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REVIEW

Understanding Endoplasmic Reticulum Stress as a Central Driver of Atherosclerosis

Alessio L. Ravani[1], **Michael I. Bukrinsky**[2] **and Anastasia V. Poznyak**[3,*]

[1]Unit for Study of Aortic, Valvular and Coronary Pathologies, Centro Cardiologico Monzino IRCCS, via Carlo Parea 4, Milan, 20138, Italy
[2]School of Medicine and Health Sciences, The George Washington University, Washington, DC 20037, USA
[3]R&D Lab, Institute for Atherosclerosis Research, Osennyaya Street 4-1-207, Moscow, 121609, Russia

*Corresponding Author: Anastasia V. Poznyak. Email: tehhy_85@mail.ru

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ABSTRACT: Atherosclerosis (AS) remains a major contributor to cardiovascular disease (CVD) mortality worldwide. Its development involves dysregulated lipid handling, persistent vascular inflammation, and endothelial cell (EC) dysfunction, influenced by genetic, environmental, and lifestyle factors. Increasing evidence highlights a pivotal role of endoplasmic reticulum (ER) stress as a molecular link between lipid dysregulation and inflammatory signaling in AS pathogenesis. ER stress is triggered by modified LDL, oxidized lipids, hyperhomocysteinemia, oxidative stress (OS), and disrupted calcium (Ca^{2+}) homeostasis, leading to activation of the unfolded protein response (UPR). Core UPR mediators—inositol-requiring enzyme 1 (IRE1), protein kinase RNA-like ER kinase (PERK), and activating transcription factor 6 (ATF6)—initially act to restore ER homeostasis but, when persistently activated, may drive pro-inflammatory cytokine production, apoptosis, and plaque destabilization. The aim of this review is to critically synthesize primary research evidence on ER stress as a mediator of lipid-driven inflammation in ECs, macrophages, and vascular smooth muscle cells (VSMCs), emphasizing disease-stage–specific effects. Current debates include whether macrophage ER stress promotes necrotic core expansion vs. apoptosis-mediated clearance, and whether ER stress in ECs is initially protective or primarily pathogenic. Emerging therapeutic strategies targeting ER stress are summarized, including chemical chaperones, AMPK activators, and natural compounds. We highlight the importance of lipid- and inflammation-specific ER stress modulation, noting limitations such as off-target effects and poor bioavailability that hinder translation. Our goal is to achieve a deeper understanding of the lipid–ER stress–inflammation axis to facilitate the design of therapies that may slow AS progression.

KEYWORDS: Atherosclerosis; cardiovascular disease; risk factors; lipoprotein; low-density lipoproteins (LDL); endoplasmic reticulum

1 Introduction

Atherosclerosis (AS) is a major problem in modern medicine. As the leading cause of cardiovascular disease (CVD) progression and related mortality, its prevention and treatment remain a global priority. AS progression is an intricate process influenced by risk factors such as abnormal lipid metabolism, genetic predisposition, diet, smoking, and physical inactivity [1]. Lesions arise from lipid deposition, thickening of the vessel walls, and persistent vascular inflammation. Impaired endothelial function and increased permeability to lipids and proteins further accelerate plaque progression [2–4].

Low-density lipoproteins (LDL) are the major source of cholesterol deposition. Modified LDL particles—including oxidized, desialylated, and glycated forms—play a particularly pathogenic role by stimulating inflammatory responses. Elevated levels of such modified LDL in the bloodstream constitute a major risk factor for AS. Lesion development is closely linked to inflammatory processes and the recruitment of immune cells (ICs) [5,6]. Resident vascular cells (e.g., vascular smooth muscle cells (VSMCs)) and infiltrating macrophages also contribute to the pathogenesis.

Trials in young subjects have shown that AS development can begin early in life and remain clinically silent for decades. With ageing, atheromatous lesions may evolve into vulnerable plaques [7–9]. Such plaques can rupture and trigger thrombosis, leading to acute cardiovascular events. Therefore, anti-AS therapies must focus not only on late-stage interventions but also on early diagnosis and prevention, which in turn requires elucidation of the cellular and molecular mechanisms driving AS [10,11].

Emerging evidence indicates a major role of endoplasmic reticulum (ER) stress in all phases of AS. The ER is a large membranous organelle responsible for protein folding and maturation. It is also central to intracellular signaling, serving as the primary Ca^{2+} reservoir and maintaining Ca^{2+} homeostasis [12–14]. Disruption of ER function—for example, by excess lipid accumulation, oxidative stress, Ca^{2+} dysregulation, defective protein folding diseases (DPFDs), or increased protein synthesis—can lead to ER stress and activation of the unfolded protein response (UPR) [15,16].

Importantly, whether ER stress acts as an adaptive response that restores vascular homeostasis or as a maladaptive process that accelerates AS progression remains controversial. This duality underpins both the scientific interest and therapeutic challenges of the field, forming the basis of this review. Therefore, the aim of the present study is to critically evaluate the context-dependent roles of ER stress in atherosclerosis across different cell types and disease stages, and to highlight unresolved controversies with implications for targeted therapeutic strategies.

2 UPR

Proteins that fail to fold correctly in the ER are typically degraded through endoplasmic-reticulum-associated protein degradation (ERAD) in the cytosol. Because protein quality control in the ER is tightly regulated, accumulation of misfolded proteins activates theUPR [17,18].

Three canonical UPR sensors—inositol-requiring enzyme 1 (IRE1), protein kinase RNA-like ER kinase (PERK), and activating transcription factor 6 (ATF6)—monitor ER protein-folding status. Their luminal domains normally bind glucose-regulated protein 78 (GRP78/BiP), which keeps them inactive. During ER stress, GRP78 dissociates, thereby activating these sensors and initiating signaling cascades [19,20]. An overview of ER stress and the canonical UPR pathways is presented in Fig. 1.

The UPR employs adaptive mechanisms such as upregulating chaperones to enhance folding, attenuating translation to reduce ER load, and expanding ER biogenesis [21–23]. If stress remains unresolved, however, the UPR shifts from adaptive to pro-apoptotic signaling, contributing to cell loss and tissue damage [24–27].

2.1 IRE1

IRE1 is the most evolutionarily conserved ER stress sensor. Upon stress, its dissociation from GRP78 and subsequent autophosphorylation activate endoribonuclease activity, which splices X-box binding protein 1 (XBP1) mRNA, producing the active transcription factor XBP1s [28–32]. XBP1s upregulates molecular chaperones and ERAD components, facilitating recovery. Additionally, IRE1-mediated mRNA degradation reduces ER protein load [33,34].

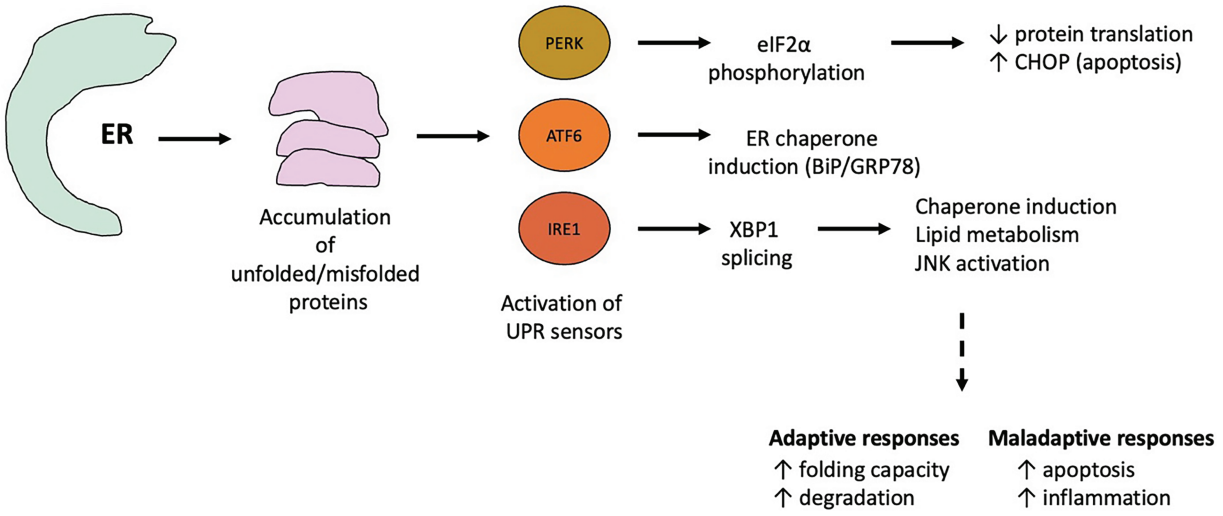

Figure 1: Overview of endoplasmic reticulum (ER) stress and the canonical unfolded protein response (UPR) pathways relevant to atherosclerosis. Under physiological conditions, the ER maintains protein folding, lipid synthesis, and Ca^{2+} homeostasis. Accumulation of misfolded or unfolded proteins—triggered by oxidative stress, lipid overload, inflammation, or Ca^{2+} dysregulation—activates ER stress and induces the UPR. The three principal UPR sensors—inositol-requiring enzyme 1 (IRE1), protein kinase RNA-like ER kinase (PERK), and activating transcription factor 6 (ATF6)—remain inactive through binding to the ER chaperone BiP/GRP78. Under stress, BiP dissociates, leading to sensor activation. eIF2*α*: Eukaryotic translation initiation factor 2*α*; XBP1: X-box binding protein 1; BiP: Binding Immunoglobulin Protein; CHOP: C/EBP Homologous Protein; GRP78: of glucose-regulated protein 78; JNK: c-Jun N-terminal kinase

However, prolonged IRE1 activation recruits TNF Receptor-associated Factor 2 (TRAF2) and caspase-12, linking ER stress to apoptosis and inflammation through Mitogen-Activated Protein Kinase (MAPK) and Nuclear Factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling [35–39]. This dual role is particularly relevant in atherosclerosis, where IRE1 may initially enhance survival but later promote chronic inflammation.

2.2 PERK

PERK, a serine/threonine kinase, is activated through a mechanism similar to IRE1 [40–42]. Once active, PERK phosphorylates eukaryotic initiation factor 2α (eIF2α), suppressing general protein synthesis while selectively allowing translation of activating transcription factor 4 (ATF4) [43,44]. ATF4 coordinates stress adaptation but also induces growth arrest and DNA damage-inducible protein (GADD)34, which restores translation via eIF2α dephosphorylation [45,46].

Critically, ATF4 also induces GADD153/C/EBP Homologous Protein (CHOP), a pro-apoptotic transcription factor that upregulates Endoplasmic Reticulum Oxidoreductin 1 Alpha (ERO1α), increases reactive oxygen species (ROS), promotes Ca^{2+} release from the ER, and suppresses anti-apoptotic proteins such as B-cell lymphoma-2 (Bcl-2) [47–50]. This signaling cascade links prolonged PERK activation to oxidative stress, mitochondrial dysfunction, and apoptosis—mechanisms strongly implicated in plaque instability [51–54].

2.3 ATF-6

ATF6 is a transmembrane ER protein that, under stress, translocates to the Golgi where it is cleaved by site-1 and site-2 proteases (S1P/S2P). The cytosolic fragment then acts as a transcription factor, upregulating

GRP78, XBP1, and ERAD components [55,56]. ATF6 also promotes Derlin-3 expression, enhancing ERAD efficiency [57–59].

Unlike IRE1 and PERK, ATF6 signaling is primarily adaptive. However, its activity may indirectly contribute to apoptosis by enhancing protein degradation and metabolic demand. The relative importance of ATF6 in vascular pathology remains debated, as most studies emphasize PERK- and IRE1-driven pathways.

Together, IRE1, PERK, and ATF6 illustrate the double-edged nature of the UPR: initially protective but ultimately pathogenic when stress is sustained. In atherosclerosis, these pathways are not equally implicated—PERK/CHOP-driven apoptosis and IRE1-mediated inflammation have been most strongly linked to plaque progression, whereas ATF6 may act more as a compensatory regulator. Future research should clarify whether selectively targeting one branch of the UPR can provide therapeutic benefit without disrupting adaptive responses.

A conceptual integration of UPR branches is necessary: IRE1–TRAF2–NF-κB links primarily to inflammation, PERK–eIF2α–ATF4–CHOP drives apoptosis, and ATF6 enhances adaptive folding but indirectly increases metabolic demand. In atherosclerosis, these signals converge on macrophage apoptosis, VSMC cap thinning, and endothelial dysfunction, collectively destabilizing plaques.

3 Endoplasmic Reticulum Stress in Endothelial Cells (ECs)

The hypothesis of vascular endothelial cell (VEC) damage response is an important pathophysiological model of AS. Impaired function of ECs facilitates AS progression. Atheromatous lesions mostly appear in sites of disturbed blood flow, e.g., where vessels bend or fork. Endothelial cells are permanently exposed to hemodynamic forces and are therefore especially vulnerable in such sites [60,61].

3.1 Shear Stress and ER Stress in ECs

In non-atherosclerotic pigs, ER stress biomarkers—IRE1, XBP1, and ATF6—undergo activation in ECs located in AS-prone regions of the aorta. Recent studies demonstrated that turbulent blood flow with lower shear stress (SS), a key factor in endothelial dysfunction, stimulates ER stress in ECs, thereby contributing to AS development [62].

In vitro studies on cultured ECs showed that SS enhanced GRP78 expression via a p38 mitogen-activated protein kinase (p38 MAPK)- and α2β1-integrin-dependent process prior to lesion development. These findings suggest a possible anti-atherogenic response to ER stress. However, other reports emphasize that SS can also induce a pro-inflammatory endothelial phenotype through ER stress activation [63,64]. This contradiction highlights that ER stress responses may be context-dependent and not uniformly detrimental.

Bailey et al. reported that SS controls the inflammatory response of aortic ECs via activation of XBP1. During this process, a temporary SS-driven increase in p38 phosphorylation promoted XBP1 nuclear translocation and upregulated vascular cell adhesion molecule-1 (VCAM1) expression [65,66]. Thus, SS increases EC sensitivity to ER stress induced by cytokines, thereby regulating pro-inflammatory processes that accelerate AS. Additionally, SS promotes apoptosis in aortic ECs through ER stress-mediated interleukin-1 receptor-associated kinase 2 (IRAK2)/GADD153 signaling [67]. Interestingly, ursodeoxycholic acid (UDCA) has been shown to mitigate these effects: in a murine model of turbulent-flow-induced AS, UDCA reduced ER stress markers (XBP1 and GADD153) in ECs and suppressed inflammation and apoptosis, ultimately inhibiting AS lesion development [68].

3.2 Homocysteine-Induced ER Stress

Homocysteine (Hcy) is another potent inducer of ER stress in ECs. Experimental data have shown that ER stress caused by Hcy promotes gene expression changes and cell death in human umbilical vein endothelial cells (HUVECs) [69,70]. In hyperhomocysteinemia, ER stress contributes to vascular inflammation and endothelial dysfunction. Mechanistically, a reactive thiol group in Hcy can alter protein function by exchanging disulfide bonds with cysteine residues in key proteins [71–73]. These alterations affect not only ER-resident proteins but also membrane-bound and secreted proteins. Consistent with this, reticulon protein (RTP) expression was increased in HUVECs under ER stress conditions [74,75]. Importantly, Hcy-induced ER stress exerts atherogenic effects not only in ECs but also in other vascular cell types [76].

3.3 LDL and ER Stress

In AS, **LDL** particles modified by oxidative or enzymatic processes impair ER Ca^{2+} metabolism, stimulating oxidative stress (OS) and endothelial unfolded protein response, while suppressing sarco/endoplasmic reticulum Ca^{2+}-ATPase (SERCA) activity. Studies have demonstrated that phospholipolyzed LDL triggers inflammatory responses in ECs via ER stress [77–79]. Moreover, oxidized LDL (oxLDL) promotes inflammatory changes in ECs, activating inflammasome signaling through apoptosis signal-regulating kinase 1 (ASK1) and NOD-like receptor family pyrin domain containing 3 (NLRP3) in an ER stress–dependent manner. OxLDL also induces EC apoptosis via the PERK/ eIF2α/GADD153 pathway [80,81]. Notably, simvastatin suppresses oxLDL-induced ER stress and apoptosis, suggesting therapeutic potential. Collectively, altered LDL is a major driver of EC dysfunction, inflammation, and apoptosis through ER stress mechanisms [82–84].

Although ER stress is fundamentally a protective response that enables cells to cope with adverse stimuli, failure of the UPR to restore ER homeostasis results in prolonged stress, activation of apoptotic pathways, and progression of AS and cardiovascular disease [85–87]. Prolonged ER stress induces mitochondrial (Mt)-mediated apoptosis in ECs. Studies have shown that GADD153 disrupts the balance of the Bcl-2 family, promoting pro-apoptotic protein activation at the mitochondrial membrane. This leads to cytochrome c (Cyt C) release and subsequent caspase-dependent apoptosis [88,89].

3.4 Calcium Dysregulation and Mitochondrial Dysfunction

Furthermore, disturbed Ca^{2+} homeostasis exacerbates mitochondrial dysfunction and increases production of ROS and nicotinamide adenine dinucleotide phosphate (NADPH), both of which impair endothelial nitric oxide synthase (eNOS) activity and reduce nitric oxide (NO) bioavailability, thereby aggravating OS and endothelial dysfunction [90–92]. Cytoplasmic Ca^{2+} overload during ER stress also activates the proenzyme procaspase-12, which is cleaved into active caspase-12 in the ER membrane, subsequently activating caspase-3 and caspase-9 via calpain-dependent mechanisms [93,94]. In apolipoprotein E knockout ($ApoE^{-/-}$) mice with AS, endothelial anti-apoptotic Bcl-2 expression was markedly reduced, while caspase-3 was elevated. Similarly, in HUVECs, silica nanoparticles (SiNPs) enhanced ER stress by activating the IRE1/c-Jun N-terminal kinase (JNK) pathway, increasing GADD153 and caspase-12 expression, and shifting the Bcl-2/Bcl-2 Associated X-protein (BAX) ratio toward apoptosis, with elevated Cyt C, caspase-3, and caspase-9 levels [95–97].

4 Macrophage Endoplasmic Reticulum Stress and AS

Macrophages are essential for pathogen defense and tissue homeostasis. However, chronic macrophage activation can contribute to tissue injury, particularly in AS and metabolic disorders such as diabetes mellitus (DM) [98,99]. Understanding the pathways leading to macrophage activation may reveal novel therapeutic opportunities.

Beyond phagocytosis of cellular debris, macrophages handle toxic lipid cargo, including altered LDL and saturated fatty acids (FAs). Macrophages are especially vulnerable to lipotoxicity in hyperlipidemia or DM, and exposure to these toxic environments can induce ER stress and apoptosis [100]. The fate of lipids, particularly cholesterol, determines whether macrophage activity is protective or deleterious: efficient cholesterol efflux promotes plaque stability, whereas lipid accumulation triggers cellular stress and pro-inflammatory signaling [101–103]. In adiposity, uptake of FAs and necrotic lipocytes initially supports clearance but ultimately impairs macrophage function, amplifying stress and cell death [104–106].

In advanced AS, macrophage apoptosis contributes to plaque instability and rupture, raising questions about whether macrophage death is protective (through removal of dysfunctional, lipid-laden cells and reduced inflammatory signaling) or harmful (due to impaired clearance of accumulated cholesterol and necrotic core expansion). Determining the stage-specific roles of macrophages is therefore critical for therapeutic targeting [107–109].

4.1 Lipotoxicity and ER Stress Pathways

The mechanisms by which toxic lipids induce macrophage apoptosis remain incompletely understood. Emerging evidence suggests that certain ER stress pathways are selectively engaged by lipids, rather than representing a nonspecific cellular decline [110,111]. Genes involved in ER stress and associated signaling appear to link metabolic dysfunction, inflammation, and apoptotic processes, highlighting ER stress as a potential target in obesity and type 2 diabetes mellitus (T2DM) [112–114].

Two critical observations underscore the importance of ER stress in macrophages: (1) ER stress pathways are activated in lipid-loaded macrophages in human and mouse AS plaques; (2) cholesterol loading *in vitro* induces ER stress and subsequent apoptosis [115–117].

4.2 Stage-Specific Roles of Macrophage ER Stress

The contribution of macrophage ER stress to AS is complex and likely stage-dependent. While most studies focus on advanced AS, ER stress-induced macrophage apoptosis may be particularly relevant for plaque rupture and sudden cardiac death (SCD) [118,119]. ER stress is partially linked to insulin resistance via IRE1-mediated JNK activation, which may exacerbate macrophage apoptosis in AS [120,121].

A useful framework is to distinguish upstream ER stress sensing and protein folding capacity from downstream apoptotic signaling, as these processes may exert different effects at various AS stages [122–124]. Some evidence suggests a double-edged effect of macrophage apoptosis: promoting early lesion formation but potentially limiting lesion expansion in advanced AS [125,126].

5 Regulators and Therapeutic Implications

Key signaling modulators—including JNK-2, GADD153, STAT-1, p38 MAPK, and Glycogen Synthase Kinase 3 (GSK3)—can influence AS outcomes following ER stress or macrophage apoptosis, impacting plaque composition and stability [127,128]. Targeting ER folding capacity or upstream stress pathways may therefore represent a therapeutic strategy, particularly when considering systemic metabolic effects, such as hepatic lipid handling [129,130].

5.1 Pharmacological Modulation of ER Stress

Chemical chaperones and ER stress modulators (e.g., phenylbutyric acid, aP2 suppression) have shown promising effects in reducing macrophage ER stress, lipid-induced apoptosis, and atherosclerotic lesion formation in murine models [131–134]. These findings highlight the translational potential of targeting

ER stress in macrophages, while also raising questions about specificity, stage-dependence, and long-term outcomes [135–137].

5.2 Lipid-Specific ER Stress Responses

Emerging data suggest that distinct lipids can selectively modulate ER stress pathways, influencing lipid metabolism, desaturation products, and membrane composition. For example, aP2-deficient macrophages exhibit increased monounsaturated fatty acids (MUFAs), alleviating ER stress and improving cellular resilience to saturated fats [138–140]. These observations suggest that ER stress modulation may extend beyond apoptosis regulation, affecting broader aspects of macrophage lipid handling and metabolic signaling [141–145].

5.3 Research Gaps and Future Directions

Further studies are needed to:

- Identify lipid-specific triggers of ER stress and UPR branches.
- Clarify whether UPR mediators act solely via ER function or through ER-independent pathways.
- Determine how ER stress in macrophages versus endothelial or smooth muscle cells contributes to AS progression.
- Explore systemic metabolic influences, including hepatic ER function, on AS development [146–149].

Overall, macrophage ER stress is a multifaceted contributor to AS, with both protective and detrimental effects depending on context, lipid load, and disease stage. Understanding these complexities may enable precision-targeted therapies to mitigate AS progression and improve cardiovascular outcomes [150,151].

6 Endoplasmic Reticulum Stress in Vascular Smooth Muscle Cells

VSMCs play a pivotal role in maintaining plaque stability, and their apoptosis can compromise the fibrous cap, increasing the risk of rupture. ER stress-mediated apoptosis in VSMCs is less studied than in endothelial cells or macrophages, representing a critical gap in understanding AS progression [152–154].

6.1 ER Stress-Induced Apoptotic Pathways

Multiple ER stressors, including 7-ketocholesterol (7KC), Hcy, glucosamine, and free cholesterol, promote GADD153-dependent apoptosis in VSMCs. This process is associated with increased ROS generation, highlighting the interplay between ER stress and oxidative stress. Notably, antioxidants such as N-acetylcysteine (NAC) can mitigate ROS-mediated apoptosis in cultured VSMCs, suggesting potential therapeutic avenues [155,156].

6.2 Homocysteine and Lipid-Induced ER Stress

Hyperhomocysteinemia (HHcy) is linked to elevated AS risk and appears to trigger ER stress by disrupting Ca^{2+} homeostasis and upregulating Sterol Regulatory Element-binding Protein 2 (SREBP2), which enhances lipid accumulation in VSMCs. Similarly, glucosamine accumulation in diabetic vessel cells stimulates ER stress through increased GRP78 expression, reflecting metabolic vulnerability in DM [157].

6.3 Critical Gaps and Translational Perspectives

Despite evidence of ER stress in VSMCs, mechanistic studies remain limited. Notably, VSMCs contribute critically to plaque stability through collagen and extracellular matrix production. Their apoptosis, often CHOP-dependent, weakens the fibrous cap and predisposes lesions to rupture. In addition to 7-ketocholesterol and homocysteine, mechanical stress and inflammatory cytokines can also trigger ER stress in VSMCs, further linking systemic metabolic and vascular factors. Compared with endothelial cells and

macrophages, VSMC ER stress pathways are underexplored, and it remains unclear whether interventions targeting VSMC ER stress would meaningfully alter AS outcomes *in vivo* [158,159].

Emerging data suggest that stage-specific roles of VSMC ER stress may exist: in early AS, mild ER stress may contribute to adaptive remodeling, whereas in advanced lesions, prolonged stress may promote cap thinning and plaque vulnerability. Targeting these pathways—either via chemical chaperones, antioxidant therapy, or lipid-modulating strategies—represents a promising but largely untested therapeutic frontier.

7 Therapeutic Potential of Endoplasmic Reticulum Stress Modulators in Atherosclerosis

Targeting ER stress and the UPR represents a promising therapeutic strategy in disorders where ER stress contributes to pathophysiology, such as AS. Chemical chaperones such as phenylbutyrate (PBA) and tauroursodeoxycholic acid (TUDCA) facilitate nonselective protein folding and trafficking, thereby reducing misfolded protein accumulation in the ER [160]. PBA, approved for urea cycle disorders, ameliorated hyperglycemia and ER stress in murine DM models, and in apolipoprotein E knockout AS models, reduced ER stress markers (GRP78, Cluster of Differentiation 36 [CD36], IRE1 phosphorylation) in macrophage-rich lesions [161–164]. However, while promising, the translational potential remains uncertain, particularly regarding optimal dosing, off-target effects, and long-term outcomes in humans. Key therapeutic classes, mechanisms of action, and reported outcomes are summarized in Table 1.

Table 1: Therapies targeting endoplasmic reticulum (ER) stress in atherosclerosis

Therapeutic agents	Mechanism of action	Stage of research	Reported outcomes	References
Chemical Chaperones (e.g., 4-phenylbutyrate [PBA], tauroursodeoxycholic acid [TUDCA])	Enhance protein folding capacity in ER, reduce misfolded protein accumulation	Preclinical (murine AS models, cell culture); limited clinical use (UCDs, metabolic diseases)	↓ ER stress, ↓ macrophage apoptosis, ↓ AS lesion formation in animal models; PBA normalized glucose levels in diabetic mice; human data in AS lacking	[121–123]
Proteasome Activators (e.g., coleonol, isoprenaline)	Promote degradation of misfolded proteins, alleviate ER stress	Preclinical (*in vitro*, limited animal data)	↓ ER stress markers, ↓ apoptosis; no clinical trials in AS	[124,125]
AMPK Modulators (e.g., atorvastatin, AICAR, PT-1, A769662)	Restore energy homeostasis, reduce ER stress	Preclinical (murine AS models, cardiomyocytes); extensive clinical use for statins	↓ ER stress, ↑ plaque stability in preclinical studies; atorvastatin effective in clinical CVD prevention but ER-specific effects in humans not confirmed	[126–128]

(Continued)

Table 1 (continued)

Therapeutic agents	Mechanism of action	Stage of research	Reported outcomes	References
Calcium Regulators (e.g., diltiazem, verapamil)	Restore ER Ca^{2+} homeostasis, improve folding capacity	Preclinical (cell/animal studies); clinical use in hypertension/angina	↓ ER stress, improved protein folding *in vitro*; potential benefit in AS suggested but no direct clinical trials	[129,130]
Natural Compounds (e.g., resveratrol, withaferin A, basiliolide A1, agelasine B)	Multiple pathways: antioxidant, Ca^{2+} regulation, suppression of IRE1/PERK signaling	Preclinical (cell culture, animal models)	↓ ER stress, ↓ inflammation, ↓ plaque progression in preclinical models; no human AS trials yet	[131–134]

Note: Abbreviations: PBA—4-phenylbutyrate; TUDCA—tauroursodeoxycholic acid; ER—endoplasmic reticulum; AS—atherosclerosis; UCDs—urea cycle disorders; AMPK—AMP-activated protein kinase; AICAR—5-Aminoimidazole-4-carboxamide ribonucleotide; IRE1—inositol-requiring enzyme 1; PERK—protein kinase RNA (PKR)-like endoplasmic reticulum kinase; CVD—cardiovascular disease.

TUDCA similarly decreased ER stress and attenuated AS lesion development in LDL receptor-deficient mice, and *in vitro* studies confirmed reduced ER stress in macrophages exposed to oxidized LDL [165,166]. Despite encouraging preclinical results, clinical validation is lacking, and the specificity of these agents for different cell types within lesions requires further investigation.

While chemical chaperones such as PBA and TUDCA show strong efficacy in animal models, their pharmacokinetics in humans (rapid clearance, poor oral bioavailability) and off-target actions (hepatic, pancreatic, and neurological effects) raise major translational barriers. For example, PBA requires gram-scale dosing for metabolic disorders, limiting feasibility in CVD patients. Moreover, very few randomized controlled trials (RCTs) have evaluated ER stress modulators in AS, and no ER stress–targeted drug has yet advanced beyond Phase II trials.

7.1 Proteasome and Translational Control

ER stress can also be alleviated by enhancing proteasome function to reduce misfolded protein accumulation. Agents such as coleonol or isoprenaline have shown protective effects by activating proteasomal degradation, while suppression of protein synthesis via eIF2α signaling may reduce ER load [167–169]. Salubrinal, an eIF2α phosphatase inhibitor, protects cardiomyocytes from ER stress-induced apoptosis but paradoxically induces severe ER stress in pancreatic β-cells, highlighting cell-specific responses and the need for precision therapy [170,171].

7.2 Targeting ER Stress Signaling Pathways

Pharmacological modulation of stress-induced signaling represents another therapeutic approach. For instance, TNF-α inhibition, pravastatin therapy, or GADD153 suppression via p38 MAPK or JNK inhibitors can mitigate ER stress-mediated apoptosis [172–174]. Valproate upregulates the ER chaperone BiP and

inhibits GADD153/caspase-12 activation, showing preclinical efficacy in AS models, yet human applicability and safety profiles remain to be determined.

7.3 Redox and AMPK Modulation

Specific inhibitors of ERO1α (EN-460, QM-295) and AMPK activators (AICAR, PT-1, atorvastatin, A769662) have been shown to reduce ER stress and protect cardiomyocytes, while AMPK inhibition exacerbates ER stress and AS [175–177]. However, AMPK agonists are mainly approved for metabolic syndromes, and their effectiveness specifically in vascular lesions requires further clinical evaluation.

7.4 Calcium Homeostasis

Restoration of ER Ca^{2+} homeostasis (via agents such as diltiazem or verapamil) may improve protein folding capacity and mitigate apoptosis, with potential crosstalk to mitochondrial Ca^{2+} regulation. Nevertheless, robust preclinical and clinical studies in AS are still limited, and off-target cardiovascular effects must be carefully assessed [178,179].

7.5 Natural Compounds

Several natural products exhibit ER stress-modulating activity, including proteasome inhibitors (tunicamycin, lactacystin, Brefeldin A [BFA]), Ca^{2+} regulators (basiliolide A1, agelasine B, thapsigargin), and IRE1/PERK pathway modulators (withaferin A, resveratrol) [180]. While these agents demonstrate mechanistic potential, their *in vivo* efficacy, bioavailability, and safety profiles remain largely unexplored, highlighting the need for rigorous translational studies. The cell-specific roles and mechanisms of ER stress in atherosclerosis are summarized in Table 2.

Table 2: Pathophysiological roles of ER stress in atherosclerosis

Cell Type/Target	Mechanism of ER Stress Contribution	Stage of Research	Reported Outcomes	References
Endothelial cells	Disturbed blood flow, oxLDL, and homocysteine induce ER stress → endothelial dysfunction, apoptosis	Preclinical (cell culture, animal models)	↑ VCAM-1 expression, ↑ apoptosis, impaired NO synthesis; UDCA reduced ER stress and lesion size in murine models	[68–72]
Vascular Smooth Muscle Cells (VSMCs)	7-ketocholesterol, homocysteine, glucosamine induce GADD153-mediated apoptosis → destabilized plaques	Preclinical (cell culture, animal models)	↑ ROS, ↑ apoptosis; NAC rescued VSMCs from apoptosis; limited human validation	[7,8,47]

(Continued)

Table 2 (continued)

Cell Type/Target	Mechanism of ER Stress Contribution	Stage of Research	Reported Outcomes	References
Macrophages	Modified LDL triggers ER stress → foam cell formation, apoptosis, inflammasome activation	Preclinical (cell/animal models); indirect clinical biomarker studies	↑ lipid accumulation, ↑ inflammatory cytokines; chemical chaperones reduced apoptosis in ApoE$^{-/-}$ mice; human data mainly observational (oxLDL, CHOP expression in plaques)	[9,36,98]
Calcium homeostasis	Disturbance in ER–mitochondria Ca^{2+} flux exacerbates apoptosis	Preclinical (*in vitro*, animal models)	↑ caspase activation, ↑ mitochondrial dysfunction; Ca^{2+} channel blockers improved ER function; clinical studies lacking	[15,16,58]
Oxidative Stress & ROS Pathways	ROS–ER stress feedback loop amplifies AS progression	Preclinical (*in vitro*, animal models)	↑ ROS and NADPH oxidase activity; antioxidants (e.g., NAC, tempol) reduced ER stress burden	[50,51,90–92]
UPR Sensors (PERK, IRE1, ATF6)	Chronic UPR activation shifts from protective → pro-apoptotic signaling	Preclinical (cell/animal models); indirect evidence in human plaques	↑ CHOP/GADD153 expression in human lesions; inhibitors (SP600125, SB203580) reduced apoptosis *in vitro*; no clinical trials yet	[19,33,48,55]

Note: Abbreviations: LDL—low-density lipoprotein; oxLDL—oxidized low-density lipoprotein; ROS—reactive oxygen species; UPR—unfolded protein response; NADPH—nicotinamide adenine dinucleotide phosphate; NAC—N-acetyl cysteine; VCAM-1—vascular cell adhesion molecule 1; UDCA—ursodeoxycholic acid; ATF6—Activating Transcription Factor 6; VSMCs—vascular smooth muscle cells; GADD153—Growth Arrest and DNA Damage-inducible Protein 153; CHOP—C/EBP homologous protein.

8 Discussion: Interplay of Lipids, ER Stress, and Inflammation in Atherosclerosis

A central theme of atherosclerosis research is the dynamic interplay between lipid metabolism and vascular inflammation. Growing evidence suggests that lipid dysregulation is not only a metabolic disorder but also a key trigger of inflammation, acting through ER stress-dependent mechanisms in various vascular cell types. This relationship is bidirectional: lipid accumulation induces inflammation through activation of ER stress, while inflammatory signaling further exacerbates lipid imbalance, creating a self-perpetuating cycle that accelerates atherogenesis.

Modified LDL particles, particularly oxLDL, electronegative LDL, and enzymatically modified LDL, exert potent proinflammatory effects on endothelial cells (ECs). Upon internalization, modified LDL disrupts calcium homeostasis in the ER and generates reactive oxygen species (ROS), promoting activation of the UPR and downstream proinflammatory pathways such as IRE1–TRAF2–NF-κB and PERK–CHOP. This leads to increased expression of adhesion molecules (VCAM-1, ICAM-1) and cytokine secretion (IL-6, IL-1β, TNF-α), thereby promoting monocyte recruitment and early plaque formation. Thus, lipids act as molecular triggers that convert endothelial cells to an inflammatory phenotype via ER stress signaling.

Macrophages are the primary cells that process lipids in plaques and play a key role in amplifying inflammation. Excess lipids in macrophages cause ER stress through the accumulation of non-esterified cholesterol and saturated fatty acids, activating the IRE1-JNK and PERK-ATF4-CHOP axes. Activation of these pathways stimulates inflammasome signaling, apoptotic cell death, and defective efferocytosis, promoting expansion of the necrotic core in advanced lesions. This demonstrates that lipid-induced ER stress not only triggers innate immune activation but also impairs inflammation resolution, highlighting its role in plaque progression and instability.

In vascular smooth muscle cells (SMCs), modified lipids induce a maladaptive phenotypic switch and apoptosis via ER stress-mediated mechanisms. While SMCs normally stabilize plaques by producing extracellular matrix components, lipid-induced ER stress shifts SMCs toward a synthetic, inflammatory, and ultimately apoptotic profile, compromising the integrity of the fibrous cap. The combined effects on endothelial cells (ECs), macrophages, and SMCs highlight that lipids mediate ER stress as a unified mechanistic pathway linking metabolic stress to chronic inflammation and plaque vulnerability.

Importantly, not all lipids exert the same negative effects. Certain lipid types, including omega-3 polyunsaturated fatty acids and lipid mediators such as resolvins, can attenuate ER stress and promote inflammation resolution. These findings highlight the need to distinguish between lipid subtypes and their context-dependent roles in modulating vascular inflammation. Therapies that selectively target lipid-induced ER stress pathways, rather than globally suppressing the UPR, may provide more effective vascular protection with fewer side effects.

Taken together, these mechanistic concepts provide a more comprehensive understanding of the pathogenesis of atherosclerosis, positioning ER stress as a mechanistic bridge between lipid dysregulation and chronic vascular inflammation. This conceptual framework not only aligns with the theme of this special issue but also identifies critical intervention points for future therapeutic approaches.

9 Conclusion and Future Perspective

Overall, while ER stress-targeted therapies hold promise, most data derive from preclinical models. Cell-specific, stage-specific, and dose-dependent effects remain poorly understood, limiting immediate clinical application. Future research should focus on defining which ER stress pathways are most pathogenic at specific AS stages, evaluating combination therapies, and establishing safety and efficacy in humans.

AS represents a multifaceted pathological condition driven by a complex interplay of metabolic, inflammatory, and cellular processes. Central to the progression of AS is ER stress, which emerges as a pivotal player influencing endothelial dysfunction, smooth muscle cell apoptosis, and macrophage responses. The intricate network of the UPR underscores the importance of cellular homeostasis in mitigating AS progression.

While the UPR can instigate protective mechanisms, its chronic activation often leads to detrimental outcomes, such as pro-inflammatory signaling and cell death, thereby exacerbating AS. Future investigations should clarify the stage-specific and cell-type–specific roles of ER stress in AS, since responses in endothelial

cells, smooth muscle cells, and macrophages appear to differ significantly. Defining these nuances is essential to avoid therapeutic strategies that inadvertently worsen disease progression in particular contexts.

Targeting the pathways associated with ER stress presents a promising therapeutic strategy for managing AS and its associated cardiovascular risks. However, translation into clinical practice remains limited. Biomarkers such as GRP78, CHOP, and spliced XBP1 show potential for monitoring ER stress activity in patients, while imaging modalities assessing plaque vulnerability could further link molecular stress responses with clinical outcomes. Although human trials directly targeting ER stress are scarce, early studies using chemical chaperones or metabolic modulators provide proof-of-concept that these pathways can be manipulated *in vivo*. Greater integration of molecular research with clinical studies will be critical for validating therapeutic targets.

Future studies are vital to unravel the specific molecular mechanisms through which ER stress contributes to AS at various stages and to identify potential pharmacological agents that can effectively restore ER function without provoking adverse effects. Promising areas include the exploration of ER–mitochondria crosstalk, identification of non-invasive ER stress biomarkers, and repurposing of clinically approved drugs with ER-modulating properties. Further, large-scale clinical trials are needed to determine whether ER stress modulators can complement existing lipid-lowering or anti-inflammatory therapies in reducing cardiovascular events.

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Abbreviations

ABs	Antibodies
AICAR	5-Aminoimidazole-4-carboxamide ribonucleotide
AIS	Acute Ischemic Stroke
AMPK	AMP-activated protein kinase
AP-1	Activator Protein-1
aP2	Adipocyte Protein 2 (also known as Fatty Acid Binding Protein 4, FABP4)
AS	Atherosclerosis
ASK	Apoptosis Signal-regulating Kinase
ATF4	Activating Transcription Factor 4
ATF6	Activating Transcription Factor 6
Bcl2	B-cell lymphoma 2
BIM	Bcl2-interacting mediator of cell death
Bnip3	Bcl2/E1B 19 kDa-interacting protein 3
BFA	Brefeldin A
Ca^{2+}	Calcium ion
C/PL ratio	Cholesterol/Phospholipid ratio
CD36	Cluster of Differentiation 36 (scavenger receptor)

CVD	Cardiovascular Disease
Cyt C	Cytochrome c
DM	Diabetes Mellitus
DPFDs	Diseases with Protein Folding Defects
ECs	Endothelial Cells
eIF2α	Eukaryotic Initiation Factor 2 Alpha
ENOX	Endoplasmic Reticulum Oxidoreductin-like protein (if you meant ERO1, see below)
ERO1α	Endoplasmic Reticulum Oxidoreductin 1 Alpha
ER	Endoplasmic Reticulum
FA	Fatty Acid
FLD	Fatty Liver Disease
GADD153	Growth Arrest and DNA Damage-inducible Protein 153 (also known as CHOP)
GSK3	Glycogen Synthase Kinase 3
HHcy	Hyperhomocysteinemia
Hcy	Homocysteine
HUVEC	Human Umbilical Vein Endothelial Cells
ICs	Immune Cells
IKK	IκB kinase
IL	Interleukin
IP3R1	Inositol 1,4,5-triphosphate receptor type 1
IRE1	Inositol-Requiring Enzyme 1
IR	Insulin Resistance
JNK	c-Jun N-terminal Kinase
KO	Knockout
LDL	Low-Density Lipoprotein
Lp	Lipoprotein
LRR	Leucine-Rich Repeat
LXRα	Liver X Receptor Alpha
MAPK	Mitogen-Activated Protein Kinase
Mt	Mitochondria
MUFA	Monounsaturated Fatty Acid
NAC	N-Acetylcysteine
NADPH	Nicotinamide Adenine Dinucleotide Phosphate (reduced form)
NF-κB	Nuclear Factor kappa-light-chain-enhancer of activated B cells
NLRP3	NOD-, LRR- and Pyrin Domain-containing Protein 3 (inflammasome)
NO	Nitric Oxide
NR	Nuclear Receptor
OS	Oxidative Stress
oxLDL	Oxidized Low-Density Lipoprotein
PBA	Phenylbutyric Acid
PERK	Protein kinase RNA-like Endoplasmic Reticulum Kinase
PKA	Protein Kinase A
PL	Phospholipid
PT-1	Phosphotyrosyl phosphatase activator-1
RTP	Response to Protein (context suggests ER stress-responsive protein, please confirm exact gene/protein)
ROS	Reactive Oxygen Species
S1P/S2P	Site-1 Protease / Site-2 Protease
SCD	Sudden Cardiac Death
SERCA	Sarco/Endoplasmic Reticulum Ca^{2+}-ATPase

SiNPs	Silica Nanoparticles
SP600125	JNK-specific inhibitor compound
SREBP2	Sterol Regulatory Element-binding Protein 2
SS	Shear Stress
STAT1	Signal Transducer and Activator of Transcription 1
T2DM	Type 2 Diabetes Mellitus
TNF-α	Tumor Necrosis Factor Alpha
TRAF2	TNF Receptor-associated Factor 2
TUDCA	Tauroursodeoxycholic Acid
UCDs	Urea Cycle Disorders
UDCA	Ursodeoxycholic Acid
UPR	Unfolded Protein Response
VCAM1	Vascular Cell Adhesion Molecule 1
VEC	Vascular Endothelial Cell
VSMCs	Vascular Smooth Muscle Cells
XBP1	X-box Binding Protein 1
7KC	7-Ketocholesterol

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