

Review

# Overview of Vascular Smooth Muscle Cells, Endothelial Cells, and Macrophages Apoptosis During Atherosclerosis Development

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**Abstract:** Atherosclerosis is a complex disease that has garnered significant attention from researchers studying its various aspects. Its pathogenesis involves a wide array of cellular and molecular components, as well as crucial mechanisms and processes crucial for cellular and organismal functioning. Atherosclerosis is considered a chronic inflammatory disease characterized by disrupted lipid metabolism, oxidative stress, and immune response. Apoptosis, a fundamental cellular process essential for normal cell and organismal function, has also been implicated in numerous pathological conditions. In this review, we aim to compile and present data on the role of apoptosis in various cell types during the progression of atherosclerosis. By examining the involvement of apoptosis in atherosclerosis, we hope to shed light on the intricate interplay between cell death and disease pathogenesis. Understanding the specific mechanisms and consequences of apoptosis in atherosclerosis can contribute to the development of targeted therapeutic strategies and interventions for this debilitating condition.

**Keywords:** Atherosclerosis, Apoptosis, Cardiovascular Disease, Macrophages, Endothelial Cells, Smooth Muscle Cells

## Introduction

Cardiovascular Diseases (CVD) are the leading cause of morbidity and mortality worldwide. Atherosclerosis, the process of vascular wall thickening and aging, is a major contributor to Coronary Heart Disease (CHD), ischemic stroke, and peripheral artery diseases.

The objective of this review is to examine the current understanding of the pathogenesis of atherosclerosis, with a focus on the role of endothelial cells, macrophages, and vascular smooth muscle cells and their contribution to plaque formation and progression.

Moreover, the review endeavors to uncover deficiencies in current understanding and to unearth promising new therapeutic avenues for preventing and treating atherosclerosis.

Current therapeutic approaches for patients include a combination of statins, aspirin,  $\beta$ -receptor inhibitors, and

angiotensin-converting enzyme inhibitors. However, despite these interventions, there remains a significant 70-80% risk of experiencing a serious acute Cardiovascular (CV) event. Current treatments primarily target lowering arterial hypertension and LDL cholesterol levels (Olvera Lopez *et al.*, 2023; Brophy *et al.*, 2017), often overlooking inflammation and other factors contributing to cell death in arterial walls, driving atherosclerosis.

Atherosclerosis develops in areas of low shear stress and disrupted blood flow, where endothelial cells become pro-inflammatory, leading to plaque formation (Sobenin *et al.*, 2013; Nigro *et al.*, 2011). Hyperlipidemia exacerbates this process by modifying LDL particles, triggering the expression of MCP-1 and VCAM-1.

Endothelial cells facilitate monocyte adhesion and migration into the subendothelium, where they become macrophages, contributing to plaque formation (Sobenin *et al.*, 2012; Linton *et al.*, 2019a).

Macrophages, foam cells, and vascular smooth muscle cells all play critical roles in plaque development and vulnerability (Chistiakov *et al.*, 2015b; McEver, 2015).

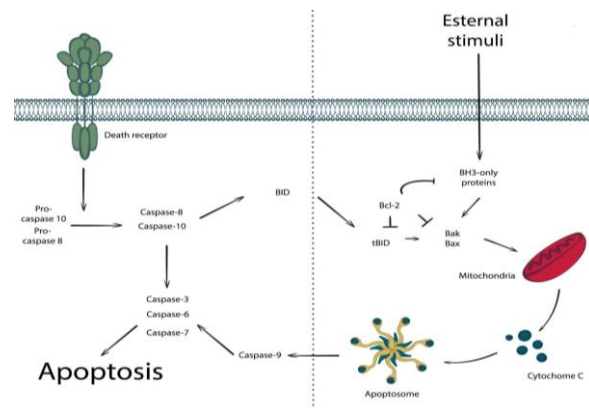
This review aims to provide a comprehensive analysis of the pathogenesis of atherosclerosis, emphasizing the roles of endothelial cells, macrophages, and vascular smooth muscle cells. By identifying gaps in current knowledge and potential novel therapeutic targets, this review aims to contribute to the advancement of enhanced strategies for averting and managing atherosclerosis.

## Methods

1. Study selection: A thorough search of the literature will target studies on atherosclerosis pathogenesis, emphasizing vascular SMCs, macrophages, and endothelial cells (Olvera Lopez *et al.*, 2023). Databases such as PubMed, Scopus, and Web of Science will be searched to ensure comprehensive coverage of the literature. The search will be limited to articles published in English. The search strategy will include keywords and controlled vocabulary terms related to atherosclerosis, endothelial cells, macrophages, and vascular SMCs
2. Data sources: PubMed, Scopus, Web of science
3. Search Strategy: An example search strategy for PubMed is as follows: "Atherosclerosis" OR "atherosclerotic plaque" OR "coronary heart disease" OR "ischemic stroke" OR "peripheral artery diseases" AND "endothelial cells" OR "endothelium" OR "macrophages" OR "foam cells" OR "vascular smooth muscle cells" OR "smooth muscle cells" AND "pathogenesis" OR "plaque formation" OR "plaque progression" OR "inflammation" OR "cell death" OR "therapeutic targets"
4. Inclusion criteria: Studies that investigate the pathogenesis of atherosclerosis, specifically focusing on endothelial cells, macrophages, and vascular SMCs. Experimental studies (*in vitro* or *in vivo*), clinical studies and review articles will be considered. Studies published in English
5. Exclusion criteria: Studies not relevant to the atherosclerosis pathogenesis or not specifically focusing on endothelial cells, macrophages, or vascular smooth muscle cells. Studies with inadequate methodology or insufficient data. Studies not published in English

## Apoptosis as a Process

Cellular demise through apoptosis is orchestrated by a group of cysteine proteases referred to as caspases, regulating programmed cell death. These activated caspases trigger apoptosis, eliminating surplus or impaired cells from the organism. Apoptosis unfolds through three core routes: The extrinsic pathway, the intrinsic pathway, and the Endoplasmic Reticulum (ER) stress-linked pathway.



**Fig. 1:** Intrinsic and extrinsic pathways of apoptosis

These pathways can lead to apoptosis together or independently (Bertheloot *et al.*, 2021). Figure 1, we provide a schematic illustration of extrinsic and intrinsic apoptotic pathways.

### The Extrinsic Apoptotic Pathway

The extrinsic apoptotic pathway, also known as the Death Receptor (DRs) pathway, involves DRs binding to specific ligands on the cell surface. DRs, including TNFR1, Fas, and TRAIL-R1/2, recruit FADD, leading to caspase-8 activation and subsequent apoptosis. Caspase-8 activates caspases 3/6/7 in type I cells and triggers Bid cleavage in type II cells, leading to mitochondrial changes and apoptosis (Green and Llambi, 2015; Pobezinskaya and Liu, 2012; Parrish *et al.*, 2013; Huang *et al.*, 2016).

### The Intrinsic Apoptotic Pathway

The intrinsic apoptotic pathway may be triggered by various factors, such as lack of nutrients, lack of growth factors, ionizing radiation, Reactive Oxygen Species (ROS), and cytotoxicity (Hekimi *et al.*, 2016).

These elements trigger Mitochondrial Outer Membrane Permeabilization (MOMP), leading to cytochrome c release. Cytochrome c binds to Apaf-1, forming an apoptosome complex, activating caspase-9, which activates caspase-3/6/7, causing apoptosis. Pro-apoptotic proteins Smac/DIABLO and Omi/HtrA2 inhibit XIAP, promoting apoptosis. Bcl-2 family proteins regulate mitochondrial permeability, with Bax, Bak, and Bok inducing MOMP, releasing apoptotic factors and activating caspases.

### The Endoplasmic Reticulum Stress-Induced Apoptosis

Endoplasmic reticulum stress occurs when unfolded or misfolded proteins accumulate as a result of diverse stressors like oxygen deprivation, nutrient deprivation, oxidative stress, and fluctuations in temperature.

In response to ER stress, cells activate the Unfolded Protein Response (UPR) to address misfolded proteins

and maintain ER balance. UPR is regulated by three sensors on the ER membrane: IRE1, PERK, and ATF6 (Sano and Reed, 2013).

### *IRE1 Pathway*

IRE1 $\alpha$  and IRE1 $\beta$  are two types of IRE1 in mammals. IRE1 $\alpha$  activates pro-apoptotic signaling during ER stress (Riaz *et al.*, 2020), interacting with Bax and Bak (Hetz *et al.*, 2006), phosphorylating Bax via JNK and p38 MAPK to induce mitochondrial apoptosis (Darling and Cook, 2014; Chistiakov *et al.*, 2015a) and interacting with procaspase-12 to promote apoptosis (Junjappa *et al.*, 2018). Additionally, IRE1 $\alpha$  inhibits the adaptive response and triggers apoptosis through RIDD. It degrades microRNAs suppressing caspase-2 mRNA translation, increasing caspase-2 expression (Lopez-Cruzan *et al.*, 2016; Brown-Suedel and Bouchier-Hayes, 2020).

### *PERK Pathway*

During prolonged ER stress, activated PERK phosphorylates and deactivates eIF2 $\alpha$ . This promotes ATF4 translation, inducing CHOP expression (Rozpedek *et al.*, 2016; Rajesh *et al.*, 2015). CHOP upregulates Bax and Bak and downregulates anti-apoptotic proteins, leading to apoptosis via the intrinsic apoptotic pathway (Redza-Dutordoir and Averill-Bates, 2016). CHOP also induces DR5-mediated apoptosis and ERO1 $\alpha$  expression, generating ROS (Hu *et al.*, 2019). CHOP triggers ER calcium release, inducing Fas receptor expression through CaMKII and JNK activation, promoting mitochondrial apoptosis (Galluzzi *et al.*, 2018).

### *ATF6 Pathway*

In response to acute and prolonged stress, ATF6 translocates from the ER to the Golgi apparatus. There, it undergoes cleavage by S1P/2P proteases, yielding cytosolic fragments. This process ultimately leads to the elevation of CHOP levels, which promotes cellular demise (Hillary and FitzGerald, 2018; Sharma *et al.*, 2019).

## **Apoptosis in Atherosclerosis**

Apoptosis plays an important role in the development of atherosclerosis (Guevara *et al.*, 2001). Various factors like oxidative stress, hypoxia, interferon- $\gamma$ , and cholesterol overload induce apoptosis in atherosclerotic plaques, affecting cell types such as endothelial cells, SMCs, T-lymphocytes, and macrophages. Endothelial cell death can lead to plaque erosion and thrombosis (Stark and Massberg, 2021; Soldatov *et al.*, 2018a-b). In SMCs, apoptosis may destabilize the fibrous cap, causing rupture. Macrophages, comprising over 40% of deceased cells in plaques, play a significant role. Studies on macrophage apoptosis regulation in atherosclerosis yield conflicting findings. Some suggest it hampers plaque

growth, while others propose it contributes to necrotic core formation and atherosclerosis.

C/EBP homologous protein knockout (–/–) mice show reduced macrophage apoptosis under cholesterol-induced stress, leading to less necrotic core formation and lower lesion development in ApoE–/– and LDL receptor–/– backgrounds (Zhou *et al.*, 2015; Sobenin *et al.*, 2014a). Conversely, ApoE–/– mice with heterozygosity for a cholesterol trafficking protein have decreased macrophage apoptosis, less necrotic tissue, and lower atherosclerosis (Zhou *et al.*, 2015; Sobenin *et al.*, 2014b). This highlights the varying effects of macrophage apoptosis at different plaque stages (Gauthier *et al.*, 1999; Babaev *et al.*, 1992; Poon *et al.*, 2014). Apoptotic intimal cells in atherosclerotic plaques serve as a source of tissue factor, promoting coagulation cascade activation. Unstable plaques, particularly in macrophage-rich areas near the necrotic core, exhibit higher tissue factor levels, correlating with increased thrombogenicity (Linton *et al.*, 2016). Additionally, plaques in diabetic patients contain abundant apoptotic debris (Zifkos *et al.*, 2021; Van Vré *et al.*, 2012). Macrophage apoptosis disrupts cellular clearance and exacerbates inflammation during plaque development, while SMC apoptosis compromises plaque integrity, potentially leading to rupture. The role of endothelial cell apoptosis in atherogenesis remains unclear (Rayner, 2017).

## **Apoptosis of VSMCs**

Vascular Smooth Muscle Cells (VSMCs) are integral to the medial layer of mature blood vessels, exhibiting contractile and synthetic/proliferative phenotypes (Bacakova *et al.*, 2018).

In normal conditions, VSMCs regulate vessel elasticity and tone with their contractile phenotype (Bacakova *et al.*, 2018). In disease states, they shift to a synthetic phenotype, acquiring proliferative and migratory capabilities. This transition enables them to move to the intima, proliferate, and produce extracellular matrix, aiding in fibrous cap formation within atherosclerotic plaques (Sorokin *et al.*, 2020). Studies suggest that VSMC apoptosis may play a role in atherosclerosis development, particularly in hypothyroidism (Wang *et al.*, 2014). Furthermore, VSMC apoptosis correlates with fibrous cap thinning and plaque rupture in advanced atherosclerosis, contributing to plaque calcification, medial expansion, degeneration, inflammation, and stenosis (Harman and Jørgensen, 2019). Delayed clearance of apoptotic VSMCs results in secondary necrosis and Interleukin-1 (IL-1) secretion (Beck-Joseph and Lehoux, 2021), stimulating adjacent VSMCs to produce proinflammatory cytokines, intensifying inflammation and fostering atherosclerosis (Beck-Joseph and Lehoux, 2021).

### *Causes of VSMC Apoptosis in Atherosclerosis*

Inflammatory cytokines, oxidized LDL, high NO levels, and mechanical damage induce VSMC apoptosis. Proinflammatory cytokines like Tumor Necrosis Factor (TNF $\alpha$ ) from plaque macrophages and Interferon (IFN)- $\gamma$  from T cells sensitize VSMCs to apoptosis via the Fas death receptor (CD95), facilitating Fas transport to the cell surface.

The Fas receptor/Fas Ligand pathway contributes to oxLDL-induced VSMC apoptosis in plaques (Grootaert *et al.*, 2018; Puchenkova *et al.*, 2020). Elevated p53 levels induce apoptosis in human plaque VSMCs under low serum conditions but not in normal medial VSMCs (Mercer *et al.*, 2005). Activated p53 increases sensitivity to Fas-mediated apoptosis by upregulating surface Fas expression (Mercer *et al.*, 2005). Additionally, VSMCs are more susceptible to p53-mediated apoptosis with increased proliferation (Cao *et al.*, 2017). Plaque VSMCs exhibit high apoptosis rates alongside low proliferation due to hypophosphorylated retinoblastoma protein predominance, promoting cellular senescence (Tucka *et al.*, 2014).

Genetic profiling of human atherosclerotic plaques has revealed high expression of Death-Associated Protein (DAP) kinase in foam cells originating from VSMCs. The role of DAP kinases in atherosclerosis remains uncertain. VSMCs in human fatty streaks show elevated expression of the pro-apoptotic Bax gene, heightening their susceptibility to apoptosis via the mitochondrial pathway (Sobenin *et al.*, 2014b; Chistiakov *et al.*, 2014).

### *Consequences of VSMC Apoptosis in Atherosclerosis*

VSMC apoptosis in advanced plaques heightens plaque vulnerability, stenosis, and medial degeneration. Additionally, it fosters platelet thrombogenicity through the exposure of phosphatidylserine on apoptotic cell surfaces, which can trigger thrombin formation and activate the coagulation cascade (Osonoi *et al.*, 2018). Apoptotic VSMC remnants within plaques act as matrix carriers and potential sites for calcification, contributing to plaque microcalcification. These microcalcifications correlate with increased plaque progression and may raise the risk of plaque rupture by inducing biomechanical stress on the fibrous cap (Shioi and Ikari, 2018).

While human VSMCs possess strong phagocytic abilities for apoptotic VSMCs, hyperlipidemia reduces their clearance efficiency. Insufficient removal of apoptotic VSMCs leads to secondary necrosis and subsequent interleukin-1-driven inflammation, worsening plaque inflammation.

### *Pharmacological Modulation of Apoptosis in VSMCs*

Given the significance of caspases in apoptosis, efforts have focused on inhibiting these proteases to mitigate apoptotic cell death and stabilize atherosclerotic plaques. Application of the broad caspase inhibitor zVAD-fmk

topically reduces VSMC apoptosis and neointimal hyperplasia. However, VSMCs lacking caspase-3 exhibit heightened vulnerability to necrosis. Notably, caspase-3 deletion in mice results in primary necrosis and plaque enlargement. Hence, suppressing apoptosis appears counterproductive in atherosclerosis mitigation (Grootaert *et al.*, 2016; Myasoedova *et al.*, 2016).

### **Apoptosis of Macrophages**

Researchers posit that macrophage apoptosis is prevalent throughout atherosclerosis and exhibits varied effects based on lesion progression. In the initial stages, macrophage apoptosis demonstrates an anti-atherosclerotic impact. Studies show that Bax deficiency reduces macrophage apoptosis, promoting early atherosclerotic lesions in LDL Receptor-Null (LDLR $^{-/-}$ ) mice. Similarly, the absence of AIM/Spa/Ap16, an apoptosis-suppressing factor, increases macrophage survival, impeding lesion development in LDLR $^{-/-}$  mice (Bian *et al.*, 2020; Chistiakov *et al.*, 2012; Linton *et al.*, 2019b).

Additionally, IKK $\alpha$  loss in macrophages inhibits Akt phosphorylation, boosting macrophage apoptosis and reducing early atherosclerosis in LDLR $^{-/-}$  mice (Babaev *et al.*, 2016). Nevertheless, with the atherosclerosis development, macrophage apoptosis is the main factor that leads to the formation of a necrotic nucleus of an atherosclerotic plaque. Since the body's ability to purify apoptotic cells decreases, apoptotic macrophages contribute to the storage of debris and secondary necrosis (Seimon and Tabas, 2009). The necrotic core releases matrix metalloproteinase, causing extracellular matrix breakdown, VSMC apoptosis, and fibrous cap thinning, increasing plaque instability. Loss of PDZK1 in macrophages induces apoptosis, impeding apoptotic cell clearance and fostering necrotic core formation. In advanced atherosclerosis, ER stress prompts macrophage apoptosis via the CHOP-Bax pathway, leading to plaque rupture (Yu *et al.*, 2018; Tsukano *et al.*, 2010).

### **Endothelial Cell Death in Atherosclerosis**

Endothelial cells lining blood vessels play a crucial role in atherosclerosis initiation and progression by regulating molecular and cellular passage between circulation and tissues. Disruption of endothelial barrier function due to apoptosis triggers leukocyte infiltration and LDL accumulation, promoting atherosclerosis (Sandoo *et al.*, 2010; Sun *et al.*, 2020; Summerhill *et al.*, 2019). Endothelial cell apoptosis elevates procoagulant properties, potentially leading to vessel blockage and embolism, causing ischemic events (Wang *et al.*, 2022). Statin therapy, known for its cardiovascular benefits, preserves endothelial cell viability by inhibiting isoprenoid synthesis and modulating various cellular processes, including apoptosis (Mansouri *et al.*, 2022;

Ward *et al.*, 2019). Studies indicate statins prevent endothelial cell apoptosis by altering BCL-2 and BAX expression, reducing oxidative stress, and suppressing pro-apoptotic signaling (Wang *et al.*, 2020; Wood *et al.*, 2013; Li *et al.*, 2015; Bao *et al.*, 2010). Understanding endothelial cell death mechanisms in atherosclerosis is vital, considering their multifaceted contribution to disease development.

#### *Induction of Endothelial Cell Apoptosis by LDL*

Atherosclerosis primarily stems from elevated levels of LDL in plasma, signifying heightened coronary risk. Various modifications render LDL atherogenic, facilitating its uptake by macrophage scavenger receptors and fostering macrophage foam cell formation (Li *et al.*, 2021). Notably, oxLDL induces endothelial cell apoptosis either through Fas-ligand-dependent pathways or ROS generation, exacerbating endothelial damage and promoting atherosclerotic complications (Salvayre *et al.*, 2002).

#### *Induction of Endothelial Cell Apoptosis by Elevated Blood Glucose*

Hyperglycemia in diabetes induces endothelial cell apoptosis (Giri *et al.*, 2018). High glucose levels trigger apoptosis in Human Umbilical Vein Endothelial Cells (HUVECs) via PI3K/AKT signaling and ROS overproduction (Zhang *et al.*, 2021; Yuan *et al.*, 2019). Pharmacological intervention for diabetes, like metformin, can mitigate endothelial cell death induced by hyperglycemia (Ganesan *et al.*, 2023; Detaille *et al.*, 2005).

#### *Induction of Endothelial Cell Apoptosis by Decreased Nitric Oxide and Oxidative Stress*

The endothelium plays a vital role in regulating vascular tone through the synthesis and release of Nitric Oxide (NO) (Förstermann and Sessa, 2012). NO, produced by endothelial NO Synthase (eNOS) in response to shear stress induced by blood flow, facilitates vasodilation, inhibits platelet aggregation, and suppresses inflammation (Förstermann and Sessa, 2012). Moreover, NO helps maintain endothelial cell viability by inhibiting apoptosis through various mechanisms (Francis *et al.*, 2010). Reduction in NO levels, often due to decreased eNOS activity or increased NO inactivation by ROS, leads to endothelial dysfunction (Widlansky and Gutterman, 2011). ROS, generated by various cells involved in atherosclerosis, contributes to endothelial dysfunction and can induce endothelial cell apoptosis (Widlansky and Gutterman, 2011). Pro-atherosclerotic factors such as ox-LDL, high blood glucose, and inflammatory mediators like TNF $\alpha$  further promote ROS production by endothelial cells, potentially initiating atherogenesis (Yuan *et al.*, 2019).

#### *Induction of Endothelial Cell Apoptosis by Low Shear Stress*

There is a significant relationship between the shear stress created by blood flow and endothelial function.

In regions of High Shear Stress (HSS), endothelial cells maintain vascular homeostasis (Zaragoza *et al.*, 2012). However, turbulent flow in areas of arterial branching leads to Low Shear Stress (LSS), causing endothelial dysfunction and apoptosis (Marchio *et al.*, 2019). HSS protects endothelial cells from apoptosis through various mechanisms, including reducing Fas receptor regulation and activating pro-survival signaling pathways (Marchio *et al.*, 2019). Conversely, LSS induces endothelial cell apoptosis by promoting mitochondrial dysfunction and increasing ROS levels (Redza-Dutordoir and Averill-Bates, 2016). The development of atherosclerotic plaques predominantly occurs in regions exposed to LSS, suggesting that endothelial cell apoptosis due to LSS may initiate atherosclerosis (Wu *et al.*, 2017). LSS also contributes to plaque rupture and thrombosis, particularly in downstream areas (Otsuka *et al.*, 2016). Endothelial cell apoptosis downstream from atherosclerotic plaques exposes necrotic remnants, triggering platelet activation and blood clot formation, leading to cardiovascular events (Khandkar *et al.*, 2021).

#### **Conclusion**

Atherosclerosis, a complex inflammatory process characterized by increased apoptosis and inadequate removal of dead cells, necessitates a comprehensive approach for effective treatment. Unfortunately, current clinical approaches often overlook the crucial role of inflammation and cell death in atherosclerotic lesions.

This review focuses on apoptosis, the programmed cell death, that occurs in various cell types within the plaque. It explores the general mechanisms of apoptosis and consolidates our understanding of its impact on plaque development and regression.

Early lesions experience apoptosis, resulting in a reduction in plaque size. Yet, in advanced stages, apoptosis results in necrotic core formation, heightening plaque vulnerability. Moreover, macrophage-mediated clearance of apoptotic cells contributes to plaque regression by initiating anti-inflammatory signaling and enhancing cholesterol efflux. Hence, enhancing the process of clearing apoptotic cells, called efferocytosis, holds tremendous therapeutic potential (May and Harrison, 2013; Moser and Chun, 2016).

Additionally, targeting Reactive Oxygen Species (ROS) through antioxidant therapy emerges as another promising approach. ROS are linked to both inflammatory signaling within atherosclerotic plaques and Endoplasmic Reticulum (ER) stress felt by macrophages, ECs, and

VSMCs. Therefore, anti-ROS agents like vitamins C and E could alleviate plaque progression, inflammation, and cell death. However, the conflicting results from studies in humans underscore the need for further research to standardize dosage conditions, assess different forms of vitamins, and consider variations within the test groups.

Moreover, understanding the intricate pathways governing inflammation, cell death, and lipid metabolism can reveal new therapeutic targets. These pathways include cholesterol metabolism, cytokine production, ER stress, autophagy (the recycling of damaged organelles and lipids), and the modulation of "don't eat me" and "eat me" signals and their respective receptors. Exploring these pathways can lead to the identification of molecules for developing innovative and effective treatments for atherosclerosis.

By unraveling the underlying mechanisms of cell death, inflammation, and apoptotic cell clearance within atherosclerotic plaques, we can pave the way for novel therapeutic strategies to combat cardiovascular disease.

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## Author's Contributions

**Anastasia Vladimirovna Poznyak:** Drafted Written.

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## Ethics

This article is original and contains unpublished material. The corresponding author confirms that all of the other authors have read and approved the manuscript and no ethical issues involved.

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