

Multifaceted role of sortilin in coronary artery disease: Insight with sex-based implication (Review)

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Abstract. Coronary artery disease (CAD) is characterized by the atherosclerotic narrowing of the coronary arteries. Sortilin regulates lipid metabolism, inflammation and vascular function, including hepatic very-low-density lipoprotein secretion and low-density lipoprotein receptor degradation. In vascular tissues, sortilin increases inflammatory cytokine release and macrophage cholesterol accumulation, leading to foam cell formation and plaque progression. It also promotes vascular calcification by increasing pro-calcific vesicle release from vascular smooth muscle cells. In adipose tissue, altered sortilin activity contributes to inflammation and insulin resistance through changes in adipokine secretion and ceramide production. Increased circulating sortilin levels have been reported in conditions, such as polycystic ovary syndrome and preeclampsia, suggesting a role in early cardiovascular risk in women. The present review describes the structure, expression and cellular functions of sortilin, and discusses its roles in lipid metabolism, insulin resistance, glucose metabolism and atherosclerosis. Sortilin may serve as a biomarker and therapeutic target in CAD by regulating lipid metabolism and vascular inflammation.

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1. Introduction

Coronary artery disease (CAD) is the leading cause of mortality among women worldwide and accounts for approximately one-third of female deaths (1,2). CAD is often diagnosed at a later stage in women, as symptoms can differ from typical chest pain. Women may present with fatigue, dyspnoea or back pain. CAD also develops ~7-10 years later in women than in men, partly due to the protective effects of oestrogen before menopause (3,4). Women may experience angina even when coronary angiography reveals no major blockage. Smaller coronary arteries, increased vascular stiffness and reduced coronary blood flow may contribute to these symptoms. Diabetes, obesity, hypertension and dyslipidaemia also increase the risk of developing CAD in women (5). Pregnancy, menopause and other female-specific factors can also lead to an increased risk of developing cardiovascular disorders (6).

Sortilin is a protein involved in lipid metabolism and the movement of substances within cells. It has been studied in metabolic disorders and cardiovascular disease. Higher serum levels of sortilin have been reported in women with polycystic ovary syndrome (PCOS), and may have value as a biomarker and therapeutic target in women with cardiometabolic risk (7). Studies are required to explain the role of sortilin in CAD in women and its use in risk assessment and treatment.

Despite the rising awareness of sex-specific risk factors, the underdiagnosis of CAD in women remains a clinical challenge. In recent years, sortilin, a multifunctional sorting receptor, has emerged as a potential molecular link connecting lipid metabolism, insulin resistance, inflammation and cardiovascular pathology. Alterations in lipid metabolism, mitochondrial function, macrophage inflammatory signaling and vascular smooth-muscle-cell responses are increasingly recognized as interconnected determinants of cardiometabolic disease. Recent studies have further emphasized the importance of genetic and molecular regulators of lipid metabolism and inflammatory pathways in disease susceptibility and biomarker development (7-9). Within this broader context, SORT1 variation and sortilin-dependent pathways may represent a

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key mechanistic interface between metabolic disturbances and atherosclerotic disease. This association may be particularly relevant in women, in whom reproductive and hormonal factors, including polycystic ovary syndrome, pregnancy-related complications and menopause, modify metabolic and vascular risk. Elevated circulating levels of sortilin reported in women with PCOS further supports the possibility that sortilin contributes to female-specific cardiometabolic risk, although the clinical and mechanistic significance of this association remains incompletely established.

2. Structural architecture and intracellular dynamics of sortilin

Sortilin belongs to the VPS10 domain receptor family and is a 100-kDa membrane protein encoded by the *SORT1* gene on chromosome 1p13.3. It helps transport proteins and other molecules through secretory and endocytic pathways. Sortilin is expressed in the brain, liver, adipose tissue, skeletal muscle and immune cells. It was first identified in human brain tissue using affinity chromatography with receptor-associated protein, which led to further studies of its biological functions (8).

Genetic research has linked *SORT1* variants with atherosclerosis, dyslipidemia and type 2 diabetes. Sortilin transports >50 molecules, including apolipoproteins, cytokines, proneurotrophins and enzymes, and also participates in neurotrophin signaling (10). Its role in lipid metabolism, glucose regulation and inflammation has made it relevant to metabolic and cardiovascular disease research. The present review describes the structure, expression and cellular functions of sortilin, and discusses its roles in lipid metabolism, insulin resistance, glucose metabolism and atherosclerosis.

Sortilin has a large extracellular region formed by a VPS10 domain containing ~700 amino acids. The domain includes an N-terminal 10-bladed β -propeller and two C-terminal cysteine-rich regions known as the ten-cysteine consensus (10CC) module. A transmembrane region and a 40-60 amino acid intracellular tail follows this domain (11,12). Within cells, sortilin is mainly present in the trans-Golgi network (TGN) and endosomes, with a smaller proportion at the cell surface. Its cytoplasmic tail contains tyrosine-based and acidic dileucine motifs that interact with adaptor proteins and the retromer complex, controlling movement between the TGN, endosomes and plasma membrane (13). Palmitoylation and phosphorylation can modify adaptor binding and regulate this movement. Sortilin is rapidly internalized and can enter constitutive or regulated secretory pathways depending on adaptor interactions (14). Proteolytic cleavage in some cells also releases soluble sortilin (15).

3. Sex-specific risk factors in CAD

The NCEP-ATP III guidelines define premature CAD (PCAD) as CAD diagnosed at ≤ 55 years in men and ≤ 65 years in women (16,17). PCAD accounts for 20-30% of CAD cases, while women represent 20-30% of PCAD cases (18,19). Genetic and environmental factors play a role in PCAD, with heritability estimated at 50-60%. Acute coronary syndrome occurs more frequently in patients with PCAD. CAD-related

mortality has decreased in men, but increased in women (20,21). Differences between men and women are also observed in the age of onset and clinical presentation of PCAD. Young women have higher myocardial infarction (MI) rates, longer periods of hospitalization stays and higher in-hospital mortality rates. Family and career demands may also influence the occurrence of PCAD in women (22).

PCAD affects patients, families and healthcare systems. Female PCAD includes conventional cardiovascular risk factors and female-specific factors, such as menopause and pregnancy, which can influence cardiovascular risk through different biological pathways. In the study by Berger *et al* (23), dietary cholesterol increased both total cholesterol and HDL cholesterol, whereas it produced a greater relative increase in low-density lipoprotein (LDL). This resulted in a significant increase in the LDL/HDL ratio, while having no significant effect on triglycerides or very-low-density lipoprotein (VLDL) and no statistically significant association with major cardiovascular or cerebrovascular outcomes in various reviewed studies (23). The Cardiovascular Risk in Young Finns Study identified sex-specific lipid risk, with young women with lipoprotein(a) [Lp(a)] levels ≥ 75 nmol/l having a 2-fold higher risk of developing atherosclerotic cardiovascular disease (ASCVD) (24).

Young patients with CAD have higher rates of diabetes and hypertension than non-CAD populations (25). These conditions have a greater cardiovascular impact in women with PCAD than in men (26,27). Hypertension is present in 69.5% of women with PCAD. Reduced estrogen activity during menopause can increase RAS activity and blood pressure. Each 20 mmHg increase in systolic blood pressure raises the cardiovascular risk by 60% (28). Diabetes increases the risk of developing PCAD by 1.4-fold in women compared with men, whereas the mortality risk is 2-3-fold higher in men (29,30).

Obesity is reported in 47.1% of PCAD populations. The prevalence is 53.2% in patients <35 years of age, 49.1% in those aged 35-45 years and 44.2% in those aged 45-55 years. Visceral adiposity can increase VLDL production and contribute to dyslipidemia, with LDL cholesterol (LDL-C) abnormalities reported in 11.2% of patients (31). The YOUNG-MI Registry reported obesity in 43.9% of young women with CAD (32). Obesity in young women aged 20-39 years was strongly associated with major cardiovascular risk factors, particularly hypertension, diabetes mellitus, dyslipidemia, and hyperuricemia. The magnitude of these associations was greater in younger adults, highlighting obesity as an important contributor to an adverse cardiovascular risk profile in young women (33).

Family history is an independent risk factor for PCAD in women. A positive family history is reported in 64% of young patients with CAD (34). Among women with PCAD, 28.5-35% report a family history of CAD, which is associated with a 4-fold higher risk of MI. In these women, 67% have dyslipidemia and hypertension, 53% are obese, 42% smoke and 33% have diabetes (35). A family history of diabetes is also associated with PCAD and ASCVD (36).

A 38% higher risk of metabolic syndrome was reported for each 1 mg/dl increase in uric acid among females aged 12-19 years in US national surveys (37). Estrogen regulates urate metabolism through the ABCG2 transporter. Estrogen increases renal ABCG2 expression and promotes urate

excretion (38). Hormonal changes before menopause and the decline in estradiol during menopause can reduce this effect. A rapid increase in uric acid from an individual baseline may then increase vascular inflammation and oxidative stress, even when the level remains within the normal range (39).

Monosodium urate crystals can directly induce endothelial injury by triggering oxidative stress and activating inflammasome pathways, notably the NLRP3 inflammasome, leading to endothelial cell apoptosis and reduced nitric oxide bioavailability (40). This endothelial dysfunction fosters a pro-inflammatory and pro-atherogenic environment independent of hormonal regulation. Additionally, urate crystals serve as danger-associated molecular patterns, activating innate immune responses through macrophage and dendritic cell inflammasome stimulation, which results in the release of pro-inflammatory cytokines, such as IL-1 β and IL-18 (41). These cytokines amplify leukocyte recruitment and vascular inflammation, accelerating atherosclerotic plaque development.

Elevated serum uric acid also promotes oxidative stress by increasing reactive oxygen species generation in endothelial and vascular smooth muscle cells (42). This oxidative milieu exacerbates lipid peroxidation and vascular remodeling, key contributors to atherogenesis. Furthermore, chronic urate exposure may induce endothelial-to-mesenchymal transition, a process implicated in vascular fibrosis and plaque instability, thereby linking hyperuricemia to adverse vascular remodeling (43).

It is important to recognize the interplay between hyperuricemia and other cardiovascular risk factors prevalent in young women, such as insulin resistance, hypertension and dyslipidemia, which synergistically exacerbate endothelial injury and atherosclerosis progression. These metabolic comorbidities may potentiate the vascular effects of urate, further increasing cardiovascular risk.

Nicotine and carbon monoxide cause endothelial injury through platelet activation, procoagulant activity, and altered vasoconstrictor and vasodilator balance. They also promote lipid abnormalities and inflammation, contributing to coronary spasm, plaque instability, and thrombosis. US surveys reported a 217% increase in e-cigarette use among young women over a period of 5 years, alongside tobacco use (44). Aerosols containing formaldehyde and acrolein activate TRPA1 channels, promote endothelial pyroptosis and increase matrix metalloproteinase (MMP)-9 activity, potentially increasing plaque vulnerability (45).

4. Sex-specific hormonal regulation of sortilin

Sex-specific hormonal regulation plays a pivotal role in modulating SORT1 expression and sortilin function, contributing to the observed differences in CAD risk and progression between women and men (46). Estrogen, the primary female sex hormone, exerts significant influence on cardiovascular physiology and pathology, with emerging evidence suggesting its involvement in regulating sortilin at multiple levels (47).

Estrogen is proposed to modulate SORT1 gene expression through estrogen receptor-mediated transcriptional pathways in hepatic and vascular tissues, although direct mechanistic studies remain limited (48). The cardioprotective effects of

estrogen prior to menopause may partly arise from its ability to downregulate sortilin-mediated proatherogenic mechanisms, including hepatic lipoprotein secretion and vascular inflammation. Declining estrogen levels during the menopausal transition are associated with dysregulation of SORT1 expression and function, potentially enhancing sortilin-driven lipoprotein secretion, vascular smooth muscle cell calcification and macrophage-mediated inflammation, thereby contributing to increased CAD risk in postmenopausal women (49).

Pregnancy and related conditions, such as preeclampsia further illustrate the hormonal modulation of sortilin. Elevated circulating levels of sortilin observed in preeclampsia cases suggest that pregnancy-associated hormonal and inflammatory changes upregulate SORT1 expression or promote sortilin shedding, linking it to endothelial dysfunction and heightened cardiovascular risk unique to women (50). The longitudinal assessment of sortilin levels throughout pregnancy and postpartum periods may provide valuable insight into its role as an early biomarker of female-specific cardiometabolic risk.

PCOS, characterized by hormonal imbalance, insulin resistance and increased cardiovascular risk, also demonstrates altered sortilin dynamics. Elevated serum sortilin levels in women with PCOS implicate androgen excess and disrupted estrogen signaling in modulating SORT1 expression and sortilin activity within adipose tissue and liver, exacerbating metabolic and vascular dysfunction (51).

Beyond estrogen, other female hormones, such as progesterone and androgens may influence sortilin expression and function, particularly in conditions involving hormonal fluctuations such as PCOS or menopause (52). The interplay between these hormones and sortilin-related pathways likely affects lipid metabolism, inflammatory responses and insulin sensitivity, further shaping sex-specific cardiovascular risk profiles.

Despite evidence of altered circulating sortilin levels in female-specific conditions, such as PCOS and preeclampsia, the robustness and clinical significance of these associations remain incompletely established. Hormonal fluctuations associated with reproductive status, pregnancy, and menopause may influence SORT1 expression and sortilin function, but direct mechanistic evidence linking estrogen, progesterone, or androgens to SORT1 regulation remains limited. Furthermore, the absence of standardized circulating sortilin assays and reference ranges stratified according to sex and menopausal status limits the translational interpretation of currently available findings. These gaps highlight the need for sex-stratified mechanistic and clinical studies before sortilin can be considered a reliable sex-specific biomarker or therapeutic target.

Integrating the sex-specific hormonal regulation of sortilin with clinical observations highlights the necessity for sex-stratified research and biomarker standardization. Establishing circulating sortilin reference ranges stratified by menopausal status and hormonal conditions will enhance risk prediction and therapeutic targeting for women. Experimental approaches employing hormone manipulation in cell-specific SORT1 knockout models, combined with single-cell transcriptomics and proteomics, are essential to elucidate the tissue- and cell-type-specific hormonal regulation of sortilin in female cardiovascular physiology and pathology.

5. Sortilin in atherogenesis

CAD is associated with elevated LDL-C, which promotes lipid accumulation, vascular inflammation and plaque formation (53). Hepatic sortilin overexpression raised plasma LDL-C and accelerated atherosclerosis in animals (54). Human genome-wide association studies (GWAS) linked 1p13.3 single nucleotide polymorphisms (SNPs) to a higher expression of *SORT1*, but to lower LDL-C and cardiovascular risk (55,56).

GWAS have identified common SNPs associated with serum LDL-C. Many are located near *LDLR*, *APOB*, *PCSK9* and *HMGCR*, which are linked to lipid disorders or LDL-C treatment. Other loci contain genes not previously linked to lipoprotein metabolism. A meta-analysis of ~100,000 individuals identified chromosome 1p13 as the locus most strongly associated with LDL-C ($P=1 \times 10^{-170}$) (57). The same SNPs were associated with MI and CAD. European ancestry individuals with major allele homozygosity had an ~40% higher risk of MI and up to 16 mg/dl higher LDL-C levels than minor allele homozygotes (57,58).

Animal models, particularly murine hepatic overexpression systems, have shown that increased levels of sortilin enhance VLDL secretion and plasma LDL-C levels, promoting atherosclerosis (54). Conversely, GWAS reveal *SORT1* gain-of-function SNPs at the 1p13.3 locus linked to increased hepatic *SORT1* expression but paradoxically lower plasma LDL-C and reduced cardiovascular risk (56). These discrepancies may arise from species-specific differences in lipid metabolism, compensatory mechanisms, or differences in experimental conditions.

The paradox between human *SORT1* gain-of-function SNPs associating with decreased LDL-C and reduced cardiovascular risk vs. animal models demonstrating that hepatic sortilin overexpression increases LDL-C and atherosclerosis remains unresolved. This discrepancy likely reflects species differences, experimental model limitations and the complex, tissue-specific functions of sortilin. Conclusions drawn from murine overexpression studies may not fully translate to human physiology due to differences in lipid metabolism pathways and compensatory mechanisms (54). Furthermore, the dual role of sortilin in both promoting VLDL secretion and mediating ApoB-100 degradation introduces complexity that is incompletely understood, warranting cautious interpretation.

The majority of mechanistic insights derive from global or hepatic overexpression and knockout mouse models, which may not capture cell-type-specific effects or the influence of post-translational modifications and intracellular trafficking on sortilin function. The absence of conditional, tissue-specific models limits the understanding of how the roles of sortilin differ between hepatocytes, vascular smooth muscle cells, macrophages and adipocytes. This gap restricts the ability to reconcile systemic lipid effects with local vascular inflammation and calcification.

Smaller LDL particles are considered more atherogenic than larger particles. LDL-C contains particles of different sizes and densities. Studies using the MDC-CC and PARC cohorts assessed LDL subclasses with ion mobility and gradient gel electrophoresis to examine the effect of the 1p13 locus (55,59).

Sortilin plays a complex role in lipoprotein metabolism. Its effects depend on cellular localization, post-translational

modifications, and interactions with apoB or the LDL receptor (10). ApoB100 is a major structural protein of liver-derived VLDL, which undergoes lipolysis in the circulation to form LDL. Genetic variants that reduce apoB100-mediated VLDL secretion can lower plasma LDL levels (60). Mutations in *APOB* or MTP can reduce hepatic VLDL production by impairing apoB lipidation, leading to lower plasma levels of LDL cholesterol. Mutations affecting LDL clearance, such as LDL receptor defects in familial hypercholesterolaemia, increase plasma LDL levels and cardiovascular disease risk (61).

This apparent contradiction highlights the complex and context-dependent role of sortilin in lipoprotein metabolism. Tissue and cell-type-specific expression may further contribute to the divergent effects of sortilin on lipid metabolism. Sortilin is expressed in hepatocytes, vascular smooth muscle cells, macrophages, adipose tissue, and other immune and metabolic tissues, where it performs distinct functions. In hepatocytes, sortilin regulates lipoprotein trafficking, including VLDL secretion, LDL uptake, and lysosomal degradation of ApoB-containing particles (62). By contrast, vascular and immune-cell sortilin is involved predominantly in inflammatory responses, macrophage lipid accumulation, and vascular calcification (63). Consequently, the effect of increased sortilin expression on circulating LDL-C cannot necessarily be extrapolated from one tissue to another. The protective association observed in human GWAS may predominantly reflect hepatic effects on lipoprotein clearance, whereas experimental overexpression models may additionally capture effects arising from altered sortilin activity in other tissues and from supraphysiological expression levels (64).

The subcellular localization and trafficking routes of sortilin influence its role in lipid metabolism (65). It cycles between the TGN, endosomes and plasma membrane, with adaptor proteins and post-translational modifications (e.g., phosphorylation, palmitoylation) regulating its sorting (66). These factors determine whether sortilin facilitates VLDL secretion, mediates LDL uptake, or directs ApoB-100-containing lipoproteins toward lysosomal degradation. Variations in these intracellular processes may shift the balance between lipid production and clearance, contributing to divergent plasma LDL-C outcomes.

Sortilin interacts with ApoB-100 in hepatocytes, influencing VLDL assembly and secretion (67). Increased sortilin can promote VLDL secretion, raising plasma LDL-C. However, sortilin also facilitates lysosomal degradation of ApoB-100-containing lipoproteins, which would lower LDL-C levels (12). The relative dominance of these opposing pathways may depend on expression levels, cellular context and regulatory cues, explaining the contradictory findings.

Sortilin is produced as an inactive precursor as a 40-amino-acid propeptide blocks ligand access to the binding site within the β -propeller structure (12). Proconvertases in the TGN remove the propeptide and activate sortilin. In liver cells, sortilin interacts with ApoB-100 and promotes VLDL assembly and secretion, increasing plasma LDL-C levels. It also promotes proprotein convertase subtilisin/kexin type 9 (PCSK9) production and release. PCSK9 causes LDL receptor degradation, reducing LDL-C clearance from the circulation (68). Sortilin enhances secretion of PCSK9, which promotes LDL receptor degradation and reduces LDL

clearance. Elevated PCSK9 levels due to sortilin overexpression could lead to increased plasma LDL-C levels. However, the extent of this effect may vary between models and physiological states, influencing net LDL-C levels.

The function of sortilin can vary with the tissue and disease condition. In CAD, inflammation and abnormal lipid levels can increase sortilin expression in vascular tissues and macrophages. Higher sortilin levels can increase cholesterol storage in macrophages, leading to foam cell formation, endothelial dysfunction, and plaque instability (69). These effects can contribute to atherosclerotic plaque development and progression. Sortilin also promotes vascular calcification. It stimulates vascular smooth muscle cells to release matrix vesicles containing tissue-nonspecific alkaline phosphatase, which promotes mineral deposition in the vessel wall (63). This microcalcification can reduce fibrous cap strength and increase the risk of plaque rupture and cardiovascular events (70).

Sortilin contributes to plaque instability and rupture through two interrelated, yet distinct pathological pathways (63,71).

- i) Microcalcification-mediated fibrous cap weakening: Sortilin promotes vascular calcification by stimulating vascular smooth muscle cells to release matrix vesicles enriched with tissue-non-specific alkaline phosphatase. These vesicles serve as nucleation sites for microcalcifications within the fibrous cap of atherosclerotic plaques. Microcalcifications create focal mechanical stress points that compromise the structural integrity of the fibrous cap, increasing its susceptibility to rupture.
- ii) Macrophage-derived inflammatory cytokine-mediated fibrous cap degradation: Separately, sortilin enhances vascular inflammation by upregulating proinflammatory cytokine release (e.g., IL-6, IFN- γ) from activated macrophages within the plaque. These cytokines promote extracellular matrix degradation by stimulating the expression and activation of MMPs, which break down collagen and other fibrous proteins critical for fibrous cap stability. This inflammatory milieu also recruits additional immune cells, amplifying local tissue damage.

The microcalcification-induced mechanical weakening and cytokine-driven enzymatic degradation function synergistically to destabilize the fibrous cap (72). While microcalcifications create physical stress concentrations that predispose the cap to rupture, inflammatory cytokines simultaneously degrade the extracellular matrix scaffold, reducing the resilience of the cap. Together, these processes accelerate plaque vulnerability beyond the effect of either mechanism alone (73).

While the involvement of sortilin in pro-inflammatory cytokine release and vascular calcification is documented, the precise molecular pathways remain incompletely delineated. For example, the interplay between sortilin-mediated microcalcification and macrophage-driven extracellular matrix degradation in plaque rupture is complex and requires further clarification.

6. Sortilin and atherosclerotic plaque formation

The inflammatory role of sortilin includes stimulation of activated macrophages to release IL-6 and IFN- γ , promoting endothelial activation, leukocyte recruitment and plaque progression (71). The reduced cytokine release from

sortilin-deficient macrophages following lipopolysaccharide stimulation further indicates its role in macrophage inflammation (69). The reduction in atherosclerotic lesions seen in *Sort1* knockout mice without changes in plasma LDL-C suggests that sortilin also acts through pathways independent of circulating LDL-C (69). The protein also promotes ABCA1 degradation, reducing cholesterol transfer to apoA-I and increasing cholesterol accumulation in macrophages and atherosclerotic plaques (74).

In hepatocytes, sortilin regulates lipoprotein metabolism via multiple mechanisms, including facilitating VLDL secretion, mediating LDL uptake and directing ApoB-100-containing lipoproteins toward lysosomal degradation (62). The net effect of these pathways may vary depending on expression levels, post-translational modifications and interaction partners, impacting plasma LDL-C differently. Sortilin expression in vascular smooth muscle cells and macrophages promotes proatherogenic processes independent of plasma LDL-C (69). These include enhanced foam cell formation, cytokine release and vascular calcification. The role of sortilin here is largely pro-inflammatory and pro-atherosclerotic, contributing to lesion progression despite systemic lipid levels. Differences in subcellular localization, adaptor protein interactions and post-translational modifications across cell types lead to distinct functional outcomes (75). For example, hepatic sortilin may promote LDL clearance or production depending on context, while in macrophages, it modulates lipid efflux and inflammatory signaling (69). The protective association observed in GWAS may reflect increased hepatic SORT1 expression enhancing LDL clearance pathways or other lipid-lowering mechanisms predominant in humans, whereas animal models with overexpression may capture additional or different aspects of sortilin function, including proatherogenic effects in other cell types or under experimental conditions (76). Conditional knockout models and single-cell analyses are required to dissect these tissue-specific roles. This approach is necessary to clarify how hepatic vs. vascular or immune cell sortilin contributes distinctly to lipid metabolism and atherosclerosis.

The role of sortilin in adipose tissue is relevant to metabolic changes associated with CAD. Sortilin is expressed in adipocytes and participates in lipid handling and intracellular vesicle movement, which are important for adipocyte development. Sortilin deficiency can impair adipocyte differentiation and increase fat deposition in non-adipose tissues, leading to ectopic fat deposition (77). Changes in sortilin expression in enlarged adipocytes can also increase the release of IL-6, TNF- α and free fatty acids, promoting insulin resistance, endothelial dysfunction and chronic inflammation (78).

The effects of sortilin also extend to glucose regulation. It regulates the formation of GLUT4 vesicles in adipose and muscle tissues, and changes in this process can reduce glucose uptake and contribute to type 2 diabetes mellitus (79). Sortilin also regulates acid sphingomyelinase activity and ceramide production (80). Ceramide inhibits insulin signaling, whereas a lower expression of sortilin is associated with reduced ceramide levels and improved insulin sensitivity (81). Reduced ceramide production with a lower expression of sortilin may therefore improve insulin sensitivity and glucose regulation. Sortilin may also have diagnostic value in inflammatory

conditions. A study on maternal circulating sortilin levels in preeclampsia found higher levels in affected women, and ROC analysis indicated its potential use as a biomarker for disease prediction (82). The mechanisms by which sortilin modulates insulin resistance via ceramide production and GLUT4 vesicle trafficking require more detailed investigations to establish causality and therapeutic potential.

Although several mechanisms have been proposed to explain the association between sortilin and cardiovascular disease, the strength of evidence supporting these pathways is heterogeneous. The majority of mechanistic evidence is derived from cellular and animal studies, whereas direct evidence establishing these pathways as causal determinants of CAD in humans remains limited. Therefore, these mechanisms should be interpreted according to the level of available evidence rather than considered uniformly established.

Macrophage-mediated inflammation has been supported primarily by experimental studies. Sortilin deficiency has been associated with reduced inflammatory cytokine production and atherosclerotic lesion formation in some experimental models (71); however, other studies have reported that macrophage sortilin deficiency reduces LDL uptake and foam-cell formation without significantly altering inflammatory cytokine responses (69,71). These findings suggest that the contribution of sortilin to macrophage inflammation may be context- and model-dependent and requires further validation in human disease.

The sortilin-ABCA1 pathway has comparatively strong mechanistic support at the preclinical level. Experimental studies have demonstrated that sortilin interacts with ABCA1 and promotes its lysosomal degradation, thereby impairing cholesterol efflux and favoring macrophage lipid accumulation and foam-cell formation (83). These findings provide a biologically plausible link between sortilin and atherogenesis; however, the extent to which this pathway contributes to human CAD has not yet been established.

Evidence linking sortilin to vascular calcification is also supported by experimental and preclinical findings. Sortilin has been identified in calcified vascular tissue, and experimental studies have demonstrated effects on the release of pro-calcific extracellular vesicles from vascular smooth muscle cells (84). Nevertheless, evidence that pharmacological modulation of sortilin can prevent or reduce clinically relevant vascular calcification in humans remains unavailable.

The proposed role of sortilin in insulin resistance should be interpreted even more cautiously. Experimental research implicates sortilin in GLUT4 vesicle trafficking and the regulation of acid sphingomyelinase and ceramide metabolism, providing a potential mechanistic connection between sortilin, metabolic dysfunction and cardiovascular risk (85). However, these associations remain predominantly preclinical, and their causal contribution to human CAD has not yet been demonstrated. Thus, these pathways may be considered as plausible mechanisms rather than established clinical mechanisms. This distinction is particularly critical when considering sortilin as a therapeutic target.

Overall, the available evidence supports sortilin as a biologically relevant regulator of multiple processes involved in atherosclerosis; however, the relative importance and clinical relevance of individual pathways remain uncertain. Human genetic and observational studies provide evidence

for an association between SORT1/sortilin and cardiovascular phenotypes, whereas mechanistic causality has been demonstrated predominantly in experimental systems. Future studies integrating tissue-specific genetic manipulation, human vascular tissue analyses and selective pharmacological inhibition will be necessary to determine which of these pathways are causally relevant and therapeutically actionable.

Pregnancy-related diabetes, hypertension and preeclampsia increase cardiovascular risk and can contribute to later CAD. Awareness of these risk factors remains limited among women and healthcare professionals. Premenopausal women generally have a lower CVD risk than age-matched men, although this difference decreases after menopause; the American Heart Association (AHA) issued its first CVD prevention guidelines for women in 1999 (86). Sex-specific risk factors require appropriate prevention and treatment. The association between increased sortilin levels and preeclampsia indicates a possible association between sortilin, systemic inflammation and vascular dysfunction. This may also be relevant to early cardiovascular risk in women and supports further study of sortilin in female CAD.

In the study by Oh *et al* (87), the area under the ROC curve for sortilin levels in predicting the presence of CAD was 0.725. A sortilin concentration of 1.35 ng/ml was identified as the optimal cut-off for detecting CAD, yielding a sensitivity of 80.6% and a specificity of 53.0%. Sortilin had an adjusted OR of ~5.29, while high-sensitivity C- (hs-CRP) had an adjusted OR of approximately 2.27 (87).

Another CAD study found a strong positive correlation between circulating sortilin and hs-CRP ($r=0.87$, $P<0.001$), supporting an association between sortilin and inflammatory activity. In that study, however, hs-CRP had an AUC of 0.750, while sortilin had an AUC of 0.650, illustrating that the relative diagnostic performance can vary substantially between populations (88). In the study by Hu *et al* (89), individuals with CAD exhibited higher PCSK9 levels, while circulating sortilin concentrations were significantly elevated specifically among statin-naïve patients with CAD. A significant positive correlation was observed between sortilin and PCSK9 levels ($r=0.37$, $P=0.001$), and this association remained significant after adjustment for potential confounding factors in both the overall study population and the statin-naïve subgroup (89).

Although elevated circulating sortilin levels exhibit potential as a biomarker of cardiometabolic and vascular risk, the current evidence remains preliminary and is derived predominantly from observational and cross-sectional studies. The diagnostic and prognostic utility of circulating sortilin therefore requires validation in larger, prospective and appropriately sex-stratified cohorts. Such studies should establish standardized reference ranges and assay cutoffs, determine the influence of age, sex, menopausal status and relevant hormonal conditions, and evaluate whether circulating sortilin provides incremental predictive value beyond established cardiovascular risk factors and biomarkers (Table I).

7. Translational and therapeutic potential of targeting sortilin

The pleiotropic involvement of sortilin in hepatic lipoprotein metabolism, macrophage inflammation, cholesterol efflux,

Table I. Key clinical and genetic studies evaluating sortilin in coronary artery disease and cardiovascular risk.

First author, year of publication	Population/design	Sortilin or genetic marker evaluated	Principal findings	Cardiovascular relevance	(Refs.)
Ogawa, 2016	Patients with cardio-vascular risk factors and CAD; clinical observational study	Circulating soluble sortilin (sortilin)	Plasma sortilin was associated with cardiovascular risk factors. In CAD patients, sortilin correlated with hs-CRP and γ -glutamyltransferase; soluble sortilin was also released from activated platelets.	Suggests an association between circulating sortilin, platelet activation, inflammation and atherothrombotic risk.	(102)
Hu, 2017	80 subjects: 43 CAD and 37 non-CAD	Serum sortilin and PCSK9	Sortilin was significantly higher in statin-naïve CAD patients than controls; sortilin correlated positively with PCSK9 ($r=0.37$, $P=0.001$), with the association remaining significant after adjustment.	Supports an association between sortilin and PCSK9-mediated lipoprotein metabolism in CAD, particularly before statin treatment.	(89)
Oh, 2017	31 statin-naïve CAD patients and 116 controls	Plasma sortilin	Plasma sortilin was independently associated with CAD. A cutoff of 1.35 ng/ml yielded an AUC of 0.725, sensitivity of 80.6% and specificity of 53.0%.	Provides early evidence for circulating sortilin as a potential diagnostic biomarker of CAD.	(87)
Werida, 2021	45 CAD patients and 42 controls; coronary CT angiography	Plasma sortilin and homocysteine	Sortilin was higher in CAD; it correlated with total cholesterol, LDL-C, triglycerides, troponin I, Gensini score and hs-CRP. Sortilin correlated strongly with Gensini score ($r=0.93$) and hs-CRP ($r=0.87$).	Suggests an association between circulating sortilin, coronary disease burden and systemic inflammation.	(88)
Linsel-Nitschke, 2010	Large human genetic cohorts/CAD case-control populations	rs599839, rs646776 and related 1p13.3 variants	The rs599839 G allele was associated with lower LDL-C and lower CAD risk; increased SORT1 expression and enhanced LDL uptake provided functional support.	Establishes the SORT1 locus as a reproducible genetic determinant of lipid levels and CAD risk.	(103)
Musunuru, 2010	Human genetic cohorts and experimental hepatocyte/liver models	rs12740374 at 1p13.3	rs12740374 creates a C/EBP binding site and alters hepatic SORT1 expression; SORT1 manipulation altered LDL-C and VLDL secretion.	Provides a mechanistic bridge between a non-coding human CAD-associated variant, SORT1 expression and lipoprotein metabolism.	(56)
Guo, 2015	13 case-control studies; 17,766 patients and 20,272 controls	rs599839 and rs646776	Both variants were significantly associated with cardiovascular disease risk; rs599839 OR 1.17 and rs646776 OR 1.13 under the reported genetic models.	Supports replication of the association between the 1p13.3 locus and CAD/MI risk across populations.	(104)
Møller, 2021	1,173 patients with suspected stable CAD undergoing coronary CT angiography	Plasma sortilin measured by ELISA and OLINK; SORT1 pQTLs	The two assays correlated poorly ($r=0.21$). SORT1 cis-pQTLs were identified, but circulating sortilin was not associated with coronary calcium, disease severity or improved discrimination of obstructive CAD.	Important negative/neutral evidence demonstrating that circulating sortilin is not yet an established clinical biomarker and that assay methodology substantially affects interpretation.	(90)

CAD, coronary artery disease; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction.

vascular calcification and metabolic dysfunction render it an attractive therapeutic target in CAD. However, therapeutic development remains at a predominantly preclinical or early translational stage, and no sortilin-directed therapy has yet been established as a standard treatment for CAD. Notably, the therapeutic objective may not necessarily be complete systemic depletion of sortilin; rather, selective interference with disease-relevant sortilin functions or tissue-specific pathways may provide a more favorable therapeutic window.

Several approaches to sortilin inhibition are currently being investigated. Monoclonal antibodies represent one of the most advanced approaches for the pharmacological blockade of sortilin, although their development has principally focused on neurological rather than cardiovascular indications (90). The monoclonal antibody AL101 (GSK4527226) binds sortilin, reduces cell-surface sortilin and partially blocks sortilin-progranulin interaction, thereby increasing circulating and cerebrospinal-fluid progranulin concentrations (91). Preclinical studies on rodents and non-human primates have demonstrated pharmacodynamic activity, and a phase 1 study on healthy volunteers demonstrated increased plasma and cerebrospinal-fluid progranulin levels following administration (91). These findings establish that sortilin can be pharmacologically modulated in humans and provide proof-of-concept for antibody-mediated targeting; however, clinical efficacy in disease populations remains to be established.

For cardiovascular disease, antibody-based strategies remain substantially less mature. Potential approaches include antibodies directed against extracellular domains of sortilin or antibodies designed to selectively block pathogenic ligand interactions rather than completely eliminate receptor function (92). Such an approach could theoretically inhibit sortilin-mediated inflammatory signaling or vascular calcification while preserving beneficial hepatic or neuronal functions. This distinction is particularly important because sortilin contains a large extracellular VPS10 domain capable of interacting with numerous ligands, and different ligand-binding sites may mediate distinct biological effects (93). Consequently, ligand-selective antibodies may ultimately be preferable to indiscriminate receptor blockade.

Antisense oligonucleotides (ASOs) provide another potentially attractive strategy as they can reduce SORT1 mRNA levels and consequently decrease sortilin protein expression (94). Recent experimental evidence provides direct cardiovascular proof-of-concept: ASO-mediated Sort1 silencing reduced atherosclerotic plaque necrotic-core size in both male and female mice and reduced vascular calcification in male mice (95). The observed sex-dependent response is particularly relevant, as it suggests that hormonal and sex-specific biological mechanisms may influence the efficacy of sortilin-directed therapy. These findings nevertheless remain preclinical, and the optimal tissue distribution, dosing interval, durability of SORT1 suppression, and long-term safety of cardiovascular ASO therapy have not been established in humans.

ASOs may provide a critical advantage over systemic antibody blockade as their distribution can potentially be optimized toward tissues, such as the liver (96). However, this strategy also presents a fundamental challenge: The hepatic

suppression of SORT1 may not reproduce the effects of sortilin inhibition in macrophages, vascular smooth muscle cells, or other vascular tissues. This is particularly relevant as human genetic studies and animal experiments have produced apparently discordant effects of SORT1 manipulation on circulating LDL-C and atherosclerosis (56,97). Sortilin has tissue-specific and sometimes opposing effects on lipoprotein production, clearance, inflammation and vascular calcification. Therefore, future ASO development should prioritize cell- or tissue-specific delivery rather than assuming that global SORT1 suppression will produce uniform cardiovascular benefit.

Small-molecule inhibitors constitute a third strategy and potentially provide advantages in oral bioavailability, tissue penetration and dosing flexibility. Structural studies have identified a ligand-binding pocket within the VPS10 domain, and compounds such as AF40431 and its optimized derivative AF38469 have been developed to interact with the neurotensin-binding site of sortilin (98). However, the functional consequences of these compounds in cardiovascular disease have not yet been established, and their development remains at the experimental/preclinical stage. More recent structure-guided drug-repurposing studies have used molecular docking, virtual screening and molecular-dynamics simulations to identify FDA-approved compounds with potential SORT1-modulating activity (99); however, these findings require biochemical validation and *in vivo* efficacy studies before they can be considered therapeutic candidates (100).

A major obstacle to small-molecule development is the complex ligand biology of sortilin. Sortilin interacts with numerous ligands through potentially distinct binding sites, and inhibition of one ligand-binding interaction may leave other pathways unaffected (101). Conversely, a broadly active inhibitor could interfere with physiological trafficking and signalling pathways that are unrelated to atherosclerosis. Consequently, detailed mapping of ligand-specific binding sites and determination of which sortilin interactions are genuinely pathogenic in CAD will be necessary for rational drug design.

The principal translational challenge for all three strategies is therefore selectivity. Sortilin is widely expressed in the nervous system, adipose tissue, skeletal muscle, liver and immune cells, and participates in neurotrophin signaling, glucose metabolism, intracellular protein trafficking and immune regulation (12). Systemic inhibition could therefore produce neurological, metabolic, or immunological adverse effects. This concern is of particular importance as sortilin is not simply a disease-associated protein; it is a multifunctional trafficking receptor with essential physiological functions.

A second challenge is the unresolved discrepancy between human genetic observations and experimental models. Human SORT1 variants associated with increased hepatic SORT1 expression have been linked to lower LDL-C and cardiovascular risk, whereas hepatic sortilin overexpression in some animal models increases VLDL secretion, LDL-C, and atherosclerosis (76). This apparent paradox may reflect species differences, tissue-specific functions, compensatory mechanisms and differences in experimental expression levels. This uncertainty argues against indiscriminate systemic inhibition until the cardiovascular effects of sortilin modulation have been clearly separated according to tissue and cellular context.

A third challenge concerns the distinction between circulating sortilin and tissue-associated sortilin. Circulating sortilin may reflect shedding or release from cells and may not directly represent the activity of membrane-associated sortilin within atherosclerotic plaques. Consequently, lowering plasma sortilin concentrations should not automatically be interpreted as evidence of effective inhibition of pathogenic sortilin signaling within the arterial wall. Development programs will therefore require pharmacodynamic biomarkers that demonstrate target engagement in the relevant tissue in addition to measuring circulating sortilin.

The sex-specific biology of sortilin represents both an additional challenge and a therapeutic opportunity. The present evidence indicates that hormonal status may influence *SORT1* expression and function, while recent ASO experiments demonstrated sex-dependent effects on vascular calcification (95). Accordingly, future clinical development should incorporate sex, menopausal status and hormonal state into trial design rather than treating these variables merely as potential confounders. This may be particularly relevant for women with PCOS, previous preeclampsia, or postmenopausal cardiometabolic risk, populations in whom altered circulating sortilin may be present.

Overall, the current therapeutic landscape supports sortilin as a promising, yet experimentally immature target rather than an immediately translatable therapeutic target for CAD. Monoclonal antibodies have demonstrated clinical proof of concept for pharmacological sortilin modulation in humans, whereas cardiovascular ASO approaches currently have encouraging animal data and small-molecule inhibitors remain largely in the discovery/preclinical phase. The most plausible future strategy may therefore involve tissue-selective or ligand-selective inhibition, particularly targeting pathogenic sortilin functions in macrophages and vascular smooth muscle cells while preserving physiological functions in the liver and nervous system. Such approaches, combined with conditional tissue-specific models, single-cell analyses, rigorous pharmacodynamic assessment, and sex-stratified clinical studies, will be essential before sortilin-directed therapy can progress from mechanistic promise to clinical application.

8. Conclusion and future perspectives

Sortilin may contribute to CAD through lipid-related and lipid-independent pathways. It regulates hepatic lipoprotein metabolism, promotes vascular inflammation and increases lipid accumulation in macrophages, contributing to atherosclerotic plaque formation. Sortilin activity in adipose tissue and its effects on inflammatory cytokines are also associated with metabolic disturbances, particularly in women with cardiometabolic risk. Circulating sortilin levels are higher in women with preeclampsia, a condition associated with endothelial dysfunction and future cardiovascular risk, indicating its potential as a biomarker in women. Further research is warranted to assess the sex-specific regulation of sortilin and its clinical relevance in cardiovascular disease in women. Elevated circulating sortilin levels show promise as a potential biomarker for identifying women at increased cardiovascular risk. However, the lack of standardized reference ranges and assay cutoffs stratified by menopausal status currently limits its clinical utility as a standalone diagnostic tool. Further

prospective studies are required to establish reliable circulating sortilin thresholds across different hormonal phases and to validate its prognostic value in diverse female populations.

Despite significant advances in understanding the molecular contributions of sortilin to CAD, critical gaps remain that need to be addressed to fully harness its translational potential. Resolving the paradox between human *SORT1* gain-of-function SNPs at the 1p13.3 locus, which associate with decreased plasma LDL-C and cardiovascular risk, and animal models where hepatic overexpression elevates LDL-C and atherosclerosis, is paramount. This requires detailed investigations into the tissue- and cell-type-specific functions of sortilin, including its subcellular localization, post-translational modifications, and interactions with lipoproteins and receptors. Employing conditional knockout models, single-cell transcriptomics and proteomics will be essential to dissect the distinct roles of hepatic, vascular, and immune cell sortilin in lipid metabolism and atherogenesis.

Given the widespread expression of sortilin in neuronal tissue, adipose tissue, skeletal muscle and immune cells, future therapeutic strategies need to carefully consider potential off-target effects. The systemic inhibition of sortilin could disrupt critical physiological processes, such as neurotrophin signaling, glucose metabolism and immune regulation, leading to adverse neurological, metabolic, or immunological outcomes. Therefore, the development of selective targeting approaches, such as tissue-specific inhibitors or targeted delivery systems, is crucial to maximize cardiovascular benefits while minimizing off-target risks. Preclinical safety evaluations should rigorously assess neurological, metabolic, and immunological endpoints, alongside dose optimization to balance efficacy and safety. The identification and monitoring of biomarkers indicative of off-target effects will be critical during clinical translation.

Establishing standardized, sex- and menopausal status-stratified circulating sortilin reference ranges through large prospective cohort studies is critical for its clinical application as a biomarker. The influence of hormonal regulation on *SORT1* expression, particularly in conditions such as polycystic ovary syndrome and preeclampsia, warrants further exploration to understand sex-specific modulation and its implications for cardiovascular risk prediction. Longitudinal studies tracking circulating sortilin during pregnancy and post-preeclampsia periods may clarify its role in early detection of female-specific cardiometabolic risk. Additionally, integrating plasma sortilin levels into existing cardiovascular risk models could enhance predictive accuracy, especially in women with autoimmune disorders, microvascular disease, or non-obstructive CAD.

Advancing the knowledge of the pleiotropic, tissue-specific functions of sortilin and addressing translational challenges related to assay standardization and therapeutic safety will be pivotal. These efforts hold promise to improve early detection, risk stratification, and targeted intervention for coronary artery disease, particularly in women who remain underrepresented in cardiovascular research.

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Authors' contributions

SR was involved in the conception and design of the study, in the literature search, the drafting of the manuscript, interpretation of data from the literature, and in the critical revision of the manuscript for important intellectual content. AKJ and SKS were involved in the literature search, in the writing of the manuscript, and in the critical revision of the manuscript for important intellectual content. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

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Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, AI tools (Quill bot and Grammarly) were used to improve the readability and language of the manuscript or to generate images, and subsequently, the authors revised and edited the content produced by the AI tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

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