VER
Vascular & Endovascular Review

Emerging Molecular Pathways in the Pathogenesis of Cardiovascular Diseases: A Comprehensive Review

Dr. N. Swapna[1], Dr. B. Birundha[2], Dr. Yugantar Wakde[3], Md Tausif Raza[4], Mithul V Mammen[5], Dr. Nikunj B. Patel[6], Sanjukta Roy[7]

[1]Assistant Professor, Department of Pathology, Aarupadai Veedu Medical College and Hospital, Vinayaka Missions Research Foundation (Deemed to be University), Puducherry, India, swapnanalli07@gmail.com
[2]Assistant Professor, Department of Pathology, Aarupadai Veedu Medical College and Hospital, Vinayaka Missions Research Foundation (Deemed to be University), Puducherry, India, bvbrindha693@gmail.com
[3]Assistant Professor, Department of Biochemistry Shri Rawatpura Sarkar Institute of Medical Science and Research (SRIMSR) Naya Raipur yugantar369@gmail.com
[4]Department of Microbiology Faculty of Science & Humanities Sankalchand Patel University Visnagar-384 315, Gujarat & Microbiologist, RTPCR Lab, Sadar Hospital, Siwan- 841226, Bihar, tausifmicro@gmail.com
[5]Department of Pharmacy Practice, Teerthanker Mahaveer College of Pharmacy, Teerthanker Mahaveer University, Moradabad, Uttar Pradesh, India -24400, mithulvmammen@gmail.com
[6]Associate Professor Department of Microbiology Faculty of Science & Humanities Sankalchand Patel University Visnagar-384 315, Gujarat, niks17micro@gmail.com
[7]PhD Scholar in Pharmaceutical Sciences (Pharmacology), Adamas University, sanjukta.roy57@gmail.com

ABSTRACT

Cardiovascular diseases (CVDs) have been the leading killer since 1970. 18.71% of people died due to CVDs in the last decade which makes it imperative to go beyond traditional disease risk factor control strategies towards gaining the molecular pathogenesis. This review combines the most recent developments in molecular cardiology with numerous examples of the contribution of endothelial dysfunction, chronic inflammation, oxidative stress, and metabolic reprogramming in the pathogenesis of CVD progression. Major mechanisms include eNOS uncoupling, EndoMT, VSMC phenotypic switching and metabolites of gut microbiome, including TMAO, that drive atherosclerosis. The coming together of single-cell transcriptomics, multi-omics data and artificial intelligence is making it possible to resolve cellular heterogeneity and intercellular crosstalk like never before, leading towards the next step towards precision medicine. Novel therapeutic strategies are on the horizon including anti-inflammatory agents (e.g. Colchicine), redox-modulating therapy, epigenetic modulators, RNA based therapy (e.g siRNA for PCSK9) and microbiome-targeted therapy. These advancements have resulted in revolution in dimension from symptomatic treatment to mechanism-based specific therapy of reversing of underlying molecular defect in CVD.

KEYWORDS: Cardiovascular disease, Molecular pathology, Inflammation, Gut-heart axis, Precision medicine, RNA therapeutics.

How to Cite: S Dr. N. Swapna, Dr. B. Birundha, Dr. Yugantar Wakde, Md Tausif Raza, Mithul V Mammen, Dr. Nikunj B. Patel, Sanjukta Roy., (2025) Emerging Molecular Pathways in the Pathogenesis of Cardiovascular Diseases: A Comprehensive Review, Vascular and Endovascular Review, Vol.8, No.13s, 367-377.

INTRODUCTION

The global burden of cardiovascular diseases (CVDs) is not just a statistic; this is a giant and growing public health crisis that knows no borders, socioeconomic background, age, or race. CVDs claim the most important number of lives in this planet (Coronado et al., 2022). In 2020 alone, an estimated 19.05 million lives have been lost due to CVD, this is a staggering 18.71% increase from the previous decade. This inexorable rise, in spite of decades of medical advancements is one of the most damning indictments of the current state of affairs It is an indication that while we have made great progress in dealing with problems that happen acutely, or risk factors like high cholesterol or blood pressure, we have not been able to stop the underlying biological processes that drive these diseases in the first place (Fossel et al., 2022). The persistence and escalation of this burden warrants a change of paradigm in the approach to the treatment of the symptom, as opposed to the knowledge-based and attack of the origin of the molecular pathology (Nogales et al., 2021).

This need for greater understanding has led to the development of the field of molecular cardiology which is a rapidly developing field and is leading to a change of face of the heart and the vasculature (Windt, 2022). Traditional therapeutic strategies, such as statins, beta-blockers and ACE inhibitors are invaluable tools and have saved countless lives due to risk mitigation and management of clinical manifestations. However, they are often "band-aids" to a complex and developing pathological process (Amadori et al., 2023). How the disease process continues in treated patients, they do not address the causes of cell dysfunction that is still contributing to this disease process. Molecular cardiology tries to overcome this limitation by deconstructing the disease at the ground level genome, transcriptome, proteome and metabolome level (Doran et al., 2021).

This granular way of looking at CVD establishes the idea that CVD is not a monolithic brand, but rather a collection of dynamic interlinked pathologies, at the molecular level. Recent advancement in technology, in particular, single cell transcriptomics, has played an important role in this (Fu & Song, 2021). These technologies have obliterated the simple view of the cardiac and vascular tissues as homogenous masses in favor of an astounding degree of cellular diversity: in their place Within the myocardium, besides the blood vessel endothelial lining, many subtypes of cells with their peculiar gene expression profiles and functions have been identified by researchers (Ding et al., 2022). This is important to us since it highlights how intercellular communication is of utmost importance: the complex multi-level crosstalk between cardiomyocytes and fibroblasts, immune cells and endothelial cells is now known as the main driving force behind the pathologic signaling that leads to diseases such as HF and atherosclerosis (Claridge et al., 2023). Disturbances of these maladaptive communication networks are a new arena of therapeutic intervention.

The insights that molecular cardiology brings to light are not on an academic level, and are rather the basis for a new wave of precision medicine. By the identification of molecular checkpoints, in this context mainly in the form of critical epigenetic modifier genes, non-coding RNAs, or dysregulated signaling pathways, it is possible to develop not only more effective, but also more focused and specifically tailored therapies (Zhu et al., 2025). For example, identification of microRNAs (miRNAs), controllers of the inflammatory pathways, or identification of particular epigenetic markings linked to endothelial dysfunction, are particular targets for the development of new drugs. Similarly, understanding of the gut-heart axis in which metabolic products of the microbiota including TMAO can directly influence the process of systemic inflammation and plaque formation opens up completely new fields for intervention either through a diet or a therapy that targets the microbiome (Caradonna et al., 2025). This shift in therapeutic approach towards mechanism-based approaches is of paramount importance to the heterogeneity of CVD challenge. A patient with HF from chronic inflammation will need a different approach to therapy than someone whose condition has resulted from the dysfunction of the mitochondria due to the metabolic syndrome (Wenzl et al., 2021). Personalized management, based on molecular profiling holds the promise to provide the right therapy to the right patient at the right time and hence achieve better results, and thus a reduction of the substantial economic and social burden of CVD (Ravindran & Rau, 2024).

Furthermore, the intersection of high end computational approaches and in particular artificial intelligence (AI) and machine learning (ML) play an essential role in the translation of this immense molecular information for clinically relevant insights. The amount and complexity of multi-omics information, which is being acquired by the latest techniques, is way beyond what the classical analysis can handle (Mukherjee et al., 2024). AI algorithms have a certain advantage in seeing subtle patterns, predicting course of disease, optimizing response to therapeutics so in essence "closing down" the bench and bedside connection (Zhang et al., 2025). This intersection of deep molecular biology and powerful data science is what the future holds in terms of CVD management so that it can shift from being reactive to proactive and predictive in nature (Rhee & Wu, 2025). The ultimate idea is to evolve from a model that is based on management of chronic diseases, to a model of early detection, prevention and appropriate correction of molecular defects. The continuous development of molecular medicine in the field of cardiology and development of new technologies promise not only prolongation of life, but also improving the quality of life and represent an exit for the future where the worldwide burden of CVD is not only controlled, but actually reversed (Smith & Edelman, 2023).

1.2 Objectives and Scope of the Review

This is an extensive review that seeks to integrate the best and most up-to-date research on the emerging molecular pathways implicated in the pathogenesis of CVD. The scope is broad, covering inflammatory, metabolic, redox, epigenetic, and regulatory cellular mechanisms. The main goal is to create a serious and authoritative reference work that provides a critical analysis of the current state of molecular discoveries providing insights into the regulated cell death pathways, the mechanisms of non-coding RNAs, and the role of the gut microbiome as well as their translational potential in early diagnosis and risk stratification of patients and the development of therapies for these targets in a precision medicine approach.

2. Inflammation and Immune Dysregulation

Transition metal carbo-chalcogenides (TMCCs), with the general formula TM_2X_2C, where TM is a transition metal and X is sulfur or selenium, are a new class of two-dimensional (2D) materials that fill the gap between transition metal dichalcogenides (TMDs) and transition metal carbide MXenes (TMCs). Unlike TMDs, which often suffer from poor electrical conductivity, and MXenes, which can experience specific restacking issues, TMCCs possess a combination of properties by integrating the metallic core of MXenes with the catalytically active chalcogen layers of TMDs into a one-phase structure in Figure 1. This eliminates the complex solid-solid interfaces that emerge in other traditional MXene-TMD heterostructures, frequently tunes charge through charging, and will result in superior small electrochemical conducting. These materials cannot only show unique characteristics, such as high electrical conductivity, good mechanical strength, chemical stability, and tunable electronic properties, but are also attractive materials for various applications.

The production of TMCCs is an ongoing problem, and the current methods for making TMCCs mainly use high-temperature processes, such as solid-state reactions and spark plasma sintering techniques, which are incompatible with large-scale production. The most common precursors used are layered ternary compounds, and successful synthesis has been reported for specific compositions using niobium, tantalum, titanium, zirconium, and hafnium. Despite such advancements, research on 2D TMCCs is in its infancy. While bulk forms of compounds such as Nb_2S_2C and Ta_2S2C have been known for some time (since the 1970s), the exfoliation of these materials into single-layer nanosheets has been accomplished very recently using techniques such as lithium intercalation followed by sonication. This difficult issue, in terms of the synthesis at low temperatures and at the scale of TMCCs, limits the availability of pure-phase TMCCs, including a wide range of applied research.

The potential applications of recovery of TMCCs are immense, especially in the area of energy storage and energy conversion. As electrode materials for batteries, due to the large interlayer spacing and high conductivity, they can have fast ion diffusion and high capacities, and have good rate capabilities. For instance, Nb_2CSe_2 has shown excellent performance in Li-ion batteries, showing stabilities in the range of thousands of charge-discharge cycles. In photocatalysis and electrocatalysis, TMCCs show tremendous potential in splitting water processes as both oxygen evolution reaction (OER) and hydrogen evolution reaction (HER) catalysts. An excellent example is Nb_2Se_2C with its low OER over potential, which is better than benchmark catalysts of noble metals, IrO_2 and RuO_2, in an alkaline environment. Its use as a cocatalyst improves hybrid systems, which are semiconductors such as TiO_2 and g-C_3N_4, which are more efficient in the production of hydrogen.

Besides in regard to energy applications, TMCCs have several other interesting properties. Some compositions are superconducting at low temperatures and therefore have potential applications in quantum technologies. They also have magnetic properties which may be controlled by putting in other transition metals in between, leading to potential applications in data storage and sensing. In addition, they have high tensile strength and good light properties, making them suitable for optoelectronic devices. But there are some challenges that need to be overcome to make them reach their full potential. These include the development of better and more efficient synthesis methods, the improvement of material stability under harsh reaction conditions, the design and engineering of surface terminations and surface defects to optimise catalytic activities, as well as the development of a deeper fundamental understanding, through advanced in-situ characterization and theoretical modelling, of their reaction mechanisms. Solving these problems will be critical in realising the transformative potential of TMCCs across a number of technology sectors.

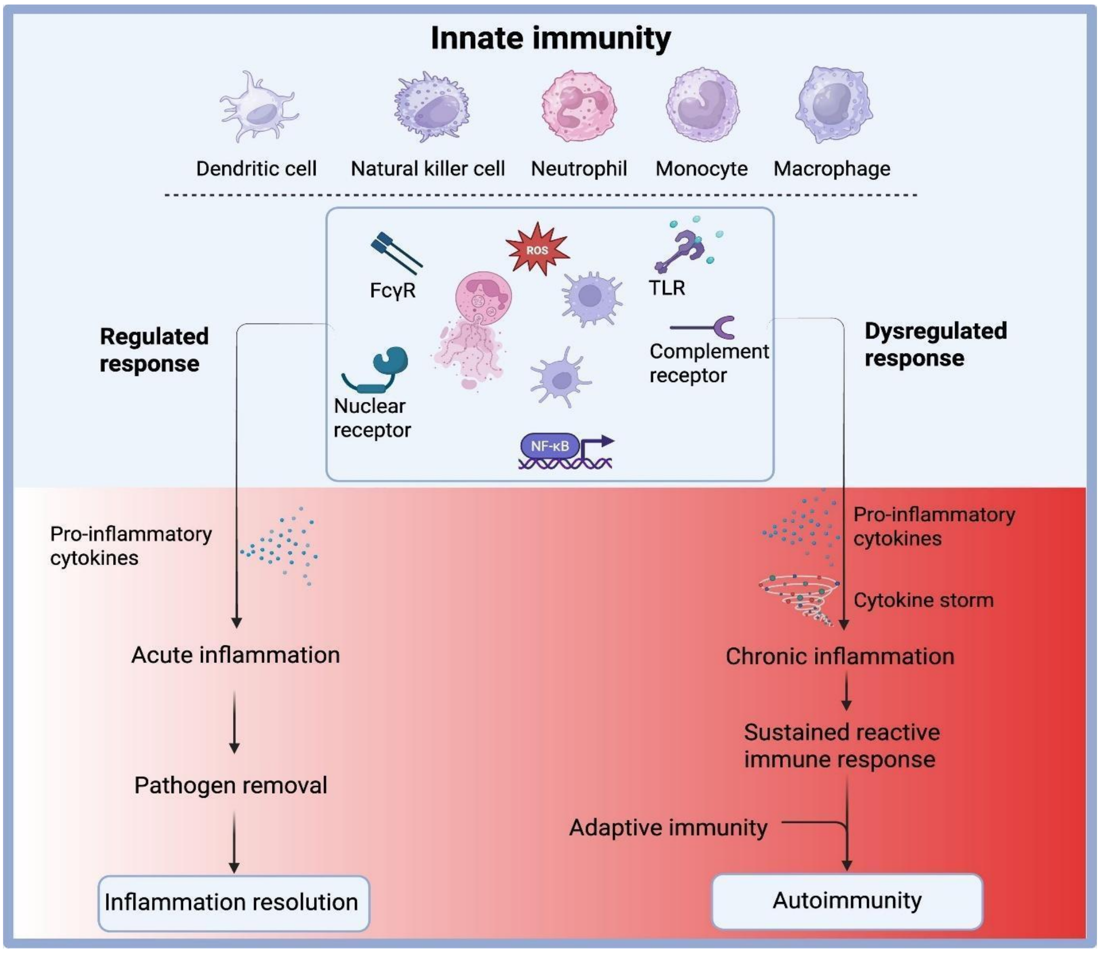

Figure 1. The dual pathways of the innate immune system: regulated response that is beneficial - leads to pathogen clearance and resolution and dysregulated response that leads to chronic inflammation and autoimmunity (Akbarzadeh et al., 2025).

3. Oxidative Stress and Redox Biology

This process starts with the stimulation of a Toll-like Receptor (TLR) at the surface of the cell. This activation results in the recruitment and activation of the IκB kinase (IKK) complex consisting of three subunits: IIKKα, IKKβ, and IKKγ in Figure 2. The activated Ikk complex in turn phosphorylates the inhibitor of beta (IκB) protein which is bound to the NF-κB transcription factor complex (composed of P50 and p65 (or c-Rel subunits).

When IκB is phosphorylated, it is labeled for destruction in a process called the ubiquitin-proteasome system. This degradation frees the NF-κB complex from the control of the proteins. The free NF-κB complex then moves into the nucleus, where it binds to specific DNA sequences found in the promoter regions of immune response target genes, initiating the transcription of these genes.

The role of reactive oxygen species (ROS) is also highlighted in this diagram by red starbursts. ROS are shown to act at several points in this pathway: they can both activate the IKK complex and are involved in the degradation of IκB, thus acting as positive regulators and enhancing the signal to ensure a strong immune response.

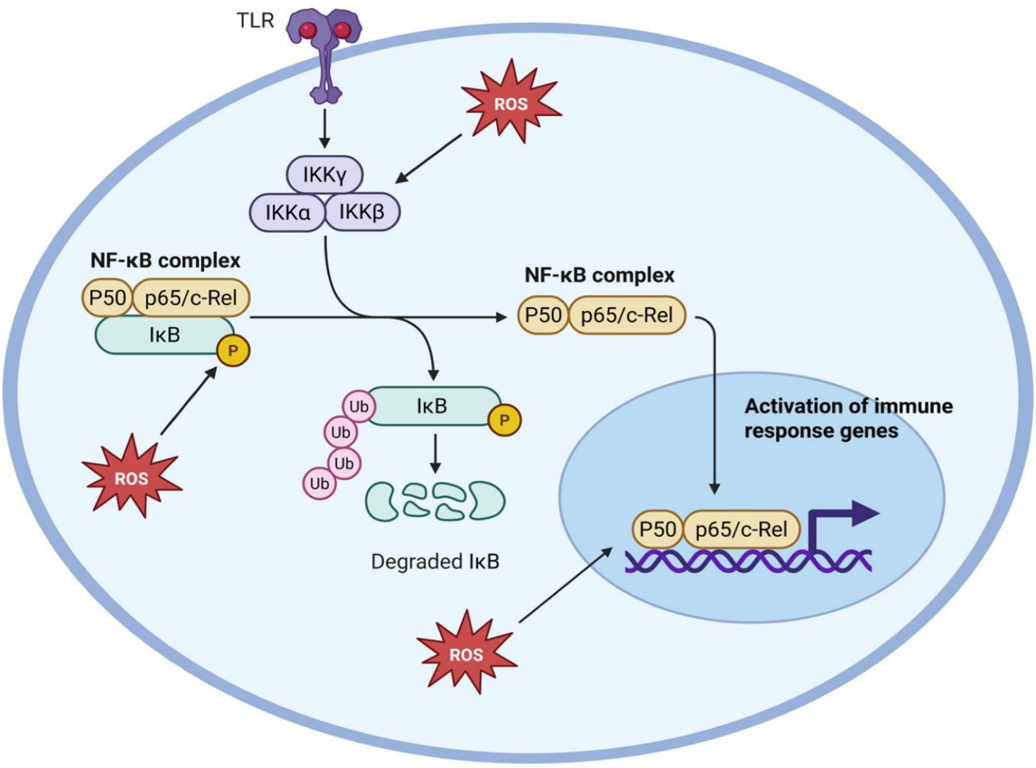

Figure 2. The canonical pathway for activating the transcription factor NF-Kb (Bellanti et al., 2025).

4. Endothelial Dysfunction and Vascular Homeostasis

Endothelial dysfunction is a key early step in CVD. It is associated with a change in the behavior of the endothelium from an anti-thrombotic, vasodilatory state to a pro-inflammatory, contractile state (Wang & He, 2024). Central to this dysfunction is the uncoupling of endothelial nitric oxide synthase (eNOS) whereby pathological conditions such as oxidative stress or deficiency in L-arginine or tetrahydrobiopterin (BH4) lead 3 to eNOS producing superoxide ($O2^-$) instead of nitric oxide (NO). This decreases NO bioavailability and increases ROS, promoting systemic inflammation and furthering the formation of foam cells in atherosclerosis (AS) (Malekmohammad et al., 2020).

Another important mechanism is Endothelial-to-Mesenchymal Transition (EndoMT), during which endothelial cells (ECs) lose epithelial markers (e.g., VE-catenin) and become mesenchymal under oxidative stress and eNOS uncoupling. These transformed cells participate in vascular remodeling and fibrosis by becoming pro-fibrotic fibroblasts (Chen et al., 2020). Similarly, Vascular Smooth Muscle Cells (VSMCs) change their phenotype from a quiescent, contractile state (characterized by MYH11 and ACTA2) to a synthetic, proliferative, and migratory state (characterized by Sca1+ expression) in response to inflammation, mechanical stress, or growth factors (Cao et al., 2022). This dedifferentiation is responsible for the media thickening, extracellular matrix deposition, and calcification characteristic of hypertension and plaque progression. The pathology of the vessel wall is therefore consistent with the loss of cellular identity, as both ECs and VSMCs adopt pro-fibrotic fates (Sorokin et al., 2020). In addition, the role of shear stress is of great importance: laminar flow is conducive to an anti-atherogenic endothelium through activation of eNOS; disturbed flow or oscillatory flow is responsible for EC dysfunction (Cheng et al., 2025). Mechanosensors, such as Piezo1, translate these hemodynamic forces into biochemical signals that modulate the fate of EndoMT and VSMC; thus, mechano-transduction appears to be an essential mechanism in CVD pathogenesis.

5. Epigenetic and Transcriptomic Regulation

Epigenetics is heritable changes in gene expression without changes in the DNA sequence (mainly through methylation of DNA and histone) in Table 1. These mechanisms are vulnerable to environmental factors such as diet, oxidative stress, and tobacco exposure that lead to long-lasting and maladaptive changes in vascular function (Shi et al., 2022). A significant advantage of epigenetic changes is that they are reversible and, as such, make these changes a prime target in the prevention of CVD.

Non-coding RNAs (ncRNAs), microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs) play an important role in the regulation of gene expression via interactions with epigenetic modifiers (Gevaert et al., 2022). These loops integrate enzymes (histone acetyltransferases and DNA methyltransferases) which reinforce abnormal gene expression patterns such as cardiovascular diseases. New single cell transcriptomics studies have provided a better understanding of cardiovascular disease because they demonstrate that heart and blood vessel tissues are highly diverse at a cellular level (Miranda et al., 2022). It has also identified different types of cells called fibroblast and immune cells, that have distinct tasks of developing a disease, with emphasis to intercellular communication in diseased signaling (Hara & Tallquist, 2023). Transition metal carbo-chalcogenides (TMCCs), found under the formula TM2X2C (TM= transition metal, which includes Ti, Co, Ni, Cr, V, etc, and X= S or Se), are emerging two-dimensional materials that blend metallic conductivity of MXenes with catalytically active chalcogen layers found in TMDs into a one-phase material (Dong et al., 2020). This integration eliminates complicated solid-solid interfaces that exist in heterostructures, thereby improving charge transfer and electrochemical performance. TMCCs have great promise in energy applications, especially as high-performance electrode materials in batteries and efficient catalysts in water splitting applications (Ren et al., 2021). However, issues arise in terms of developing scalable, low-temperature synthesis techniques and forming stable, defect-engineered 2D nanosheets for practical applications in energy, electronics, and quantum technologies.

Table 1: Key Non-Coding RNA Regulatory Axes in Atherosclerosis (AS)

ncRNA Type	**Example**	**Target Molecule / Axis**	**Cell Type**	**Action Mechanism**	**Pathogenic Effect (Upon Deregulation)**
miRNA	miR-146a-5p	TRAF6, IRAK1	ECs	Transcriptional repression	Endothelial inflammation and senescence (when repressed)
miRNA	miR-19b	PPARγ	ECs	Transcriptional repression	Increased inflammatory cytokine production (when upregulated)
circRNA	circMTO1	miR-182-5p / RASA1	VSMCs	miRNA sponging, RASA1 regulation	VSMC proliferation and migration (when reduced)
circRNA	circHIPK3	miR-190b / ATG7	HUVECs	Autophagy regulation	Lipid accumulation and impaired autophagy (when repressed)
miRNA (EV-delivered)	miR-1	KLF4	ECs	Promotes endothelial inflammation	Atherosclerosis is strongly linked to NAFLD-associated vascular dysfunction.

6. Metabolic Reprogramming in Cardiovascular Diseases

A conceptual diagram that systematically describes the various molecular and cellular mechanisms by which different cancer treatments contribute to cardiovascular toxicity. with the central focus on "Cancer Therapy-Related Cardiovascular Toxicity." The structure of this diagram is that of a radial chart, with the central icon representing a human heart surrounded by six different therapeutic categories: Chemotherapy, Targeted therapy, Endocrine therapy, Immunotherapy, Radiotherapy, and Surgical resection. Each segment describes the specific pathophysiological pathways that are activated by that therapy in Figure 3.

Chemotherapy: This section focuses on direct cardiotoxic mechanisms, including mitochondrial impairment, induction of oxidative stress, lipid peroxidation leading to ferroptosis, and microtubule damage, which can result in abnormal calcium metabolism.

Targeted Therapy: This is my favorite category, and it is focused on how to disrupt the critical signaling pathway. It links targeted agents to mitochondrial disorders and high levels of ROS, accumulated lipid peroxidation, and activation of pro-inflammatory signals.

Endocrine Therapy: This section covers the metabolic disturbances, such as the induction of insulin resistance and hyperglycemia, decreased steroid synthesis, and increased blood glucose levels. These factors lead to a strain on the cardiovascular system.

Immunotherapy: In this section, immune-mediated injuries, such as mitochondrial dysfunction, inhibition of lipid metabolism, substrate accumulation in the β-oxidation process, carnitine/acylcarnitine transport system, glycogen metabolic changes, and inflammasome NLRP3 activation, resulting in pyroptosis, are the primary focus of attention.

Radiotherapy: The sequelae of radiation-induced injury are overproduction of ROS and reactive nitrogen species (RNS), mitochondrial calcium overload, inhibition of fatty acid beta oxidation, and release of proinflammatory cytokines, e.g., TGF-beta, TNF-alpha, interleukin 1, and interleukin 6.

Surgical Resection: This section discusses the physiological stress response to surgery, such as transient insulin resistance, inflammatory cytokine release, activation of the HPA-axis, and release of cortisone hormone, and depletion of glutamine that can have a downstream effect on cardiac function.

Overall, the diagram provides a multi-modal, whole-body view of the convergence of various oncological treatments at standard pathological endpoints (e.g., mitochondrial dysfunction, oxidative stress, inflammation) that can induce cardiovascular complications, identifying potential therapeutic intervention points.

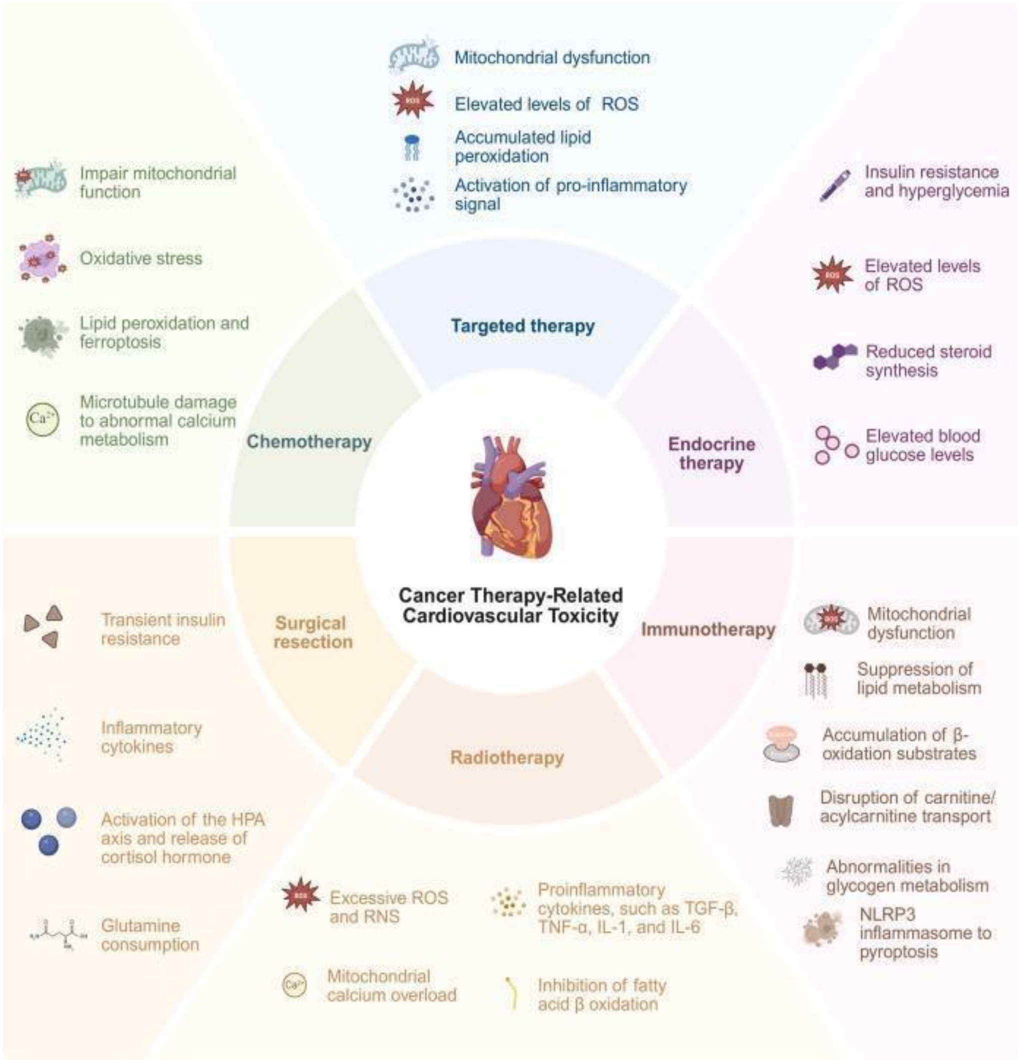

Figure 3. Cancer Therapy-Related Cardiovascular Toxicity (Zeng et al., 2025)

7. Gut Microbiota and Cardiovascular Pathophysiology

The gut-heart axis has become an important concept in the prevention of CVD, which focuses on the role of metabolites produced in the gut by microbiota in systemic pathology modulation. The best pathway described is that of trimethylamine N-oxide (TMAO) (Mohsenzadeh et al., 2025). The gut microbial TMA lyases convert dietary nutrients like choline, carnitine, and lecithin to trimethylamine (TMA), which is absorbed and transformed in the liver by flavin-containing monooxygenase 3 (FMO3) to TMAO (Xu et al., 2020). Elevated circulating levels of TMAOs are highly correlated with increased atherosclerotic CVD risk, and, therefore, microbial TMA lyases would be potential therapeutic targets for intervention (Steinke et al., 2020).

Gut barrier dysfunction further exacerbates the risk of CVD by allowing bacterial products, such as lipopolysaccharide (LPS), to enter the bloodstream, thereby stimulating endotoxemia throughout the body. This is the chronic, low-grade inflammation termed meta-inflammation, which activates innate immune pathways, such as the NLRP3 inflammasome, in vascular cells, thereby promoting endothelial dysfunction and the progression of plaque (Bai et al., 2020).

On the other hand, the gut microbiota also produces protective metabolites: SFCA's, i.e., acetate, propionate, and butyrate (short-chain fatty acids), produced during the fermentation of dietary fibre. SCFAs act as signaling molecules through free fatty acid receptors (FFAR2/3) in immunity and enteroendocrine cells to play anti-inflammatory roles, enhance glucose metabolism, and obesity-induced metabolic health, all of which are associated with decreased risk of atherosclerosis (Birkeland et al., 2023).

These opposing influences of microbes demonstrate the necessity of identifying therapeutic strategies that will simultaneously suppress unfavourable pathways (i.e., TMAO production) and stimulate beneficial outputs (i.e., SCFAs production). In addition, some alterations in microbial composition linked to CVD dysbiosis have significant potential as diagnostic or prognostic biomarkers for the increased personalisation of cardiovascular risk assessment and management (Tang & Hazen, 2024).

8. Therapeutic Targeting of Emerging Molecular Pathways

Molecular discoveries are opening the door to a new era of cardiovascular treatments, where the treatment will target specific pathways. The success of drugs targeting the NXT3PM/IL-1β axis such as, Canakinumab in the CANTOS trial and colchicine attest to meta-inflammation being important in cardiovascular disease (D'Aiello et al., 2024). Both drugs have demonstrated efficacy in secondary prevention, colchicine is now approved for this use based upon its ability to block the release of IL-1-beta by an immunogenic inflammasome (termed the NLRP3 inflammasome) (Potere et al., 2024). However, the issue of timing therapy and patient selection is critical, as illustrated by the varying results with Anakinra, which was beneficial in early STEMI but potentially harmful in NSTEMI in Table 2.

The complexity of ROS signaling, combined with the simplicity of broad antioxidant therapy, necessitates a unique approach. Given that the Nox4-derived H2O2 produced exhibits vasoprotective activities, it can be suggested that future redox-modulating drugs should be isoform-specific in their suppressing effect by inhibiting the deleterious superoxide production of Nox1 and Nox2, while leaving Nox4 activity uncontrolled (Sylvester et al., 2022).

An area that can help enhance the collection is epigenetic modulators. Since epigenetic alterations are reversible, the use of inhibitors of enzyme function, including DNA methyltransferases and histone deacetylases, is being investigated to reprogram maladaptive gene expression and restore the health of the vascular system (Lin et al., 2022).

RNA-based therapeutics, including antisense oligonucleotides (ASOs) and siRNAs, provide a revolutionary platform for targeting hitherto ungradable pathways. These are programmable biological agents designed to silence specific genes. The clinical approval of siRNA-based PCSK9 inhibitors, such as Inclisiran, with an effective lowering of LDL-C, is high proof of concept (Soffer et al., 2022). Continuing trials are investigating the use of RNA treatments for hypercholesterolemia and myocardial infarction, and are a potential revolution in CVD treatment.

Finally, there are targeted interventions against the microbiome, in the form of the reduction of harmful metabolites, such as TMAO, by using inhibitors of microbial TMA lyases. Complementary strategies of diet modifications, prebiotics, and probiotics therapy will be designed in order to elevate the number of positive microflora and boost protective short-chain fatty acid (SCFA) output, ultimately translating into better cardiovascular outcomes, via the gut-heart axis (Qu et al., 2024).

Table 2: Clinical Translation of Molecular Targets in CVD Therapeutics

Target Pathway	Molecular Target	Therapeutic Agent Class	Example Agent	Mechanism / Action	Clinical Status / Significance
Inflammation	NLRP3 Inflammasome / IL-1β	Alkaloid / Monoclonal Antibody	Colchicine, Canakinumab	Inhibits IL-1β release / Neutralizes IL-1β	Approved for secondary prevention; reduced MACE risk (CANTOS)
Lipid Metabolism	PCSK9	siRNA	Inclisiran	Reduces PCSK9 synthesis	High-efficacy LDL-C lowering; established RNA therapeutic
Gene Expression	ncRNAs / mRNA	RNA-based Therapeutics (ASO/siRNA)	(Pipeline targets)	Modulates splicing or degrades target mRNA	Enables targeting of "undruggable" factors; high molecular specificity
Redox Signaling	Nox1 / Nox2	Small-Molecule Inhibitor	(Developmental agents)	Inhibits excessive superoxide generation	Requires high isoform selectivity to avoid blocking protective Nox4 activity
Cell Death	RIPK1	Kinase Inhibitor	Nec-1 (Preclinical)	Blocks necroptosis-mediated inflammation	Potential strategy to reduce ischemia-induced tissue injury

9. Future Directions

The future of molecular approaches in cardiovascular research is the combination of complex molecular data to bring about a truly personalised medicine. A key part of this transformation is the use of AI and ML in parsing highly voluminous datasets with high dimensions that arise from multi-omics analyses (genomics, proteomics, metabolomics) and from advances in high dimensional imaging (Li et al., 2023). AI is good at finding complex patterns in this information, which can be used to more accurately stratify risk, accurately predict individual therapeutic response, and better manage patient. AI is being applied in the case of analyzing left atrial volume and predicting atrial fibrillation. But rigorous and on-going validation is critical in order for these ML models to become safely incorporated into clinical practice and better tools than current tools (Antoun et al., 2025).

With the complex multi-level etiology of CVD, including cell-to-cell cross-talk, single pathway treatment is often inadequate. Future drug development will be more focused on multi-target strategies that make it possible to treat convergent pathological processes (Azer & Leaf, 2023). This includes designing agents to deal with hemodynamic stress, reduction of ROS, and reversal of maladaptive epigenetic changes, and use of pleiotropic agents like PCSK9 inhibitors with effects on lipid metabolism, inflammation, and mitochondrial functions (Csiszár et al., 2023).

Despite the strong, attractive preclinical results, there have been significant challenges in getting the preclinical results transferred into the clinical arena. These include inherent heterogeneity of patient populations and treatment responses, and difficulties in optimizing the safety, efficacy, and precise dosing (therapeutic window) of new classes of anti-inflammatory or gene-modulating therapies (Zhang et al., 2025). Overcoming these translational hurdles is vital in realizing the overall potential of molecular cardiology and providing successful care on an individual basis.

CONCLUSION

The present state of the art of cardiovascular research is characterised by the depth of molecular resolution enabled by the performance of high-throughput sequencing and the synergy created by running the high-throughput algorithm with bioinformatic tools. Pathogenesis is also being understood, less in terms of structural damage and more in terms of malfunction in cell fate maintenance (e.g., EndoMT, VSMC switching), programmed inflammatory response against metabolic stress, activation of the NLRP3 inflammasome, pyroptosis, as well as breakdown of communication between organ systems (e.g., the gut-heart axis). The identification of essential checkpoints of regulation, which comprise ncRNAs and selected NOX isoforms, provides unique and specific therapeutic options. With the established molecular therapies, such as PCSK9 inhibition via siRNA, and targeted anti-inflammatories, such as colchicine, and in the context of clinical practice, and the potential of AI to incorporate the complexity of multi-omics-based data, the possibility to redefine the CVD prevention and treatment using molecular precision has never been better.

REFERENCES

Akbarzadeh, R., Humrich, J. Y., Németh, T., & Amber, K. T. (2025). Editorial: Innate immune dysregulation: A driving force of autoimmunity and chronic inflammation. *Frontiers in Immunology*, *16*, 1632416. https://doi.org/10.3389/fimmu.2025.1632416

Amadori, L., Calcagno, C., Fernandez, D., Koplev, S., Fernandez, N., Kaur, R., Mury, P., Khan, N. S., Sajja, S., Shamailova, R., Cyr, Y., Jeon, M., Hill, C. A., Chong, P. S., Naidu, S., Sakurai, K., Ghotbi, A. A., Soler, R., Eberhardt, N., … Giannarelli, C. (2023). Systems immunology-based drug repurposing framework to target inflammation in atherosclerosis. *Nature Cardiovascular Research*, *2*(6), 550. https://doi.org/10.1038/s44161-023-00278-y

Antoun, I., Abdelrazik, A., Eldesouky, M., Li, X., Layton, G. R., Zakkar, M., Somani, R., & Ng, G. A. (2025). Artificial intelligence in atrial fibrillation: emerging applications, research directions and ethical considerations. *Frontiers in Cardiovascular Medicine*, *12*, 1596574. Frontiers Media. https://doi.org/10.3389/fcvm.2025.1596574

Azer, K., & Leaf, I. A. (2023). Systems biology platform for efficient development and translation of multitargeted therapeutics. *Frontiers in Systems Biology*, *3*, 1229532. https://doi.org/10.3389/fsysb.2023.1229532

Bai, B., Yang, Y., Wang, Q., Li, M., Tian, C., Liu, Y., Aung, L. H. H., Li, P., Yu, T., & Chu, X. (2020). NLRP3 inflammasome in endothelial dysfunction. *Cell Death and Disease*, *11*(9), 776. Springer Nature. https://doi.org/10.1038/s41419-020-02985-x

Bellanti, F., Coda, A. R., Trecca, M. I., Lo Buglio, A., Serviddio, G., & Vendemiale, G. (2025). Redox Imbalance in Inflammation: The Interplay of Oxidative and Reductive Stress. *Antioxidants*, *14*(6), 656. https://doi.org/10.3390/antiox14060656

Birkeland, E., Gharagozlian, S., Valeur, J., & Aas, A. (2023). Short-chain fatty acids as a link between diet and cardiometabolic risk: a narrative review. *Lipids in Health and Disease*, *22*(1). BioMed Central. https://doi.org/10.1186/s12944-023-01803-5

Cao, G., Xuan, X., Hu, J., Zhang, R., Jin, H., & Dong, H. (2022). How vascular smooth muscle cell phenotype switching contributes to vascular disease. *Cell Communication and Signaling*, *20*(1). BioMed Central. https://doi.org/10.1186/s12964-022-00993-2

Caradonna, E., Abate, F., Schiano, E., Paparella, F., Ferrara, F., Vanoli, E., Difruscolo, R., Goffredo, V. M., Amato, B., Setacci, C., Setacci, F., & Novellino, E. (2025). Trimethylamine-N-Oxide (TMAO) as a Rising-Star Metabolite: Implications for Human Health. *Metabolites*, *15*(4), 220. Multidisciplinary Digital Publishing Institute. https://doi.org/10.3390/metabo15040220

Chen, P., Schwartz, M. A., & Simons, M. (2020). Endothelial-to-Mesenchymal Transition, Vascular Inflammation, and Atherosclerosis. *Frontiers in Cardiovascular Medicine*, *7*. Frontiers Media. https://doi.org/10.3389/fcvm.2020.00053

Cheng, C. K., Wang, N., Wang, L., & Huang, Y. (2025). Biophysical and Biochemical Roles of Shear Stress on Endothelium: A Revisit and New Insights. *Circulation Research*, *136*(7), 752. Lippincott Williams & Wilkins. https://doi.org/10.1161/circresaha.124.325685

Claridge, B., Rai, A., Lees, J. G., Fang, H., Lim, S. Y., & Greening, D. W. (2023). Cardiomyocyte intercellular signalling increases oxidative stress and reprograms the global- and phospho-proteome of cardiac fibroblasts. *Journal of Extracellular Biology*, *2*(12). https://doi.org/10.1002/jex2.125

Coronado, F., Melvin, S. C., Bell, R. A., & Zhao, G. (2022). Global Responses to Prevent, Manage, and Control Cardiovascular Diseases. *Preventing Chronic Disease*, *19*. https://doi.org/10.5888/pcd19.220347

Csiszár, A., Tarantini, S., Yabluchanskiy, A., & Ungvári, Z. (2023). PCSK9: an emerging player in cardiometabolic aging and its potential as a therapeutic target and biomarker. *GeroScience*, *46*(1), 257. Springer International Publishing. https://doi.org/10.1007/s11357-023-01003-0

D'Aiello, A., Filomia, S., Brecciaroli, M., Sanna, T., Pedicino, D., & Liuzzo, G. (2024). Targeting Inflammatory Pathways in Atherosclerosis: Exploring New Opportunities for Treatment. *Current Atherosclerosis Reports*, *26*(12), 707. Springer Science+Business Media. https://doi.org/10.1007/s11883-024-01241-3

Ding, S., Zhang, X., Qiu, H., Wo, J., Zhang, F., & Na, J. (2022). Non-cardiomyocytes in the heart in embryo development, health, and disease, a single-cell perspective. *Frontiers in Cell and Developmental Biology*, *10*. Frontiers Media. https://doi.org/10.3389/fcell.2022.873264

Dong, L. M., Ye, C., Zheng, L. L., Gao, Z. F., & Xia, F. (2020). Two-dimensional metal carbides and nitrides (MXenes): preparation, property, and applications in cancer therapy. *Nanophotonics*, *9*(8), 2125. https://doi.org/10.1515/nanoph-2019-0550

Doran, S., Arif, M., Lam, S., Bayraktar, A., Türkez, H., Uhlén, M., Borén, J., & Mardinoğlu, A. (2021). Multi-omics approaches for revealing the complexity of cardiovascular disease. *Briefings in Bioinformatics*, *22*(5). Oxford University Press. https://doi.org/10.1093/bib/bbab061

ossel, M., Bean, J., Khera, N., & Kolonin, M. G. (2022). A Unified Model of Age-Related Cardiovascular Disease. *Biology*, *11*(12), 1768. Multidisciplinary Digital Publishing Institute. https://doi.org/10.3390/biology11121768

Fu, M., & Song, J. (2021). Single-Cell Transcriptomics Reveals the Cellular Heterogeneity of Cardiovascular Diseases. *Frontiers in Cardiovascular Medicine*, *8*, 643519. Frontiers Media. https://doi.org/10.3389/fcvm.2021.643519

Gevaert, A. B., Wood, N., Boen, J. R. A., Davos, C. H., Hansen, D., Hanssen, H., Krenning, G., Moholdt, T., Osto, E., Paneni, F., Pedretti, R. F. E., Plösch, T., Simonenko, M., & Bowen, T. S. (2022). Epigenetics in the primary and secondary prevention of cardiovascular disease: influence of exercise and nutrition. *European Journal of Preventive Cardiology*, *29*(17), 2183. Oxford University Press. https://doi.org/10.1093/eurjpc/zwac179

Hara, A., & Tallquist, M. D. (2023). Fibroblast and Immune Cell Cross-Talk in Cardiac Fibrosis. *Current Cardiology Reports*, *25*(6), 485. Springer Science+Business Media. https://doi.org/10.1007/s11886-023-01877-8

Li, T., Shi, W., Isgut, M., Zhong, Y., Lais, P., Gloster, L., Sun, J., Swain, A., Giuste, F., & Wang, M. D. (2023). Integrating Multi-Omics Data With EHR for Precision Medicine Using Advanced Artificial Intelligence. *IEEE Reviews in Biomedical Engineering*, *17*, 80. Institute of Electrical and Electronics Engineers. https://doi.org/10.1109/rbme.2023.3324264

Lin, Z., Ding, Q., Li, X., Feng, Y., Hao, H., Huang, C., & Zhu, Y. Z. (2022). Targeting Epigenetic Mechanisms in Vascular Aging. *Frontiers in Cardiovascular Medicine*, *8*, 806988. Frontiers Media. https://doi.org/10.3389/fcvm.2021.806988

Malekmohammad, K., Sewell, R. D. E., & Rafieian-Kopaei, M. (2020). Mechanisms of Medicinal Plant Activity on Nitric Oxide (NO) Bioavailability as Prospective Treatments for Atherosclerosis. *Current Pharmaceutical Design*, *26*(22), 2591. Bentham Science Publishers. https://doi.org/10.2174/1381612826666200318152049

Miranda, A. M. A., Janbandhu, V., Maatz, H., Kanemaru, K., Cranley, J., Teichmann, S. A., Hübner, N., Schneider, M., Harvey, R. P., & Noseda, M. (2022). Single-cell transcriptomics for the assessment of cardiac disease. *Nature Reviews Cardiology*, *20*(5), 289. Nature Portfolio. https://doi.org/10.1038/s41569-022-00805-7

Mohsenzadeh, A., Pourasgar, S., Mohammadi, A., Nazari, M., Nematollahi, S., Karimi, Y., Firoozbakhsh, P., Mohsenzadeh, H., Kamali, K., & Elahi, R. (2025). The gut microbiota and cardiovascular disease: Exploring the role of microbial dysbiosis and metabolites in pathogenesis and therapeutics. *PubMed*, 123981. National Institutes of Health. https://doi.org/10.1016/j.lfs.2025.123981

Mukherjee, A., Abraham, S., Singh, A., Balaji, S., & Mukunthan, K. S. (2024). From Data to Cure: A Comprehensive Exploration of Multi-omics Data Analysis for Targeted Therapies. *Molecular Biotechnology*. Springer Science+Business Media. https://doi.org/10.1007/s12033-024-01133-6

Nogales, C., Mamdouh, Z. M., List, M., Kiel, C., Casas, A. I., & Schmidt, H. (2021). Network pharmacology: curing causal mechanisms instead of treating symptoms. *Trends in Pharmacological Sciences*, *43*(2), 136. Elsevier BV. https://doi.org/10.1016/j.tips.2021.11.004

Potere, N., Bonaventura, A., & Abbate, A. (2024). Novel Therapeutics and Upcoming Clinical Trials Targeting Inflammation in Cardiovascular Diseases. *Arteriosclerosis Thrombosis and Vascular Biology*, *44*(12), 2371. Lippincott Williams & Wilkins. https://doi.org/10.1161/atvbaha.124.319980

Qu, J., Meng, F., Wang, Z., & Xu, W. (2024). Unlocking Cardioprotective Potential of Gut Microbiome: Exploring Therapeutic Strategies. *Journal of Microbiology and Biotechnology*, *34*(12), 2413. Springer Science+Business Media. https://doi.org/10.4014/jmb.2405.05019

Ravindran, S., & Rau, C. (2024). The multifaceted role of mitochondria in cardiac function: insights and approaches. *Carolina Digital Repository (University of North Carolina at Chapel Hill)*. https://doi.org/10.17615/4z6x-ah96

Ren, K., Liu, Z., Wei, T., & Fan, Z. (2021). Recent Developments of Transition Metal Compounds-Carbon Hybrid Electrodes for High Energy/Power Supercapacitors. *Nano-Micro Letters*, *13*(1). Springer Science+Business Media. https://doi.org/10.1007/s40820-021-00642-2

Rhee, S., & Wu, J. C. (2025). From one-size-fits-all to precision cardiovascular medicine. *Frontiers in Science*, *3*. https://doi.org/10.3389/fsci.2025.1703653

Shi, Y., Zhang, H., Huang, S., Yin, L., Wang, F., Luo, P., & Huang, H. (2022). Epigenetic regulation in cardiovascular disease: mechanisms and advances in clinical trials. *Signal Transduction and Targeted Therapy*, *7*(1), 200. Springer Nature. https://doi.org/10.1038/s41392-022-01055-2

Smith, B. R., & Edelman, E. R. (2023). Nanomedicines for cardiovascular disease [Review of *Nanomedicines for cardiovascular disease*]. *Nature Cardiovascular Research*, *2*(4), 351. Nature Portfolio. https://doi.org/10.1038/s44161-023-00232-y

Soffer, D., Stoekenbroek, R. M., & Plakogiannis, R. (2022). Small interfering ribonucleic acid for cholesterol lowering – Inclisiran. *Journal of Clinical Lipidology*, *16*(5), 574. Elsevier BV. https://doi.org/10.1016/j.jacl.2022.06.009

Sorokin, V. A., Vickneson, K., Kofidis, T., Woo, C. C., Lin, X., Foo, R., & Shanahan, C. M. (2020). Role of Vascular Smooth Muscle Cell Plasticity and Interactions in Vessel Wall Inflammation. *Frontiers in Immunology*, *11*. Frontiers Media. https://doi.org/10.3389/fimmu.2020.599415

Steinke, I., Ghanei, N., Govindarajulu, M., Yoo, S., Zhong, J., & Amin, R. (2020). Drug Discovery and Development of Novel Therapeutics for Inhibiting TMAO in Models of Atherosclerosis and Diabetes. *Frontiers in Physiology*, *11*. Frontiers Media. https://doi.org/10.3389/fphys.2020.567899

Sylvester, A. L., Zhang, D. X., Ran, S., & Zinkevich, N. S. (2022). Inhibiting NADPH Oxidases to Target Vascular and Other Pathologies: An Update on Recent Experimental and Clinical Studies. *Biomolecules*, *12*(6), 823. Multidisciplinary Digital Publishing Institute. https://doi.org/10.3390/biom12060823

Tang, W. H. W., & Hazen, S. L. (2024). Unraveling the Complex Relationship Between Gut Microbiome and Cardiovascular Diseases. *Circulation*, *149*(20), 1543. https://doi.org/10.1161/circulationaha.123.067547

Wang, X., & He, B. (2024). Endothelial dysfunction: molecular mechanisms and clinical implications. *MedComm*, *5*(8). Wiley. https://doi.org/10.1002/mco2.651

Wenzl, F. A., Ambrosini, S., Mohammed, S. A., Kraler, S., Lüscher, T. F., Costantino, S., & Paneni, F. (2021). Inflammation in Metabolic Cardiomyopathy [Review of *Inflammation in Metabolic Cardiomyopathy*]. *Frontiers in Cardiovascular Medicine*, *8*, 742178. Frontiers Media. https://doi.org/10.3389/fcvm.2021.742178

Windt, L. J. D. (2022). Grand challenges in molecular cardiology. *Frontiers in Molecular Medicine*, *2*. https://doi.org/10.3389/fmmed.2022.920039

Xu, D., Wang, K., Yuan, L., Lin, Q., Li, H., Xu, Y., Wei, L., Chen, L., & Jin, K. (2020). Dysbiosis of Gut Microbiota with Increased Trimethylamine N-oxide Level in Patients with Large Artery Atherosclerotic and Cardioembolic Strokes. *Research Square (Research Square)*. https://doi.org/10.21203/rs.3.rs-22813/v1

Zeng, C., Gao, Y., Lan, B., Wang, J., & Ma, F. (2025). Metabolic reprogramming in cancer therapy-related cardiovascular toxicity: Mechanisms and intervention strategies. *Seminars in Cancer Biology*, *113*, 39-58. https://doi.org/10.1016/j.semcancer.2025.05.009

Zhang, H., Hu, N., Wang, Z., & Zhai, S. (2025). Liposome-mediated macrophage reprogramming: emerging strategies for chronic disease therapy. *Frontiers in Immunology*, *16*. https://doi.org/10.3389/fimmu.2025.1653642

Zhang, K., Yang, X., Wang, Y., Yu, Y., Huang, N., Li, G., Li, X., Wu, J. C., & Yang, S. (2025). Artificial intelligence in drug development [Review of *Artificial intelligence in drug development*]. *Nature Medicine*, *31*(1), 45. Nature Portfolio. https://doi.org/10.1038/s41591-024-03434-4

Zhu, Z., Shen, J. P., Ho, P. C.-L., Hu, Y., Ma, Z., & Wang, L. (2025). Transforming cancer treatment: integrating patient-derived organoids and CRISPR screening for precision medicine. *Frontiers in Pharmacology*, *16*. Frontiers Media. https://doi.org/10.3389/fphar.2025.1563198