef]
2. Santovito D, Steffens S. DNA damage and extranuclear DNA sensors: a dangerous duo in atherosclerosis. *Eur Heart J*. 2021;42(42):4349-4351. [CrossRef]
3. DeFilippis AP, Trainor PJ, Thanassoulis G, et al. Atherothrombotic factors and atherosclerotic cardiovascular events: the multi-ethnic study of atherosclerosis. *Eur Heart J*. 2022; 43(10):971-981. [CrossRef]
4. Ballegaard CR, Pham MHC, Sigvardsen PE, et al. Aortic enlargement and coronary artery calcification in a general population cohort. *Eur Heart J Cardiovasc Imaging*. 2022;23(6):855-862. [CrossRef]
5. Ntaios G, Wintermark M, Michel P. Supracardiac atherosclerosis in embolic stroke of undetermined source: the underestimated source. *Eur Heart J*. 2021;42(18):1789-1796. [CrossRef]
6. Parry R, Majeed K, Pixley F, Hillis GS, Francis RJ, Schultz CJ. Unravelling the role of macrophages in cardiovascular inflammation through imaging: a state-of-the-art review. *Eur Heart J Cardiovasc Imaging*. 2022;23(12):e504-e525. [CrossRef]