Mohammad, S. 2026
J. Basic Appl. Res. Biomed. 12(1): 58-71

JBAAR
Journal of Basic and Applied Research in Biomedicine
ISSN 2710-1479

Review Article

Context-Dependent MicroRNA Regulation in Atherosclerosis: Cell Type, Stage, Strand and Comorbidity, and Implications for Coronary Artery Disease Therapy

Sahem Mohammad[1*]

[1]Institute of Life Course & Medical Sciences, Faculty of Health and Life Sciences, University of Liverpool, Liverpool, UK.

*Corresponding Author: sahem@liverpool.ac.uk

HISTORY:
Received: 04-09-2026
Revised: 13-10-2026
Published: 28-10-2026

FUNDING
This research received no specific grant from any public, commercial, or non-profit funding agency.

CONFLICT OF INTEREST
The authors declare no conflict of interest in this study.

DATA AVAILABILITY
No new datasets were generated in this narrative review. Any additional data are available from the author on reasonable request.

ABSTRACT:
Background: MicroRNAs (miRNAs) regulate gene expression in endothelial cells, smooth muscle cells and macrophages and have been proposed as biomarkers and therapeutic targets in atherosclerosis and coronary artery disease, yet individual miRNAs are often reported as protective in one study and harmful in another.
Objectives: To organise the primary evidence by context (cell type, disease stage, vascular bed, strand, model, sex, comorbidity and sampling compartment) and to ask what this implies for therapy.
Methods: This narrative, non-systematic review draws on PubMed and Scopus (2006 to August 2026) and on a ClinicalTrials.gov search. Studies with validated targets and in vivo or human data were prioritised. No formal risk-of-bias assessment was performed.
Results: Studies that varied a single factor within one design show that the direction of effect can reverse with stage (miR-155, miR-21), differ between vascular beds (miR-26b, miR-155, miR-92a), diverge between cell types (miR-221/222) and depend on the strand targeted (miR-126, miR-181a, miR-26b). Circulating levels differ from lesion levels, are influenced by diabetes, sex and drug treatment, and have modest diagnostic accuracy. Delivery systems that reach plaque in mice have been described for several miRNAs, but to date no registered trial tests a miRNA-targeting drug in atherosclerosis or coronary artery disease, whereas a miR-132 inhibitor has completed a Phase 2 trial in heart failure.
Conclusions: Claims that a miRNA is a therapeutic target in coronary artery disease remain provisional until its context is defined. A context-defined approach to target selection, strand choice, delivery and trial design is proposed.

Keywords: *microRNA; atherosclerosis; coronary artery disease; strand-specific regulation; extracellular vesicles; therapeutics*

Cite this article as: Mohammad, S. (2026) Context-Dependent MicroRNA Regulation in Atherosclerosis: Cell Type, Stage, Strand and Comorbidity, and Implications for Coronary Artery Disease Therapy. Journal of Basic and Applied Research in Biomedicine, 12(1): 58-71

This work is licensed under a Creative Commons Attribution 4.0 License. You are free to copy, distribute and perform the work. You must attribute the work in the manner specified by the author or licensor.

1. INTRODUCTION

Coronary artery disease (CAD) is the clinical expression of atherosclerosis in the coronary arteries. Deaths from all cardiovascular diseases combined rose from 13.1 million in 1990 to 19.2 million in 2023, and ischaemic heart disease was among the leading cardiovascular causes of disability-adjusted life years (Global Burden of Cardiovascular Diseases and Risks 2023 Collaborators, 2025). Lipid-lowering and anti-inflammatory therapies reduce events, but residual risk remains (Reijnders et al., 2023). In a pooled analysis of three randomised trials in statin-treated patients, baseline high-sensitivity C-reactive protein was significantly associated with incident major adverse cardiovascular events, whereas residual cholesterol risk was not (Ridker et al., 2023). Inflammatory and haemodynamic stresses reshape gene expression in vessel-wall cells, and miRNAs fine-tune these networks after transcription (section 4). Residual inflammatory risk, together with the limits of existing drugs, has turned attention partly to post-transcriptional regulators such as microRNAs.

Two developments make a reassessment timely. First, oligonucleotide therapeutics have matured: modifications developed for antisense agents, such as 2'-O-methoxyethyl, underlie approved drugs including mipomersen and nusinersen (Hill & Hall, 2023), and miRNA-directed agents have been reviewed across clinical settings (Diener et al., 2022). Second, single-cell sequencing of human carotid plaques identified 14 distinct cell populations (Depuydt et al., 2020), a reminder that tissue-level miRNA measurements integrate signals from many cell types and states.

MicroRNAs are short non-coding RNAs that repress target messenger RNAs, and a single miRNA can act on many targets. Dozens have been linked to endothelial, smooth muscle and macrophage function in atherosclerosis, and recent reviews catalogue them, often cell type by cell type (Li et al., 2023; Prus et al., 2026; Wang et al., 2025). A reader of this literature meets a repeated problem: the same miRNA is reported as protective in one study and harmful in another. For miR-155, haematopoietic loss increased lesions in Ldlr-/- recipients (Donners et al., 2012), while whole-body loss in Apoe-/- mice reduced aortic root lesions (Du et al., 2014). Earlier reviews noted that such contradictions may depend on stage or model (Cao et al., 2016; Ma et al., 2013), but none of the recent reviews examined here systematically organised the primary evidence around these contextual variables as an integrated framework.

This narrative review addresses that question. The argument developed here is that the direction of a miRNA's effect in atherosclerosis depends on a small set of identifiable variables: cell type, disease stage, vascular bed, strand, model and sex, and comorbidity. The review then considers what this means for treatment, and why, to date, no registered trial tests a miRNA-targeting drug for atherosclerosis or coronary artery disease, although a miR-132 inhibitor has advanced in heart failure.

The review is not systematic. Studies with validated targets and in vivo or human data were prioritised, the primary studies that carry the central argument were read in full, and statements that rest on reviews alone are identified as such.

The review is organised as follows. Section 2 describes how the literature was identified and selected. Section 3 summarises plaque biology and the experimental models, and section 4 summarises miRNA biology and the therapeutic tools. Section 5 examines endothelial cells and opens with Table 1, which collects the main findings across cell types; section 6 considers smooth muscle cells, section 7 macrophages and lipid handling, and section 8 vesicle-mediated crosstalk. Section 9 develops the context framework (Table 2), section 10 addresses strand-

specific biology, and section 11 asks what the framework implies for therapy and why no miRNA-targeting drug has reached trials in atherosclerosis. Section 12 considers circulating miRNAs, and section 13 sets out limitations and directions for future work.

2. METHODS

2.1 Design and scope

This is a narrative, non-systematic review. It aims to organise the experimental and clinical evidence on miRNAs in atherosclerosis and coronary artery disease by context (cell type, disease stage, vascular bed, strand, model, sex, comorbidity and sampling compartment) and does not attempt to catalogue every miRNA. The literature search covered 2006 to August 2026 (section 2.2).

2.2 Literature search

PubMed and Scopus were searched from 2006 to August 2026 using combinations of the terms atherosclerosis, coronary artery disease, microRNA, miR, endothelial, smooth muscle, macrophage, foam cell, cholesterol efflux, antagomir and nanoparticle. The PubMed search, run in August 2026, combined title/abstract and MeSH terms using Boolean operators and was limited to records dated 2006 to 31 August 2026. The Scopus search (title, abstract and keywords; run in August 2026) was limited by year only, so its range ran from 2006 to the end of 2026. The full search strings are given in Supplementary Material S1. Reference lists of recent reviews and targeted searches for individual miRNAs and delivery approaches that emerged during the synthesis supplemented the database searches. Only articles published in English were considered.

2.3 Selection of studies

Studies with validated targets and in vivo or human data were prioritised, and earlier landmark papers were included. Primary studies were favoured if they tested a miRNA by loss-of-function, gain-of-function or pharmacological modulation in an atherosclerosis model or in human tissue, or if they reported a human cohort measurement relevant to coronary artery disease. Titles and abstracts were read and studies were selected for relevance by the author. No formal screening, duplicate removal or exclusion counts were recorded. Reviews were used for background. Studies were not excluded on the basis of the direction of effect. Selection was not exhaustive.

2.4 Data extraction and synthesis

For each primary study, the miRNA and strand, cell type or compartment, validated target, model and species, sex, diet, treatment dose, route and timing, lesion site analysed and principal outcome were recorded where reported. These data are summarised in Table 1 and organised by context in Table 2. Because the studies differ in design, results are synthesised narratively. No formal risk-of-bias assessment was performed. Gene and protein symbols follow the species convention of the cited studies (mouse in sentence case, for example Tab2; human in capitals, for example TAB2).

2.5 Clinical trial registry search

ClinicalTrials.gov was searched in August 2026 for registered studies of atherosclerosis or coronary artery disease combined with miRNA terms, and separately for registered studies of miRNA-targeting agents (CDR132L, MRG-110, cobomarsen and miravirsen). Records were screened by the author. The findings for these agents are summarised in section 11.4. Trial results were not available for all registered studies at the time of the search. The limitations of this approach are discussed in section 13.

3. PATHOBIOLOGY OF CORONARY ARTERY DISEASE IN BRIEF

Atherosclerosis begins with endothelial activation at sites of disturbed flow and lipoprotein retention in the intima (Björkegren & Lusis, 2022; Libby, 2021). Monocytes enter, differentiate into macrophages and take up modified lipoprotein to form foam cells, while smooth muscle cells migrate from the media and proliferate (Björkegren & Lusis, 2022; Libby, 2021). Over time the lesion develops a necrotic core and a fibrous cap. Plaque rupture or erosion with thrombosis causes most acute coronary events (Libby, 2021), and gradual stenosis is described as a less frequent cause (Raajasekar, 2026). One review states that vulnerable plaques have a large necrotic core, a thin fibrous cap and abundant inflammatory cells (Raajasekar, 2026), although the term is contested, because most thin-capped plaques seldom cause clinical events and plaque erosion appears to be on the rise (Libby, 2021).

The cellular composition of the lesion is more complex than this outline suggests. Single-cell transcriptomic profiling of human carotid plaques resolved 14 distinct cell populations (Depuydt et al., 2020), and combined spatial and single-cell sequencing has drawn attention to the plaque microvasculature (Bleckwehl et al., 2025). For miRNA research this means that the label “macrophage” or “smooth muscle cell” in a mechanistic study is a simplification, and that bulk plaque measurements combine contributions from many cell types and spatial niches.

Three features of this process matter for miRNAs. First, stage: early lesions are driven by monocyte supply and lipid uptake, while advanced lesions depend on efferocytosis, smooth muscle cap formation and necrotic core size. A miRNA that lowers early lesion size can destabilise advanced plaque, as miR-21 loss does in Apoe-/- mice (Chipont et al., 2019). Second, location: lesions form at predilection sites with low or disturbed shear, and miRNA effects differ between arch, root and descending aorta (section 9). Third, mouse lesions develop in the aortic root, arch and aorta of hypercholesterolaemic Apoe-/- or Ldlr-/- mice, whereas human disease affects the coronary arteries, which mouse models approximate only in part (van der Vaart et al., 2024).

The experimental models deserve a brief comment because nearly all interventional miRNA data come from them. Apoe-/- and Ldlr-/- mice have been used since the early 1990s. Apoe-/- mice are hypercholesterolaemic on a regular chow diet (total cholesterol up to 10 to 15 mM), whereas Ldlr-/- mice reach lower levels on chow (5 to 8 mM) and develop accelerated atherosclerosis on a cholesterol-enriched diet; neither strain expresses human CETP (van der Vaart et al., 2024). APOE*3-Leiden.CETP mice, developed later, appear to mirror human lipoprotein metabolism more closely and respond to standard lipid-lowering drugs (van der Vaart et al., 2024). The mouse interventional studies discussed below used Apoe-/- or Ldlr-/- animals, so findings on lipoprotein handling in particular may not transfer directly to patients. Human plaque tissue, in contrast, is usually obtained from advanced lesions at surgery, for example carotid endarterectomy specimens (Depuydt et al., 2020; Fitzsimons et al., 2020; Jin et al., 2018), so human and mouse data often describe different stages.

Sex is a further source of variation. Atherosclerosis differs between men and women in several respects, and sex is increasingly regarded as a biological variable that experimental studies should address (Man et al., 2020). Most of the miRNA intervention studies reviewed here used male animals (section 9.5).

4. miRNA BIOLOGY IN THE VESSEL WALL

The miRNA genes are transcribed and processed by Drosha and Dicer to a duplex of two strands, 5p and 3p. One strand is usually loaded into the silencing complex, and the other, the passenger strand, is described as degraded (Raajasekar, 2026), although several vascular studies show that passenger strands can be active (section 10). A miRNA binds its targets mainly through a seed sequence, which means it can regulate many genes in the same pathway and that two miRNAs sharing a seed can overlap, as proposed for mouse miR-712 and human miR-205 (Son et al., 2013). Not every miRNA follows the canonical route: miR-712 arises from pre-ribosomal RNA independently of DGCR8 (Son et al., 2013). Its proposed human counterpart, miR-205, is a canonical miRNA that shares seed homology with miR-712 and is not an orthologue produced by the same non-canonical pathway (Son et al., 2013).

Function of a miRNA is regulated at several levels beyond transcription, including biogenesis and the availability of target messenger RNAs (Gebert & MacRae, 2019). A measured change in miRNA abundance, whether in plaque or in plasma, therefore does not by itself predict a change in function.

Naming conventions are relevant to the argument of section 10. A designation such as miR-155 identifies the miRNA gene or precursor and does not say which mature strand was measured or manipulated, whereas miR-155-5p and miR-155-3p name the two strands. Many of the studies discussed here report the gene-level name, so the strand responsible for an effect is often unstated.

A miRNA's effect depends on which targets are expressed in the cell. This is the molecular basis of cell-type dependence. miR-221 and miR-222 act through p27Kip1, p57Kip2 and c-kit, and the target expression profile differs between smooth muscle and endothelial cells, which fits their opposite effects (Liu et al., 2012). Expression also responds to flow, lipids and inflammation: miR-92a depends on STAT3 under low shear and oxidised LDL (Loyer et al., 2014), and the flow-responsive factor KLF2 suppresses miR-155 in macrophages (He et al., 2015). Finally, miRNAs leave their cell of origin in vesicles and circulate (section 8), so a level measured in blood or in a lesion is a mixture of origins.

The main therapeutic tools are miRNA inhibitors and mimics. Inhibitors (anti-miRs and antagomirs) are antisense oligonucleotides that bind and sequester the mature miRNA, whereas mimics are double-stranded RNAs that restore a miRNA whose function is lost. Chemical modifications that increase nuclease resistance and target binding, such as 2'-O-methoxyethyl (Hill & Hall, 2023), locked nucleic acid and 2'-fluoro groups, are widely used for miRNA inhibitors, and the field has been reviewed from cells to the clinic (Diener et al., 2022). In the plaque studies discussed below, inhibitors were 2'-fluoro/2'-O-methoxyethyl (Rayner et al., 2011) or locked nucleic acid (Kavanagh et al., 2026; Marquart et al., 2013) oligonucleotides, or antagomirs (Bonauer et al., 2009; Loyer et al., 2014), and mimics were delivered in lipid nanoparticles (Peters et al., 2025), microparticles (Ma et al., 2016), nanoparticles (Bai et al., 2022), micelles (Chin et al., 2020), viral vectors (Lovren et al., 2012) or microbubbles (Jin et al., 2018); these carriers are described in section 11.1. The choice of chemistry, dose and route differs across these studies (section 9.5), which is one reason why results are hard to compare.

5. ENDOTHELIAL CELLS

Table 1 collects the miRNAs discussed in sections 5 to 7 and 11, with the model used and the main finding for each.

Table 1. Key miRNAs, cell types and context-specific findings in atherosclerosis and related settings.

miRNA	Cell or tissue	Target as reported	Context-specific finding	Model	Ref.
miR-155	Macrophage (haematopoietic)	Csf1r (early), Bcl6 (advanced)	Knockout enlarged lesions and raised macrophage proliferation at 12 weeks but slowed progression from 12 to 24 weeks, with a smaller necrotic core and less unengulfed apoptotic debris. The later benefit was in the aortic root, not the whole aorta.	Apoe-/- mice, high-cholesterol diet; bone marrow chimeras	(Wei et al., 2015)
miR-155	Whole-body knockout (macrophage inflammation and efflux assessed)	Socs1; cholesterol efflux	Deficiency lowered macrophage inflammation, improved efflux and reduced aortic root lesions, while the arch and descending aorta did not differ.	Apoe-/- and double knockout mice, Western diet	(Du et al., 2014)
miR-155	Macrophage	Socs1, Il-10 (downstream of KLF2)	KLF2 suppressed miR-155 in oxidised-LDL-treated macrophages; adenoviral KLF2 reduced arch lesions and miR-155 there. A study of miR-155 regulation, not of miR-155 manipulation in vivo.	Male Apoe-/- mice, high-fat diet; peritoneal macrophages	(He et al., 2015)
miR-155	Haematopoietic cells (bone marrow chimeras)	Cytokine and monocyte-subset changes	Opposite direction: miR-155-/- marrow increased aortic root lesion area by 18% after 10 weeks of diet, with more advanced lesions, more recruited macrophages, fewer regulatory T cells, more Ly6C-high monocytes and less IL-10.	Female Ldlr-/- recipients of knockout or wild-type marrow	(Donners et al., 2012)
miR-155	Human CAD (blood, plaque, urinary vesicles)	Not stated	Plasma miR-155 was lower in stable CAD (36 patients vs 17 controls, replicated in 31; and 69 patients vs 30 controls), whereas aortic lesion levels were higher in mice and humans and urinary vesicle levels were higher in unstable than in stable CAD (12 vs 12). Reviews describe conflicting results across stages and compartments.	Human cohorts; reviews	(Cao et al., 2016; Du et al., 2014; Faccini et al., 2017; Fichtlscherer et al., 2010; Fitzsimons et al., 2020; Letonja & Petrovič, 2024)
miR-155-5p	Macrophage, VSMC	Socs1	In streptozotocin-diabetic mice a locked nucleic acid inhibitor (2 mg/kg twice weekly for 6 weeks, started 2 weeks after diabetes induction) reduced lesion area, M1 macrophages and synthetic smooth muscle markers and lowered soluble MerTK; Socs1 adenovirus had similar effects.	Streptozotocin-induced diabetic male Apoe-/- mice	(Kavanagh et al., 2026)
miR-33	Macrophage, liver	Abca1 (Abcg1 in mouse)	Mixed. A 2'F/MOE anti-miR-33 (10 mg/kg weekly for 4 weeks after a switch to chow) raised HDL cholesterol 35% and cut aortic sinus lesion area 35%. A locked nucleic acid anti-miR-33 (7 mg/kg weekly for 14 weeks with continued Western diet) gave a transient HDL rise, higher triglycerides and no change in lesion size or composition.	Ldlr-/- mice	(Madrigal-Matute et al., 2013; Marquart et al., 2013; Rayner et al., 2011)
miR-122	Liver	Not extracted	A 2'-O-methoxyethyl antisense inhibitor lowered plasma cholesterol in normal and diet-induced obese mice, raised hepatic fatty-acid oxidation and improved steatosis. No atherosclerosis endpoint.	Normal and diet-induced obese mice	(Esau et al., 2006)
miR-126-5p	Endothelium	Dlk1 (Notch1 inhibitor)	Loss worsened atherosclerosis at nonpredilection sites, whereas at predilection sites disturbed flow lowers miR-126-5p and raises Dlk1. An intravenous mimic cut lesions, including when started at week 8 of 12. In human lesions miR-126-5p, not -3p, tracked with lower DLK1.	Apoe-/- mice with or without Mir126 deletion; partial carotid ligation	(Schober et al., 2014)

miRNA	Cell or tissue	Target as reported	Context-specific finding	Model	Ref.
miR-92a	Endothelium	Klf2, Klf4, Socs5; integrin alpha5 in angiogenesis	Antagomir-92a improved vessel growth in limb ischaemia and myocardial infarction. In Ldlr-/- mice it (16 mg/kg, started at week 4 of a 14-week diet) cut aortic sinus lesions 23% and gave more stable plaques; arch lesions fell significantly, descending thoracic aorta lesions much less. miR-92a was higher in low-shear regions of human carotid plaque.	Male Ldlr-/- mice; limb ischaemia and infarction models	(Bonauer et al., 2009; Loyer et al., 2014; Prus et al., 2026)
miR-181a-5p and -3p	Endothelium	Tab2 (5p), Nemo (3p)	Both strands were lower in mouse plaque and plasma and in the plasma of 20 CAD patients versus 15 controls. Mimics given for 4 weeks after 8 weeks of diet cut plaque area, and the two strands together suppressed endothelial inflammation more than either alone.	Apoe-/- mice, high-fat diet	(Su et al., 2019)
miR-146a and miR-181b	Endothelium	Traf6 (146a), importin-alpha3 (181b)	E-selectin-targeted microparticles lowered plaque size, macrophages and chemokines and raised smooth muscle and collagen; the same miRNAs in untargeted PEG/PEI nanoparticles did not reduce plaque size.	Male Apoe-/- mice, Western diet, injected biweekly for 12 weeks	(Ma et al., 2016)
miR-146a	Plaque macrophages, endothelium	Irak2 (NF-kB pathway)	Iron-oxide nanoparticles reached about 1.2% of the injected dose in plaque via scavenger receptor A. Injections twice weekly in weeks 10 to 12 cut aortic lesion area about 30% and root lesion area about 20% and raised collagen.	Apoe-/- mice, high-cholesterol diet	(Bai et al., 2022)
miR-712	Endothelium under disturbed flow	Timp3, Reck	VCAM1-targeted lipoparticles (1 mg/kg twice weekly) matched naked anti-miR-712 (5 mg/kg) without off-target silencing. miR-712 arises from pre-ribosomal RNA independently of DGCR8; miR-205 is a potential human homolog. Early-lesion model, male mice.	Mouse partial carotid ligation plus high-fat diet	(Kheirolomoom et al., 2015; Son et al., 2013)
miR-26b	Myeloid cells, whole body	Annexin A2; Mmp3, Mmp8 downstream	Whole-body loss raised aortic arch lesions 2.8-fold at 12 weeks with no change in the root; myeloid-specific loss gave 2.5-fold. The 5p strand mainly drove the cytokine rescue. Mimic nanoparticles (2 mg/kg every 3 days for 4 weeks) cut arch plaques but were given from the start of the diet.	Apoe-/- Mir26b-/- and LysM-Cre mice; human plaque ex vivo	(Peters et al., 2025)
miR-145	VSMC	Klf4 (down), myocardin (up)	Smooth-muscle-specific lentivirus given before the 12-week diet cut plaque size at three sites, enlarged the fibrous cap, reduced necrotic core, raised collagen and lowered macrophage content.	Apoe-/- mice, Western diet	(Lovren et al., 2012)
miR-145	VSMC	Klf4/5, Elk1 (down); myocardin, calponin (up), in vitro	CCR2-targeting micelles halted plaque growth in mid-stage mice; one dose in early disease cut lesion growth by up to 49%. Preprint.	Apoe-/- mice; patient-derived VSMCs	(Chin et al., 2020)
miR-143 and miR-145	VSMC	Klf4, myocardin, Elk-1	Both fall in injured or atherosclerotic vessels with dedifferentiated smooth muscle. Knockout mice show incomplete smooth muscle differentiation; levels were lower in Apoe-/- aorta and human aneurysm; overexpression reduced neointima in rat carotid injury. Loss-of-function and injury studies, not plaque treatment.	Mouse, rat, human tissue	(Cordes et al., 2009; Elia et al., 2009)
miR-21	Monocytes and macrophages; VSMC	REST feedback loop and PTEN (VSMC); monocyte survival	Stage-dependent. Loss cut early lesions by almost 30% (aortic sinus) and almost 50% (aorta), but at advanced stages lesion size was similar and plaques were less stable. In a plaque-rupture model loss raised atherothrombotic events to 93% from 57%; a mimic delivered by ultrasound-targeted microbubbles rescued the phenotype. miR-21 was lower in ruptured human fibrous caps.	Male Apoe-/-miR-21-/- mice; carotid ligation with cast; human carotid plaques	(Chipont et al., 2019; Jin et al., 2018)
miR-221 and miR-222	VSMC and endothelium	p27Kip1, p57Kip2, c-kit	Opposite effects by cell type: pro-proliferative and anti-apoptotic in VSMCs, anti-proliferative and pro-apoptotic in endothelial cells. Knockdown reduced neointima in balloon-injured rat carotid. An injury model, not atherosclerosis.	Cultured cells; rat carotid	(Liu et al., 2012; Liu et al., 2009)
miR-132	Cardiomyocyte (heart failure, not atherosclerosis)	FOXO3	Phase 1b: 28 patients with ischaemic heart failure, two infusions 4 weeks apart (0.32 to 10 mg/kg); safe, dose-dependent fall in plasma miR-132, and at 1 mg/kg or more median NT-proBNP fell 23.3% versus a 0.9% rise on placebo. HF-REVERT Phase 2: 294 patients randomised after myocardial infarction (280 analysed); primary endpoint not significantly different from placebo. No atherosclerosis endpoint.	Humans	(Bauersachs et al., 2026; Täubel et al., 2021)

Abbreviations: CAD, coronary artery disease; LNA, locked nucleic acid; MOE, 2'-O-methoxyethyl; VSMC, vascular smooth muscle cell.

Endothelial miRNAs respond to flow and lipids, and the best-characterised ones act on flow-sensitive transcription factors and inflammatory signalling. miR-92a is higher in the aortic arch than in the descending aorta, is further raised by hypercholesterolaemia in Ldlr-/- mice, and was highly expressed in low-shear regions of human carotid plaque. Its expression depends on STAT3 under low shear stress and oxidised LDL, and it represses KLF2, KLF4 and SOCS5 (Loyer et al., 2014). Blocking it with an antagomir, started at week 4 of a 14-week diet, reduced endothelial inflammation, cut aortic sinus lesions by 23% and produced more stable plaques. The same drug direction improves vessel growth in ischaemic limb and myocardium, where the validated target is integrin alpha5 (Bonauer et al., 2009), so the effect depends on the tissue and disease being treated.

The concept of atheromiRs, endothelial miRNAs that are selectively regulated by shear stress and oxidised LDL, comes from the miR-92a work: profiling in human endothelial cells identified miR-92a as a candidate, and its expression was

preferentially raised by the combination of low shear stress and oxidised LDL (Loyer et al., 2014).

miR-126-5p works the other way: it supports endothelial proliferation and repair through Dlk1, and its loss worsened atherosclerosis at nonpredilection sites (Schober et al., 2014). Disturbed flow lowers it at predilection sites, and an intravenous mimic cut lesions. The 181 family adds inflammatory control: miR-181a-5p and -3p target Tab2 and Nemo, were low in mouse plaque and in the plasma of 20 patients with coronary disease versus 15 controls, and mimics reduced plaque area (Su et al., 2019). miR-146a and miR-181b acted through Traf6 and importin-alpha3 when delivered in E-selectin-targeted microparticles (Ma et al., 2016). miR-712 rises under disturbed flow, represses Timp3 and Reck, and promotes endothelial inflammation (Kheirolomoom et al., 2015; Son et al., 2013). Finally, miR-221/222 slow endothelial proliferation and migration and promote apoptosis, the opposite of their effect in smooth muscle (Liu et al., 2012).

Delivery studies show that endothelial miRNAs can be reached in plaque. VCAM1-targeted lipoparticles carrying anti-miR-712 matched the effect of a five-fold higher dose of the naked inhibitor and avoided silencing in other organs (Kheirolomoom et al., 2015), and E-selectin-targeted microparticles carrying miR-146a and miR-181b reduced plaque size and macrophage content, which untargeted nanoparticles carrying the same miRNAs did not (Ma et al., 2016). These results link the biology of this section to the delivery questions of section 11, because the surface markers that make targeting possible depend on endothelial activation.

Taken together, endothelial miRNAs divide into flow-sensitive ones (miR-92a, miR-712, miR-126-5p) and inflammation-limiting ones (miR-181 family, miR-146a), and their effects often differ by vascular bed (section 9).

Three limits apply to the endothelial evidence. First, most interventional data are from male mice, and the miR-712 study used an early-lesion model (Kheirolomoom et al., 2015). Second, the vascular bed is often reported for one site only, although miR-92a and miR-126-5p show site-dependent effects (section 9.3). Third, the human evidence is correlative and small: miR-181a-5p and -3p in plasma from 20 patients and 15 controls (Su et al., 2019), miR-92a in low-shear regions of human carotid plaque (Loyer et al., 2014) and miR-126-5p in human lesions (Schober et al., 2014). None of these shows that changing the miRNA in humans alters the lesion.

6. VASCULAR SMOOTH MUSCLE CELLS

The central question for smooth muscle is the switch between a contractile and a synthetic, proliferative state, and the miR-143/145 cluster governs it. In Cordes et al. (2009) both miRNAs were downregulated in injured or atherosclerotic vessels containing proliferating, less differentiated smooth muscle cells. miR-145 was necessary for myocardin-induced reprogramming of fibroblasts into smooth muscle and sufficient to induce differentiation of neural crest stem cells, and together with miR-143 it targets Klf4, myocardin and Elk-1 to promote differentiation and repress proliferation. Klf4 and myocardin act in opposition: Klf4 represses smooth muscle gene expression driven by myocardin and serum response factor, so repression of Klf4 by miR-145 relieves this brake, while myocardin and serum response factor in turn drive miR-143/145 transcription, a loop that reinforces the contractile state (Cordes et al., 2009; Elia et al., 2009). Elia et al. (2009) added that knockout mice show incomplete smooth muscle differentiation, that levels are lower in Apoe-/- aorta and human aortic aneurysm, and that overexpression reduced neointima in rat carotid injury. Both are mechanistic and loss-of-function studies. The treatment evidence comes from Lovren et al. (2012), where a smooth-muscle-specific miR-145 lentivirus given before the 12-week diet cut plaque size at three sites, enlarged the fibrous cap and lowered macrophage content, and from Chin et al. (2020; a preprint that has not been peer reviewed), where CCR2-targeting micelles carrying miR-145 halted plaque growth in mid-stage mice.

Other smooth muscle miRNAs show how context cuts both ways. miR-221/222 promote proliferation, migration and survival of smooth muscle cells through p27Kip1 and p57Kip2, and knockdown reduced neointima after balloon injury in rats, an injury model (Liu et al., 2012; Liu et al., 2009). miR-21 supports smooth muscle proliferation and survival: in a plaque-rupture model its loss reduced proliferation, increased apoptosis and raised rupture, through a REST feedback loop and PTEN (Jin et al., 2018). In diabetic mice miR-155-5p promoted a synthetic smooth muscle phenotype together with Socs1 suppression (Kavanagh et al., 2026).

Human data on smooth muscle miRNAs are limited and indirect. Plasma miR-145 was lower in patients with stable coronary artery disease than in controls in two cohorts (Faccini et al., 2017; Fichtlscherer et al., 2010), which is in the direction expected if contractile smooth muscle is lost, but plasma levels derive from many tissues and do not show that vessel-wall miR-145 is reduced (section 12). Single-cell sequencing of human plaques resolves multiple cell populations (Depuydt et al., 2020), whereas the smooth muscle studies in Table 1 manipulated or measured bulk smooth muscle cells, so effects on individual smooth muscle states remain unknown.

The point for plaque stability is that a miRNA that drives proliferation can be harmful when it enlarges the lesion but helpful when it thickens the fibrous cap, which is why the same intervention can look opposite in early and advanced disease.

7. MACROPHAGES AND LIPID HANDLING

Macrophage miRNAs control inflammation, monocyte supply, efferocytosis and cholesterol efflux. miR-155 is the most studied and the least settled (section 9). Its macrophage mechanisms include Csf1r early and Bcl6 in advanced lesions (Wei et al., 2015), Socs1 and efflux (Du et al., 2014), and Socs1 and MerTK shedding in diabetes (Kavanagh et al., 2026). KLF2 suppresses miR-155 in oxLDL-treated macrophages, lowering MCP-1 and IL-6 (He et al., 2015). miR-21 sustains Ly-6C-low monocyte survival and early lesion growth but protects advanced plaque stability through efferocytosis (Chipont et al., 2019). miR-26b acts through Annexin A2: whole-body loss raised arch lesions 2.8-fold, with more collagen, smooth muscle and necrotic core and fewer macrophages, and a mimic given in lipid nanoparticles cut arch plaques when started with the diet (Peters et al., 2025). miR-146a delivered on iron-oxide nanoparticles to scavenger receptor A reduced lesions through Irak2 (Bai et al., 2022).

Efferocytosis, the clearance of apoptotic cells, links several of these findings to plaque stability. In bone marrow chimeras the late benefit of miR-155 loss was accompanied by a smaller necrotic core and less unengulfed apoptotic debris (Wei et al., 2015); miR-21 deficiency reduced early lesions but left advanced plaques equal in size and less stable, with larger necrotic cores (Chipont et al., 2019); and in diabetic mice inhibition of miR-155-5p lowered soluble MerTK, a marker of better efferocytosis (Kavanagh et al., 2026). A large necrotic core is a defining feature of the plaques described as vulnerable (Raajasekar, 2026), although not every such plaque causes events (Libby, 2021), so studies that report only total lesion area can miss a change that may matter for events.

For lipid handling, miR-33 targets Abca1 and Abcg1. In Rayner et al. (2011) anti-miR-33 raised HDL by 35% and reduced aortic sinus lesion area by 35% in Ldlr-/- mice after a diet switch, and it enhanced ABCA1 expression and cholesterol removal in plaque macrophages directly. Marquart et al. (2013) found no change in lesions with a different design. miR-122 is a liver miRNA, and its inhibition lowered plasma cholesterol in mice (Esau et al., 2006), but no atherosclerosis outcome was tested. The effect arose from hepatic lipid metabolism, including higher hepatic fatty-acid oxidation, and not from an action on plaque macrophages. It sits in this section as a lipid example rather than a plaque one.

miR-26b illustrates the value of cell-specific tools. It was about five-fold more abundant in human atherosclerotic plaques than in healthy vessels, and its loss produced a more advanced plaque

phenotype in the aortic arch, with more collagen, smooth muscle cells and necrotic core and relatively fewer macrophages; the phenotype was also seen after 4 weeks of Western diet (Peters et al., 2025). Because myeloid-specific deletion reproduced the arch effect, and macrophages from knockout mice secreted more proinflammatory cytokines that mimic-loaded nanoparticles rescued, the effect is attributed to myeloid cells, with Annexin A2 identified as one target (Peters et al., 2025).

The cell-type sections together show a pattern that section 9 develops: each miRNA acts in more than one cell, at more than one stage, and at more than one site, and the net plaque result depends on which combination dominates.

8. INTERCELLULAR CROSSTALK THROUGH EXTRACELLULAR VESICLES

Cells in the plaque do not act alone. Extracellular vesicles, which include exosomes, microvesicles and apoptotic bodies, carry miRNAs between endothelial cells, smooth muscle cells and macrophages and can change the recipient cell's behaviour (Chistiakov et al., 2015; Paone et al., 2019; Pfeifer et al., 2015). This adds a further source of context to section 9, because the effect of a miRNA depends on which cell packaged it, what stimulus that cell received, and which cell took it up.

Endothelial cells also release vesicles. Apoptotic bodies and other vesicles derived from endothelial cells have been linked to the progression of atherosclerosis (Paone et al., 2019).

Macrophage vesicles are the best documented. Vesicles from oxidised-LDL-treated macrophages, and vesicles from blood mononuclear cells of patients with atherosclerosis, were enriched in miR-503-5p. The miRNA moved to co-cultured human coronary artery endothelial and smooth muscle cells, where it reduced endothelial proliferation and angiogenesis, increased smooth muscle proliferation and migration, and lowered Smad1, Smad2 and Smad7. Lentiviral inhibition of miR-503-5p reduced aortic lesions in atherosclerotic mice (Wang et al., 2021). In a second study, macrophage-derived exosomal miR-4532 injured endothelial cells by targeting SP1 and NF-kB p65 signalling, raising ET-1, ICAM-1 and VCAM-1 and lowering eNOS, and either a miR-4532 inhibitor or the exosome inhibitor GW4869 reversed the injury (Liu et al., 2022). Both studies were largely in vitro.

The stimulus changes the cargo. Macrophages exposed to nicotine released exosomes enriched in miR-21-3p, which targets PTEN and raised smooth muscle migration and proliferation. Nicotine given to male Apoe-/- mice on a high-fat diet for 12 weeks increased lesions and plaque exosome retention (Zhu et al., 2019). This is the 3p strand of miR-21, and it contrasts with the miR-21 studies in sections 6 and 9, which concern the whole locus or the 5p strand in a different cell type, so the strand and the source cell both matter.

Vesicles also carry disease context between tissues. Exosomes from vascular smooth muscle cells of diabetic donors, but not non-diabetic donors, raised endothelial ICAM-1, monocyte adhesion and inflammatory monocyte polarisation in a miR-221/222-dependent way, and intravenous injection of these vesicles into Apoe-/- mice on a Western diet for 6 weeks increased plaque (Yu et al., 2023). In the cell studies of Liu et al. (2012), miR-221/222 acted differently in endothelium and smooth muscle; here the diabetic smooth muscle cell exports them as a pro-atherogenic signal. Adipose tissue from diet-induced obese mice released exosomes containing miR-132/212, which promoted endothelial apoptosis through Gna12 and smooth muscle proliferation and migration through PTEN and worsened atherosclerosis, while melatonin lowered the exosomal miR-132/212 (Guo et al., 2024). The miR-132 locus is the target of CDR132L in heart failure (section 11), so the same locus has an opposite-direction rationale in another organ and another disease, and no atherosclerosis endpoint has been tested for the drug.

Three cautions apply. First, vesicle experiments often use supraphysiological doses, and how much miRNA reaches a recipient cell in a plaque is largely unknown. Second, every study above links a vesicle miRNA to an effect in one direction, but none tested the same miRNA across several sources, cell types and stages in one design, which is exactly the comparison that the context framework needs. Third, vesicle isolation and characterisation differ between studies (for example ultracentrifugation, size-exclusion chromatography or precipitation), and preparations may contain co-isolated lipoproteins or RNA-binding proteins that also carry miRNAs, which limits comparison across studies. For therapy, vesicles also raise the possibility of delivering miRNAs to plaque, and of blocking harmful vesicle cargo, but this remains at the cell and mouse stage.

The vesicle literature also bridges to the circulating biomarker problem of section 12. Urinary extracellular vesicles from patients with unstable coronary artery disease (n = 12) carried more miR-155 than those from patients with stable disease (n = 12), although the overall concentration of vesicles was lower in unstable disease (Fitzsimons et al., 2020). Whether such differences reflect plaque biology, systemic inflammation or renal handling is unknown.

9. WHY EFFECTS CONFLICT: A CONTEXT FRAMEWORK

9.1 One miRNA, opposite results

The clearest illustration of the problem is miR-155. Three bone marrow or whole-body knockout studies in mice, each carefully done, do not agree. Donners and colleagues transplanted miR-155-deficient marrow into female Ldlr-/- recipients and found an 18% larger aortic root lesion after 10 weeks of high-cholesterol diet, with more advanced plaques, more newly recruited macrophages, fewer regulatory T cells, more Ly-6C-high monocytes and less IL-10 (Donners et al., 2012). Du and colleagues, using whole-body deficiency in Apoe-/- mice, found less macrophage inflammation, better cholesterol efflux and smaller aortic root lesions, while the arch and descending aorta did not differ (Du et al., 2014). Wei and colleagues, using Apoe-/- bone marrow chimeras, found that loss of miR-155 enlarged lesions and raised macrophage proliferation at 12 weeks, yet slowed progression between 12 and 24 weeks, with a smaller necrotic core, and that this late benefit appeared in the aortic root but not in the whole aorta (Wei et al., 2015). A fourth study, in diabetic Apoe-/- mice, found that a locked nucleic acid inhibitor of miR-155-5p reduced lesion area, M1 macrophages and synthetic smooth muscle markers (Kavanagh et al., 2026). Figure 1 compares these studies.



Figure 1. Effect of miR-155 loss or inhibition on lesion size in four mouse studies (Donners et al., 2012; Du et al., 2014; Kavanagh et al., 2026; Wei et al., 2015). Triangles show the direction reported by each study; "not reported" means that the study summary does not give a result for that column. The studies differ in model, sex, cell source, diet duration and lesion site as well as stage, so the columns cannot be read as a controlled comparison.

Experimental regression adds another angle. In Apoe-/- mice, miR-155 expression in the aorta rose on a 1% cholesterol diet and fell when atherosclerosis regressed after dietary supplementation with conjugated linoleic acid, and in human THP-1 macrophages a miR-155 mimic lowered the anti-inflammatory proteins BCL-6 and phosphorylated STAT3 (Fitzsimons et al., 2020). These findings fit an inflammatory role for miR-155 in established lesions, but they describe regulation and in vitro function, not the effect of removing miR-155 in vivo.

The human data add a further layer. Circulating miR-155 was lower in patients with stable coronary artery disease than in controls (Faccini et al., 2017; Fichtlscherer et al., 2010), whereas Du and colleagues reported higher miR-155 in human aortic lesions (Du et al., 2014). Urinary vesicles from patients with unstable disease carried more miR-155 than those from patients with stable disease (Fitzsimons et al., 2020). Reviews have noted this conflict and suggested that disease stage or animal model may explain it (Cao et al., 2016; Ma et al., 2013). That suggestion is correct but incomplete, because stage and model are only two of several variables that differ between the studies. The sections below set out the variables that the primary papers allow to be separated and point to where the evidence cannot yet distinguish them.

9.2 Disease stage

Stage is the best-supported source of reversal. In Wei et al. (2015) the same genetic change worsened early disease and improved late disease, and the authors tied this to different targets: Csf1r early and Bcl6 in advanced lesions. Expression of miR-155 rose in lesional macrophages between 12 and 24 weeks of diet; early on it restrained macrophage proliferation by suppressing Csf1r, whereas later it impaired efferocytosis by suppressing Bcl6 and thereby activating RhoA (Wei et al., 2015). miR-21 shows the same pattern from a different angle. In Apoe-/- mice, loss of miR-21 limited early lesions by almost 30% in the aortic sinus and almost 50% in the aorta, through fewer Ly-6C-low monocytes and more macrophage apoptosis. miR-21 was more abundant in circulating Ly-6C-low than in Ly-6C-high monocytes, which fits the effect of its loss on that subset (Chipont et al., 2019). At later stages lesion size was similar, but plaques were less stable, with larger necrotic cores, attributed to impaired efferocytosis (Chipont et al., 2019). In a carotid plaque-rupture model, miR-21 deficiency raised atherothrombotic events to 93% from 57%, and a miR-21 mimic delivered locally rescued the phenotype (Jin et al., 2018). A miRNA can therefore be harmful when lesions begin and protective when they have matured, which means that the same inhibitor could help or harm depending on when a patient is treated.

9.3 Vascular bed

Lesions at different sites respond differently, and this is often overlooked because many studies report only one site. miR-155 loss helped the aortic root but not the arch or descending aorta in Du et al. (2014), and the late benefit in Wei et al. (2015) was in the root but not the whole aorta. For miR-26b the pattern reversed: whole-body loss raised arch lesions 2.8-fold at 12 weeks with no change in the aortic root (Peters et al., 2025). Antagomir-92a reduced lesions significantly in the aortic arch but much less in the descending thoracic aorta, while aortic sinus lesions fell by 23% (Loyer et al., 2014). For miR-126-5p, loss worsened atherosclerosis at nonpredilection sites, whereas at predilection sites disturbed flow lowers miR-126-5p and raises its target Dlk1 (Schober et al., 2014). These differences fit a role for local haemodynamics: miR-92a was higher in the arch and in low-shear regions of human carotid plaque (Loyer et al., 2014), and KLF2, a flow-responsive factor, suppressed miR-155 in macrophages, with adenoviral KLF2 lowering arch lesions (He et al., 2015). The practical consequence is that a result from one site cannot be assumed to hold at another, and coronary arteries have their own haemodynamics that mouse aortic sites only approximate.

9.4 Cell type and how it is manipulated

A miRNA that is expressed in several cell types can act in opposite ways in each. miR-221 and miR-222 promote proliferation and migration and block apoptosis in smooth muscle cells, but do the reverse in endothelial cells, through p27Kip1, p57Kip2 and c-kit (Liu et al., 2012). That work used a balloon-injury model, so it shows the principle rather than a plaque effect. Manipulation matters as well. Whole-body deletion of miR-26b raised arch lesions 2.8-fold, myeloid-specific deletion raised them 2.5-fold, yet only the whole-body knockout changed plaque composition and circulating leukocytes (Peters et al., 2025). Donners et al. (2012) altered only haematopoietic cells, and Du et al. (2014) altered every cell. Part of the miR-155 disagreement may therefore come from where the gene was removed, not only from when or how long.

9.5 Model, sex and treatment design

Studies differ in model, sex, diet length and timing, often all at once. The miR-155 studies above used Ldlr-/- or Apoe-/- mice, female or male animals, and diets of 10 to 24 weeks. miR-33 is a clear case of design, not biology, driving the result. Anti-miR-33

given to Ldlr-/- mice after a switch to chow, as a 2'F/MOE oligonucleotide at 10 mg/kg subcutaneously for 4 weeks, raised HDL cholesterol by 35% and reduced aortic sinus lesion area by 35% (Rayner et al., 2011). The same strategy given as a locked nucleic acid at 7 mg/kg intraperitoneally for 14 weeks, with a continued Western diet, produced only a transient HDL rise, higher triglycerides and no change in lesion size or composition (Marquart et al., 2013). These studies differ in chemistry, dose, route, duration, diet and treatment of established versus developing plaque, so neither is simply right. Treatment timing also separates the delivery studies reviewed in section 11: miR-145 lentivirus, miR-26b nanoparticles and E-selectin-targeted microparticles were given with the diet, whereas miR-146a nanoparticles, miR-126-5p mimic and miR-181a mimics were started after lesions had formed and run for 3 to 4 weeks, all in mice.

Sex is rarely a studied variable. Among the interventional studies in Table 1, those that state the sex of the animals used males, for example (Kavanagh et al., 2026; Kheirolomoom et al., 2015; Marquart et al., 2013), or, in the miR-155 marrow transplant, female recipients (Donners et al., 2012), and none compares the two. Because atherosclerosis itself differs between men and women (Man et al., 2020), a miRNA effect established in one sex cannot be assumed to hold in the other.

9.6 Comorbidity and sampling compartment

Diabetes changes the miR-155 story. In streptozotocin-diabetic Apoe-/- mice, vascular miR-155-5p rose with lesion size and fell with Socs1, and inhibition lowered lesions and improved efferocytosis, as indicated by lower soluble MerTK (Kavanagh et al., 2026). That study used male mice only, and its authors list this as a limitation. Sex and diabetes may matter in humans. In the cohorts of Fichtlscherer and colleagues, circulating miR-155 was higher in women than in men in the validation cohort and was inversely related to age, and diabetes was associated with lower levels of some vascular miRNAs, although among patients with coronary disease only a trend toward lower miR-145 remained (Fichtlscherer et al., 2010). The study was not designed to test either factor. Sampling site matters too. Circulating miR-155 is lower in coronary disease while lesion miR-155 is higher, so a plasma assay and a plaque assay answer different questions (see section 12).

9.7 What the evidence cannot yet separate

In nearly every conflict above, several variables change together, so the primary papers cannot assign the cause. Donners et al. (2012) and Du et al. (2014) differ in model, sex, diet, cell source and lesion site at once. The strongest inferences come from the few studies that vary one factor internally: Wei et al. (2015) on stage, Peters et al. (2025) on whole-body versus myeloid deletion, Chipont et al. (2019) on early versus advanced lesions. A related risk is selective citation. A recent review presents miR-33 inhibition as having dual benefit on cholesterol and inflammation without mentioning the null Ldlr-/- result (Raajasekar, 2026), which is the kind of omission that a context framework is meant to prevent.

It is proposed here that future studies report, at minimum, the model, sex, diet and treatment timing, the lesion sites analysed, the site of manipulation (whole-body, cell-specific or bone marrow), the strand tested (section 10), the comorbidity present and the sampling compartment, and that conclusions be limited to the combination actually tested. Table 2 summarises these variables, with an example study for each, and Figure 2 shows them schematically.

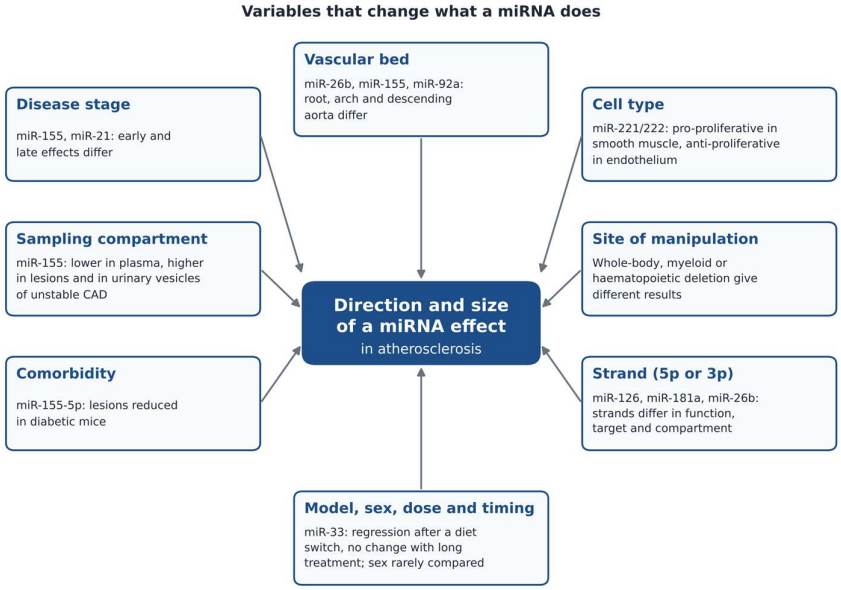

Figure 2. Context variables that change the direction or size of a miRNA effect in atherosclerosis, each with an example from the studies reviewed (see Table 2 for references).

Table 2. Context variables that change the direction or size of a miRNA effect, with example studies.

Variable	Example	What changed	Ref.
Disease stage	miR-155; miR-21	Loss of miR-155 enlarged early lesions but slowed late progression; loss of miR-21 cut early lesions but left advanced plaques less stable	(Chipont et al., 2019; Wei et al., 2015)
Vascular bed	miR-26b; miR-155; miR-92a	Effects at the aortic root, arch and descending aorta differed within the same study	(Du et al., 2014; Loyer et al., 2014; Peters et al., 2025)
Cell type	miR-221/222	Pro-proliferative in smooth muscle, anti-proliferative in endothelium	(Liu et al., 2012)

Variable	Example	What changed	Ref.
Site of manipulation	miR-26b; miR-155	Whole-body versus myeloid-specific deletion; haematopoietic versus whole-body deficiency	(Donners et al., 2012; Du et al., 2014; Peters et al., 2025)
Strand	miR-126; miR-181a; miR-26b	5p and 3p differed in function, target and compartment	(Peters et al., 2025; Schober et al., 2014; Su et al., 2019)
Model, sex, dose and timing	miR-33	Lesion regression after a diet switch versus no change with long-term treatment on diet; sex was compared in none of the studies	(Marquart et al., 2013; Rayner et al., 2011)
Comorbidity	miR-155-5p	Inhibition reduced lesions and improved efferocytosis in diabetic mice	(Kavanagh et al., 2026)
Sampling compartment	miR-155	Lower in plasma, higher in lesions and in urinary vesicles of unstable CAD	(Du et al., 2014; Fichtlscherer et al., 2010; Fitzsimons et al., 2020)

10. STRAND-SPECIFIC BIOLOGY (5P VERSUS 3P)

A miRNA duplex yields two mature strands, and textbook accounts say that one, the guide strand, is loaded into the silencing complex while the other, the passenger strand, is degraded (Raajasekar, 2026). The vascular literature shows that this rule is too simple, and that many reports which name a miRNA without a strand mix two different molecules.

The clearest case is miR-126. Schober and colleagues called miR-126-5p the passenger strand, yet showed that it, not miR-126-3p, drives endothelial proliferation and repair through the Notch1 inhibitor Dlk1 (Schober et al., 2014). Loss of miR-126-5p worsened atherosclerosis at nonpredilection sites, an intravenous mimic cut lesions even when started at week 8 of a 12-week diet, and in human lesions miR-126-5p, not miR-126-3p, tracked with lower DLK1 and more endothelial proliferation. The same paper cites a report that miR-126-3p carried by apoptotic-cell microparticles limits atherosclerosis, so the two strands act through different routes and in different compartments. A recent review table lists miR-126-5p as promoting inflammation (Wang et al., 2025), which does not match what the primary study reports and illustrates how strand-level errors enter secondary sources.

The two strands can also cooperate. miR-181a-5p and miR-181a-3p were both lower in mouse plaque and plasma and in the plasma of 20 patients with coronary artery disease than in 15 controls. The strands act on different targets, Tab2 for 5p and Nemo for 3p, and together they suppressed endothelial inflammation more than either alone. Mimics given for 4 weeks after 8 weeks of diet reduced plaque area (Su et al., 2019). Su and colleagues describe miR-181a-3p as the passenger strand of miR-181a-5p; restoring either strand retarded plaque formation without affecting lipid metabolism, decreased proinflammatory gene expression and reduced the infiltration of macrophages, leukocytes and T cells into lesions (Su et al., 2019). For miR-26b, the 5p strand mainly drove the cytokine rescue and the 3p strand did so only partly (Peters et al., 2025).

The strand question also affects how earlier studies should be read. Whole-gene knockouts of miR-155 remove both strands and therefore cannot assign a phenotype to either (Donners et al., 2012; Du et al., 2014; Wei et al., 2015), whereas the diabetic-mouse study used a locked nucleic acid inhibitor directed at miR-155-5p specifically (Kavanagh et al., 2026). A difference in strand targeting is therefore one more candidate explanation for discordant results that has seldom been examined.

Three points follow for a clinician or a trialist. First, a mimic or inhibitor should name its strand, because a 5p inhibitor and a 3p inhibitor are different drugs. Second, a passenger strand in a database is not evidence of an inactive strand, so strand choice should come from functional tests, as in these studies. Third, biogenesis can also be atypical: miR-712 arises from pre-ribosomal RNA by a route independent of DGCR8, and its proposed human homolog miR-205 is a different molecule (Son et al., 2013).

A limit applies. Few of the primary studies in Table 1 tested both strands head to head. The evidence for strand-specific function is therefore a handful of well-characterised cases, not a general rule, and the strand question remains open for most vascular miRNAs.

11. THERAPEUTIC TARGETING AND THE TRANSLATION GAP

11.1 What the preclinical work shows

In mice, miRNA mimics and inhibitors alter plaque, but nearly every success depends on how the molecule is delivered and when it is given. Naked oligonucleotides reach the liver and other organs, which is why several groups designed targeted carriers. Lipoparticles carrying anti-miR-712 and decorated with a VCAM1-binding peptide matched the effect of naked anti-miR-712 at one fifth of the dose (1 mg/kg twice weekly versus 5 mg/kg) and avoided off-target silencing in other organs (Kheirolomoom et al., 2015). The particles carried roughly 1,400 anti-miR-712 molecules with a loading efficiency above 95%, and the targeting peptide was VHPK (Kheirolomoom et al., 2015). E-selectin-targeted microparticles carrying miR-146a and miR-181b lowered plaque size, macrophages and chemokines and raised smooth muscle and collagen, while the same miRNAs in nanoparticles without targeting did not reduce plaque size (Ma et al., 2016). Iron-oxide nanoparticles carrying miR-146a and aimed at scavenger receptor A reached about 1.2% of the injected dose in plaques, and injections twice weekly in weeks 10 to 12 cut aortic lesion area about 30% and root lesion area about 20% (Bai et al., 2022). CCR2-targeting micelles carrying miR-145 halted plaque growth in mid-stage mice (Chin et al., 2020, a preprint that has not been peer reviewed), and a smooth-muscle-specific lentivirus for miR-145 enlarged the fibrous cap (Lovren et al., 2012). Local delivery is also possible: a miR-21 mimic given into carotid plaque by ultrasound-targeted microbubbles rescued a rupture-prone phenotype in knockout mice (Jin et al., 2018).

11.2 Timing, models and what was actually tested

These studies are encouraging but narrow. Several were preventive, with treatment starting alongside the diet (miR-145 lentivirus, miR-26b nanoparticles, E-selectin microparticles), which does not model a patient with established disease. Those that began after lesions had formed (miR-146a nanoparticles, miR-126-5p mimic, miR-181a mimics) treated for 3 to 4 weeks, all in mice. Most used male animals, and the miR-712 study used an early-lesion model with male mice only. The contrast between the two miR-33 studies in section 9 shows how much a result can shift with chemistry, route, dose and timing. A caution also applies to species: miR-712 is a mouse miRNA, and its proposed human homolog, miR-205, rests on shared seed sequence and cell data (Son et al., 2013).

11.3 Strand, cell type and stage as design constraints

The context framework of section 9 turns into design rules. A drug must name its strand (section 10). It must reach the cell type in which the effect is wanted, because miR-221/222 act in opposite directions in smooth muscle and endothelium (Liu et al., 2012). And it must be given at a stage when the effect is beneficial, since miR-21 loss helps early lesions but destabilises advanced ones (Chipont et al., 2019; Jin et al., 2018).

11.4 What has reached patients

The one miRNA programme with substantial human data targets heart failure, not plaque. CDR132L, an antisense inhibitor of miR-132, was tested in a first-in-human Phase 1b study of 28 patients with chronic ischaemic heart failure, in two intravenous infusions 4 weeks apart at 0.32 to 10 mg/kg. It was safe and well tolerated, lowered plasma miR-132 in a dose-dependent way, and at 1 mg/kg or more produced a median NT-proBNP fall of 23.3% against a 0.9% rise on placebo (Täubel et al., 2021). The Phase 2 HF-REVERT trial planned 280 patients with ejection fraction of 45% or less after acute myocardial infarction, giving 5 or 10 mg/kg in three doses 28 days apart, with left ventricular end-systolic volume index as the primary endpoint (Bauersachs et al., 2024). The trial has since been reported: 294 patients were randomised and 280 analysed, CDR132L was well tolerated, and the primary endpoint did not differ significantly from placebo at either dose, nor did left ventricular ejection fraction, global longitudinal strain or NT-proBNP; exploratory analyses suggested possible benefit in patients with advanced adverse remodelling at baseline (Bauersachs et al., 2026). Further CDR132L trials are registered in heart failure with preserved or mildly reduced ejection fraction and in a subcutaneous formulation. Other miRNA-targeting agents were registered in other conditions: MRG-110, an inhibitor of miR-92a, for wound healing, cobomarsen, an inhibitor of miR-155, for cutaneous T-cell lymphoma, and miravirsen, an inhibitor of miR-122, for hepatitis C, and none was registered for atherosclerosis or coronary artery disease (ClinicalTrials.gov, 2026). An early antisense study also showed that inhibiting miR-122 lowers plasma cholesterol in mice (Esau et al., 2006).

Searches of ClinicalTrials.gov in August 2026 (section 2.5; ClinicalTrials.gov, 2026) found no registered trial of a miRNA-targeting drug for atherosclerosis or coronary artery disease. The registered studies in these conditions are observational biomarker studies or unrelated drug and behavioural trials. Figure 3 contrasts what has been tested in plaque and in heart failure.

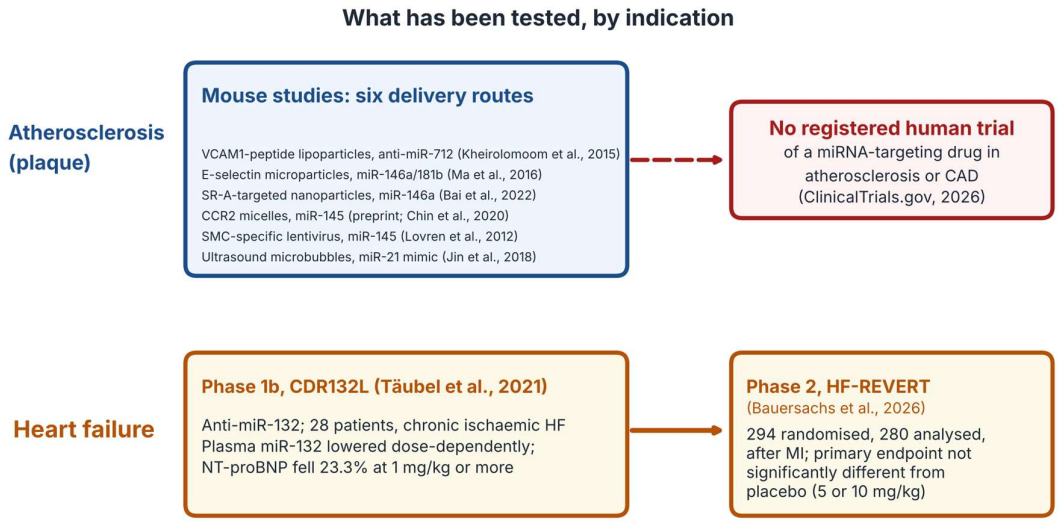

Figure 3. miRNA therapeutics by indication. In atherosclerosis, delivery to plaque has been shown only in mice (Bai et al., 2022; Chin et al., 2020; Jin et al., 2018; Kheirolomoom et al., 2015; Lovren et al., 2012; Ma et al., 2016), and no registered human trial of a miRNA-targeting drug was found (ClinicalTrials.gov, 2026). In heart failure, the miR-132 inhibitor CDR132L has completed a Phase 1b study (Täubel et al., 2021), and the Phase 2 HF-REVERT trial has reported no significant difference from placebo in its primary endpoint (Bauersachs et al., 2026). MI, myocardial infarction; SR-A, scavenger receptor A; SMC, smooth muscle cell.

11.5 Why the gap exists

Three features explain much of it, and they follow from the evidence above. First, CDR132L has a plasma marker of target engagement and a systemic target in the heart, and it could be dosed intravenously. Plaque miRNAs have no equivalent marker, and the carriers that reach plaque in mice have not been tested in humans. Second, the preclinical plaque studies are heterogeneous in model, sex, timing and strand, so there is no consensus target to carry forward. Third, atherosclerosis develops over decades and its clinical endpoints are slow, so a short trial needs an imaging or biomarker endpoint that the miRNA field has not yet established. These are reasons to design the first plaque trials around a context-defined population, not to abandon the approach.

11.6 Implications for a first plaque trial

The framework suggests four design requirements. The first is a defined context: patients with established disease, a stated vascular territory and a known comorbidity profile, because the clearest signal for miR-155-5p inhibition comes from diabetic mice (Kavanagh et al., 2026) and the effects of miR-21 and miR-155 manipulation depend on stage (Chipont et al., 2019; Wei et al., 2015). The second is a named strand and a delivery system with access to the target cell, for which scavenger receptor A, VCAM1, E-selectin and CCR2 have each been used as targeting handles in mice (Bai et al., 2022; Chin et al., 2020; Kheirolomoom et al., 2015; Ma et al., 2016). The third is a pharmacodynamic marker of target engagement, the feature that made CDR132L testable in heart failure (Täubel et al., 2021). The fourth is an endpoint that fits the pace of the disease: serial imaging of plaque volume and composition has been used to follow regression (Dawson et al., 2022), and inflammatory biomarkers such as high-sensitivity C-reactive protein identify patients with residual inflammatory risk who might be enrolled (Ridker et al., 2023). These requirements are demanding, but each follows from a specific result in the preclinical literature, which makes them more useful than a general call for further research.

12. CIRCULATING miRNAS IN CAD: USES AND LIMITS

Circulating miRNAs are attractive because blood is easy to sample, and several studies report differences between patients with coronary artery disease and controls. Fichtlscherer and colleagues found that plasma miR-155 and the smooth-muscle-enriched miR-145 were lower in 36 patients with stable coronary disease than in 17 healthy volunteers, and replicated this in a second cohort of 31 patients (Fichtlscherer et al., 2010). Faccini and colleagues measured miR-145, miR-155, miR-92a and let-7c in 69 patients and 30 controls and found lower let-7c, miR-145 and miR-155 in patients (Faccini et al., 2017).

Extracellular vesicles offer a different compartment. In a small study, miR-155 was higher in urinary vesicles from 12 patients with unstable coronary artery disease than from 12 with stable disease, whereas plasma studies of stable disease report lower miR-155 (Faccini et al., 2017; Fichtlscherer et al., 2010; Fitzsimons et al., 2020). The comparison involves different fluids, populations and disease categories, so it cannot be read as a contradiction, but it shows how compartment and clinical stage change the apparent direction.

The diagnostic value is modest. In Faccini et al. (2017) the area under the ROC curve was 0.654 for let-7c, 0.620 for miR-155 ($p = 0.056$) and 0.670 for miR-145, with sensitivities and specificities between about 59% and 78% at the chosen cut-offs, while miR-92a had an AUC of 0.520 and was not specific. Combining let-7c, miR-145 and miR-155 raised the AUC to 0.708. These values are well below what would justify clinical use on their own.

Context limits the signal in the same way it limits the mechanistic results of section 9. Fichtlscherer et al. (2010) found only a trend toward lower miR-145 in coronary disease patients with diabetes than in those without, and that statin treatment was associated with lower vascular miRNAs, including miR-155, though only miR-17 stayed significantly different when only patients with coronary disease were compared by statin use. Sex, diabetes and drug treatment therefore change circulating levels, so a case-control difference can reflect treatment or comorbidity as much as plaque. The direction of the miR-155 result also depends on the compartment: circulating levels are lower in coronary disease while lesion levels rose in Du et al. (2014), and reviews list both increases and decreases of miR-155 in blood and plaque across studies (Letonja & Petrovič, 2024).

Measurement is a second problem. Fichtlscherer and colleagues could not normalise to a housekeeping miRNA because many circulating miRNAs change in disease, and used a spiked-in Caenorhabditis elegans miR-39 control instead, which corrects for extraction efficiency but not for biological variation. Faccini also normalised to cel-miR-39. Pre-analytical variables also affect circulating miRNA measurements: haemolysis, platelet contamination of plasma, centrifugation speed, and storage or repeated freeze-thaw cycles can all change measured levels, so these steps should be reported and standardised. Studies that use different normalisers, platforms and sample types are hard to compare, and the same miRNA can go in different directions between cohorts. Letonja and Petrovič (Letonja & Petrovič, 2024) note, for example, a meta-analysis in type 2 diabetes in which seven studies reported higher miR-155 and eleven reported lower.

The cohorts are small, cross-sectional and drawn from stable coronary disease, and none tests whether a miRNA predicts events. For this review the main point is that circulating levels are the sum of many cells, stages, drugs and comorbidities, so they carry the same context-dependence as the tissue data and should not be read as a direct readout of plaque biology. Registered studies in coronary disease are mostly this kind of biomarker work, not miRNA-targeting drugs (section 11).

A useful circulating signature would require pre-specified sampling and normalisation, adjustment for sex, diabetes and statin use, validation in an independent cohort, and event-based outcomes. Until such studies exist, circulating miRNAs are better regarded as hypothesis-generating markers of context, for example of inflammatory state, than as validated diagnostic tests.

13. LIMITATIONS AND FUTURE DIRECTIONS

This review has limits. It is narrative, not systematic, so study selection is not exhaustive and may favour studies that are easy to find or that reached open-access repositories. Primary papers were read in full where possible; some background statements in sections 5 to 7 rest on reviews and should be treated as less certain.

Publication patterns add a further limit. Null results such as that for anti-miR-33 in Ldlr-/- mice (Marquart et al., 2013) are likely to be published less often than positive ones, and a literature built mainly on positive findings is likely to overstate efficacy and to understate how often an effect depends on context.

The evidence itself is limited. Almost all interventional data are from mice, most of them males: Kavanagh et al. (2026), Marquart et al. (2013) and Kheirolomoom et al. (2015) used male mice, Donners et al. (2012) used female recipients, and none of these compares sexes. Sex differences in miRNA function in atherosclerosis therefore remain largely unexamined, although Fichtlscherer et al. (2010) noted sex-related differences in circulating levels. Treatments are mostly short and often preventive, human cohorts are small and cross-sectional, and strand-specific work covers a handful of miRNAs.

Future work should vary one context factor at a time within a single design, for example the same miRNA manipulated in whole-body and cell-specific models, at early and advanced stages, at several lesion sites, in both sexes and with and without diabetes. Strand-specific tools, single-cell and spatial methods, and human plaque cohorts with standardised sampling would help to separate cell-level from tissue-level effects (Bleckwehl et al., 2025; Depuydt et al., 2020). For therapy, the first plaque trials will need a target-engagement marker, a delivery route that reaches lesions, and an endpoint that fits the slow course of atherosclerosis, and they will need to specify the context in which each miRNA is expected to help.

14. CONCLUSIONS

The evidence reviewed here does not support treating a vascular miRNA as simply protective or harmful. The same miRNA can enlarge early lesions and stabilise advanced ones (miR-155, miR-21), act in opposite directions in endothelial and smooth muscle cells (miR-221/222), differ between vascular beds (miR-26b, miR-155, miR-92a) and depend on which strand is manipulated (miR-126, miR-181a, miR-26b). Comorbidity and compartment matter as well, as shown by the diabetic mouse data for miR-155-5p and by the divergence between circulating and lesion levels. For therapy, the practical conclusions are that a miRNA drug for atherosclerosis must name its strand, target a defined cell type and stage, reach the plaque and be paired with a marker of target engagement, and that the first trials will need to specify the context in which benefit is expected. Until studies vary one context factor at a time, claims that a given miRNA is a therapeutic target in coronary artery disease remain provisional.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable. This study did not involve human participants, human data, or animals.

CONSENT FOR PUBLICATION

Not applicable.

DECLARATION OF GENERATIVE AI AND AI-ASSISTED TECHNOLOGIES

During the preparation of this work, the author used [Gemini 3.8 Flash] for language editing. The author reviewed and edited all output and takes full responsibility for the content of the publication. The AI tool did not generate data or interpret results.

DATA AVAILABILITY

No new datasets were generated in this narrative review. Any additional data are available from the author on reasonable request.

CONFLICT OF INTEREST

The authors declare no conflict of interest in this study.

FUNDING

This research received no specific grant from any public, commercial, or non-profit funding agency.

AUTHORS' CONTRIBUTIONS

The study was conducted by a single author, S.M., who is solely responsible for the conception, literature search, analysis, writing and revision of the manuscript and for its content.

REFERENCES

Bai, Q., Xiao, Y., Hong, H., Cao, X., Zhang, L., Han, R., Lee, L. K. C., Xue, E. Y., Tian, X. Y., & Choi, C. H. J. (2022). Scavenger receptor-targeted plaque delivery of microRNA-coated nanoparticles for alleviating atherosclerosis. *Proceedings of the National Academy of Sciences of the United States of America, 119*, Article e2201443119. https://doi.org/10.1073/pnas.2201443119

Bauersachs, J., Solomon, S. D., Anker, S. D., Antorrena-Miranda, I., Batkai, S., Viereck, J., Rump, S., Filippatos, G., Granzer, U., Ponikowski, P., de Boer, R. A., Vardeny, O., Hauke, W., & Thum, T. (2024). Efficacy and safety of CDR132L in patients with reduced left ventricular ejection fraction after myocardial infarction: Rationale and design of the HF-REVERT trial. *European Journal of Heart Failure, 26*(3), 674–682. https://doi.org/10.1002/ejhf.3139

Bauersachs, J., Solomon, S. D., Anker, S. D., Antorrena-Miranda, I., de Boer, R. A., Filippatos, G. S., Friede, T., Hauke, W., Ponikowski, P. P., Vardeny, O., Altschul, R., Gamborg, M., Vinther, K., & Thum, T. (2026). The microRNA inhibitor CDR132L in patients with reduced left ventricular ejection fraction after myocardial infarction: A randomized phase 2 trial. *Nature Medicine, 32*(7), 2654–2661. https://doi.org/10.1038/s41591-026-04408-4

Björkegren, J. L. M., & Lusis, A. J. (2022). Atherosclerosis: Recent developments. *Cell, 185*(10), 1630–1645. https://doi.org/10.1016/j.cell.2022.04.004

Bleckwehl, T., Babler, A., Tebens, M., Maryam, S., Nyberg, M., Bosteen, M., Halder, M., Shaw, I., Fleig, S., Pyke, C., Hvid, H., Voetmann, L. M., van Buul, J. D., Sluimer, J. C., Das, V., Baumgart, S., Kramann, R., & Hayat, S. (2025). Encompassing view of spatial and single-cell RNA sequencing renews the role of the microvasculature in human atherosclerosis. *Nature Cardiovascular Research, 4*(1), 26–44. https://doi.org/10.1038/s44161-024-00582-1

Bonauer, A., Carmona, G., Iwasaki, M., Mione, M., Koyanagi, M., Fischer, A., Burchfield, J., Fox, H., Doebele, C., Ohtani, K., Chavakis, E., Potente, M., Tjwa, M., Urbich, C., Zeiher, A. M., & Dimmeler, S. (2009). MicroRNA-92a controls angiogenesis and functional recovery of ischemic tissues in mice. *Science, 324*(5935), 1710–1713. https://doi.org/10.1126/science.1174381

Cao, R. Y., Li, Q., Miao, Y., Zhang, Y., Yuan, W., Fan, L., Liu, G., Mi, Q., & Yang, J. (2016). The emerging role of microRNA-155 in cardiovascular diseases. *BioMed Research International, 2016*, Article 9869208. https://doi.org/10.1155/2016/9869208

Chin, D. D., Poon, C., Wang, J., Joo, J., Ong, V., Jiang, Z., Cheng, K., Plotkin, A., Magee, G. A., & Chung, E. J. (2020). *Nanoparticle-mediated microRNA-145 delivery for vascular smooth muscle cell phenotype modulation and atherosclerosis treatment* [Preprint]. bioRxiv. https://doi.org/10.1101/2020.09.09.290361

Chipont, A., Esposito, B., Challier, I., Montabord, M., Tedgui, A., Mallat, Z., Loyer, X., & Potteaux, S. (2019). MicroRNA-21 deficiency alters the survival of Ly-6Clo monocytes in ApoE−/− mice and reduces early-stage atherosclerosis—Brief report. *Arteriosclerosis, Thrombosis, and Vascular Biology, 39*, 170–177. https://doi.org/10.1161/ATVBAHA.118.311942

Chistiakov, D. A., Orekhov, A. N., & Bobryshev, Y. V. (2015). Extracellular vesicles and atherosclerotic disease. *Cellular and Molecular Life Sciences, 72*(14), 2697–2708. https://doi.org/10.1007/s00018-015-1906-2

ClinicalTrials.gov. (2026). *Registered studies for atherosclerosis or coronary artery disease combined with microRNA terms, and for CDR132L* [Database search, August 2026]. U.S. National Library of Medicine. https://clinicaltrials.gov

Cordes, K. R., Sheehy, N. T., White, M. P., Berry, E. C., Morton, S. U., Muth, A. N., Lee, T.-H., Miano, J. M., Ivey, K. N., & Srivastava, D. (2009). miR-145 and miR-143 regulate smooth muscle cell fate and plasticity. *Nature, 460*(7256), 705–710. https://doi.org/10.1038/nature08195

Dawson, L. P., Lum, M., Nerleker, N., Nicholls, S. J., & Layland, J. (2022). Coronary atherosclerotic plaque regression: JACC state-of-the-art review. *Journal of the American College of Cardiology, 79*(1), 66–82. https://doi.org/10.1016/j.jacc.2021.10.035

Depuydt, M. A. C., Prange, K. H. M., Slenders, L., Örd, T., Elbersen, D., Boltjes, A., de Jager, S. C. A., Asselbergs, F. W., de Borst, G. J., Aavik, E., Lönnberg, T., Lutgens, E., Glass, C. K., den Ruijter, H. M., Kaikkonen, M. U., Bot, I., Slütter, B., van der Laan, S. W., Ylä-Herttuala, S., … Pasterkamp, G. (2020). Microanatomy of the human atherosclerotic plaque by single-cell transcriptomics. *Circulation Research, 127*(11), 1437–1455. https://doi.org/10.1161/CIRCRESAHA.120.316770

Diener, C., Keller, A., & Meese, E. (2022). Emerging concepts of miRNA therapeutics: From cells to clinic. *Trends in Genetics, 38*(6), 613–626. https://doi.org/10.1016/j.tig.2022.02.006

Donners, M. M. P. C., Wolfs, I. M. J., Stöger, L. J., van der Vorst, E. P. C., Pöttgens, C. C. H., Heymans, S., Schroen, B., Gijbels, M. J. J., & de Winther, M. P. J. (2012). Hematopoietic miR155 deficiency enhances atherosclerosis and decreases plaque stability in hyperlipidemic mice. *PLoS ONE, 7*, Article e35877. https://doi.org/10.1371/journal.pone.0035877

Du, F., Yu, F., Wang, Y., Hui, Y., Carnevale, K., Fu, M., Lu, H., & Fan, D. (2014). MicroRNA-155 deficiency results in decreased macrophage inflammation and attenuated atherogenesis in apolipoprotein E–deficient mice. *Arteriosclerosis, Thrombosis, and Vascular Biology, 34*, 759–767. https://doi.org/10.1161/ATVBAHA.113.302701

Elia, L., Quintavalle, M., Zhang, J., Contu, R., Cossu, L., Latronico, M. V. G., Peterson, K. L., Indolfi, C., Catalucci, D., Chen, J., Courtneidge, S. A., & Condorelli, G. (2009). The knockout of miR-143 and -145 alters smooth muscle cell maintenance and vascular homeostasis in mice: Correlates with human disease. *Cell Death & Differentiation, 16*(12), 1590–1598. https://doi.org/10.1038/cdd.2009.153

Esau, C., Davis, S., Murray, S. F., Yu, X. X., Pandey, S. K., Pear, M., Watts, L., Booten, S. L., Graham, M., McKay, R., Subramaniam, A., Propp, S., Lollo, B. A., Freier, S., Bennett, C. F., Bhanot, S., & Monia, B. P. (2006). miR-122 regulation of lipid metabolism revealed by in vivo antisense targeting. *Cell Metabolism, 3*(2), 87–98. https://doi.org/10.1016/j.cmet.2006.01.005

Faccini, J., Ruidavets, J.-B., Cordelier, P., Martins, F., Maoret, J.-J., Bongard, V., Ferrières, J., Roncalli, J., Elbaz, M., & Vindis, C. (2017). Circulating miR-155, miR-145 and let-7c as diagnostic biomarkers of the coronary artery disease. *Scientific Reports, 7*, Article 42916. https://doi.org/10.1038/srep42916

Fichtlscherer, S., De Rosa, S., Fox, H., Schwietz, T., Fischer, A., Liebetrau, C., Weber, M., Hamm, C. W., Röxe, T., Müller-Ardogan, M., Bonauer, A., Zeiher, A. M., & Dimmeler, S. (2010). Circulating microRNAs in patients with coronary artery disease. *Circulation Research, 107*(5), 677–684. https://doi.org/10.1161/CIRCRESAHA.109.215566

Fitzsimons, S., Oggero, S., Bruen, R., McCarthy, C., Strowitzki, M. J., Mahon, N. G., Ryan, N., Brennan, E. P., Barry, M., Perretti, M., & Belton, O. (2020). microRNA-155 is decreased during atherosclerosis regression and is increased in urinary extracellular vesicles during atherosclerosis progression. *Frontiers in Immunology, 11*, Article 576516. https://doi.org/10.3389/fimmu.2020.576516

Gebert, L. F. R., & MacRae, I. J. (2019). Regulation of microRNA function in animals. *Nature Reviews Molecular Cell Biology, 20*(1), 21–37. https://doi.org/10.1038/s41580-018-0045-7

Global Burden of Cardiovascular Diseases and Risks 2023 Collaborators. (2025). Global, regional, and national burden of cardiovascular diseases and risk factors in 204 countries and territories, 1990–2023. *Journal of the American College of Cardiology, 86*(22), 2167–2243. https://doi.org/10.1016/j.jacc.2025.08.015

Guo, B., Zhuang, T.-T., Li, C.-C., Li, F., Shan, S.-K., Zheng, M.-H., Xu, Q.-S., Wang, Y., Lei, L.-M., Tang, K.-X., Ouyang, W., Duan, J.-Y., Wu, Y.-Y., Cao, Y.-C., Ehsan Ullah, M. H., Zhou, Z.-A., Lin, X., Wu, F., Xu, F., … Yuan, L.-Q. (2024). MiRNA-132/212 encapsulated by adipose tissue-derived exosomes worsen atherosclerosis progression. *Cardiovascular Diabetology, 23*, Article 331. https://doi.org/10.1186/s12933-024-02404-x

He, S., Yang, L., Li, D., & Li, M. (2015). Krüppel-like factor 2-mediated suppression of microRNA-155 reduces the proinflammatory activation of macrophages. *PLoS ONE, 10*, Article e0139060. https://doi.org/10.1371/journal.pone.0139060

Hill, A. C., & Hall, J. (2023). The MOE modification of RNA: Origins and widescale impact on the oligonucleotide therapeutics field. *Helvetica Chimica Acta, 106*, Article e202200169. https://doi.org/10.1002/hlca.202200169

Jin, H., Li, D. Y., Chernogubova, E., Sun, C., Busch, A., Eken, S. M., Saliba-Gustafsson, P., Winter, H., Winski, G., Raaz, U., Schellinger, I. N., Simon, N., Hegenloh, R., Perisic Matic, L., Jagodic, M., Ehrenborg, E., Pelisek, J., Eckstein, H.-H., Hedin, U., … Maegdefessel, L. (2018). Local delivery of miR-21 stabilizes fibrous caps in vulnerable atherosclerotic lesions. *Molecular Therapy, 26*(4), 1040–1055. https://doi.org/10.1016/j.ymthe.2018.01.011

Kavanagh, M., Herrero del Real, I., Prieto, I., Alvarez-Moreno, R., Egido, J., Lopez-Franco, O., Lázaro, I., & Gomez-Guerrero, C. (2026). Opposing functions of miR-155-5p and Socs1 drive vascular inflammation in diabetes-accelerated atherosclerosis. *Cardiovascular Diabetology, 25*, Article 106. https://doi.org/10.1186/s12933-026-03121-3

Kheirolomoom, A., Kim, C. W., Seo, J. W., Kumar, S., Son, D. J., Gagnon, M. K. J., Ingham, E. S., Ferrara, K. W., & Jo, H. (2015). Multifunctional nanoparticles facilitate molecular targeting and miRNA delivery to inhibit atherosclerosis in ApoE−/− mice. *ACS Nano, 9*, 8885–8897. https://doi.org/10.1021/acsnano.5b02611

Letonja, J., & Petrovič, D. (2024). A review of microRNAs and lncRNAs in atherosclerosis as well as some major inflammatory conditions. *Biomedicines, 12*, Article 1322. https://doi.org/10.3390/biomedicines12061322

Li, Z., Zhao, Y., Suguro, S., & Suguro, R. (2023). MicroRNAs regulate function in atherosclerosis and clinical implications. *Oxidative Medicine and Cellular Longevity, 2023*, Article 2561509. https://doi.org/10.1155/2023/2561509

Libby, P. (2021). The changing landscape of atherosclerosis. *Nature, 592*(7855), 524–533. https://doi.org/10.1038/s41586-021-03392-8

Liu, P., Wang, S., Wang, G., Zhao, M., Du, F., Li, K., Wang, L., Wu, H., Chen, J., Yang, Y., & Su, G. (2022). Macrophage-derived exosomal miR-4532 promotes endothelial cells injury by targeting SP1 and NF-κB P65 signalling activation. *Journal of Cellular and Molecular Medicine, 26*(19), 5165–5180. https://doi.org/10.1111/jcmm.17541

Liu, X., Cheng, Y., Yang, J., Xu, L., & Zhang, C. (2012). Cell-specific effects of miR-221/222 in vessels: Molecular mechanism and therapeutic application. *Journal of Molecular and Cellular Cardiology, 52*(1), 245–255. https://doi.org/10.1016/j.yjmcc.2011.11.008

Liu, X., Cheng, Y., Zhang, S., Lin, Y., Yang, J., & Zhang, C. (2009). A necessary role of miR-221 and miR-222 in vascular smooth muscle cell proliferation and neointimal hyperplasia. *Circulation Research, 104*(4), 476–487. https://doi.org/10.1161/CIRCRESAHA.108.185363

Lovren, F., Pan, Y., Quan, A., Singh, K. K., Shukla, P. C., Gupta, N., Steer, B. M., Ingram, A. J., Gupta, M., Al-Omran, M., Teoh, H., Marsden, P. A., & Verma, S. (2012). MicroRNA-145 targeted therapy reduces atherosclerosis. *Circulation, 126*(11, Suppl. 1), S81–S90. https://doi.org/10.1161/CIRCULATIONAHA.111.084186

Loyer, X., Potteaux, S., Vion, A.-C., Guérin, C. L., Boulkroun, S., Rautou, P.-E., Ramkhelawon, B., Esposito, B., Dalloz, M., Paul, J.-L., Julia, P. L., Maccario, J., Boulanger, C. M., Mallat, Z., & Tedgui, A. (2014). Inhibition of microRNA-92a prevents endothelial dysfunction and atherosclerosis in mice. *Circulation Research, 114*(3), 434–443. https://doi.org/10.1161/CIRCRESAHA.114.302213

Ma, S., Tian, X. Y., Zhang, Y., Mu, C., Shen, H., Bismuth, J., Pownall, H. J., Huang, Y., & Wong, W. T. (2016). E-selectin-targeting delivery of microRNAs by microparticles ameliorates endothelial inflammation and atherosclerosis. *Scientific Reports, 6*, Article 22910. https://doi.org/10.1038/srep22910

Ma, X., Ma, C., & Zheng, X. (2013). MicroRNA-155 in the pathogenesis of atherosclerosis: A conflicting role?. *Heart, Lung and Circulation, 22*, 811–818. https://doi.org/10.1016/j.hlc.2013.05.651

Madrigal-Matute, J., Rotllan, N., Aranda, J. F., & Fernández-Hernando, C. (2013). MicroRNAs and atherosclerosis. *Current Atherosclerosis Reports, 15*, Article 322. https://doi.org/10.1007/s11883-013-0322-z

Man, J. J., Beckman, J. A., & Jaffe, I. Z. (2020). Sex as a biological variable in atherosclerosis. *Circulation Research, 126*(9), 1297–1319. https://doi.org/10.1161/CIRCRESAHA.120.315930

Marquart, T. J., Wu, J., Lusis, A. J., & Baldán, Á. (2013). Anti-miR-33 therapy does not alter the progression of atherosclerosis in low-density lipoprotein receptor–deficient mice. *Arteriosclerosis, Thrombosis, and Vascular Biology, 33*, 455–458. https://doi.org/10.1161/ATVBAHA.112.300639

Paone, S., Baxter, A. A., Hulett, M. D., & Poon, I. K. H. (2019). Endothelial cell apoptosis and the role of endothelial cell-derived extracellular vesicles in the progression of atherosclerosis. *Cellular and Molecular Life Sciences, 76*(6), 1093–1106. https://doi.org/10.1007/s00018-018-2983-9

Peters, L. J. F., Bidzhekov, K., Bonnin-Marquez, A., Sundararaman, S. S., Huchzermeier, R., Maas, S. L., Abschlag, K., Jans, A., Lin, C., Haberbosch, M., Jansen, Y., Yu, B., Sluimer, J. C., Gijbels, M. J., Jankowski, J., Bartneck, M., Biessen, E. A. L., Weber, C., Döring, Y., & van der Vorst, E. P. C. (2025). MicroRNA-26b−/− augments atherosclerosis, while mimic-loaded nanoparticles reduce atherogenesis. *Cardiovascular Research, 121*, 2700–2713. https://doi.org/10.1093/cvr/cvaf234

Pfeifer, P., Werner, N., & Jansen, F. (2015). Role and function of microRNAs in extracellular vesicles in cardiovascular biology. *BioMed Research International, 2015*, Article 161393. https://doi.org/10.1155/2015/161393

Prus, K., Sanvitti, M., & Bilotta, F. (2026). MicroRNA profiling of the pathophysiological mechanisms underlying carotid atherosclerosis progression. *Biomolecules, 16*, Article 1026. https://doi.org/10.3390/biom16071026

Raajasekar, S. (2026). MicroRNA-mediated regulation of macrophage polarization in cardiovascular inflammation and atherosclerotic disease. *Genetics and Molecular Research, 25*(8s). https://geneticsmr.com/index.php/gmr/article/view/1448

Rayner, K. J., Sheedy, F. J., Esau, C. C., Hussain, F. N., Temel, R. E., Parathath, S., van Gils, J. M., Rayner, A. J., Chang, A. N., Suarez, Y., Fernandez-Hernando, C., Fisher, E. A., & Moore, K. J. (2011). Antagonism of miR-33 in mice promotes reverse cholesterol transport and regression of atherosclerosis. *Journal of Clinical Investigation, 121*(7), 2921–2931. https://doi.org/10.1172/JCI57275

Reijnders, E., van der Laarse, A., Jukema, J. W., & Cobbaert, C. M. (2023). High residual cardiovascular risk after lipid-lowering: Prime time for Predictive, Preventive, Personalized, Participatory, and Psycho-cognitive medicine. *Frontiers in Cardiovascular Medicine, 10*, Article 1264319. https://doi.org/10.3389/fcvm.2023.1264319

Ridker, P. M., Bhatt, D. L., Pradhan, A. D., Glynn, R. J., MacFadyen, J. G., & Nissen, S. E. (2023). Inflammation and cholesterol as predictors of cardiovascular events among patients receiving statin therapy: A collaborative analysis of three randomised trials. *The Lancet, 401*, 1293–1301. https://doi.org/10.1016/S0140-6736(23)00215-5

Schober, A., Nazari-Jahantigh, M., Wei, Y., Bidzhekov, K., Gremse, F., Grommes, J., Megens, R. T. A., Heyll, K., Noels, H., Hristov, M., Wang, S., Kiessling, F., Olson, E. N., & Weber, C. (2014). MicroRNA-126-5p promotes endothelial proliferation and limits atherosclerosis by suppressing Dlk1. *Nature Medicine, 20*(4), 368–376. https://doi.org/10.1038/nm.3487

Son, D. J., Kumar, S., Takabe, W., Kim, C. W., Ni, C.-W., Alberts-Grill, N., Jang, I.-H., Kim, S., Kim, W., Kang, S. W., Baker, A. H., Seo, J. W., Ferrara, K. W., & Jo, H. (2013). The atypical mechanosensitive microRNA-712 derived from pre-ribosomal RNA induces endothelial inflammation and atherosclerosis. *Nature Communications, 4*, Article 3000. https://doi.org/10.1038/ncomms4000

Su, Y., Yuan, J., Zhang, F., Lei, Q., Zhang, T., Li, K., Guo, J., Hong, Y., Bu, G., Lv, X., Liang, S., Ou, J., Zhou, J., Luo, B., & Shang, J. (2019). MicroRNA-181a-5p and microRNA-181a-3p cooperatively restrict vascular inflammation and atherosclerosis. *Cell Death & Disease, 10*, Article 365. https://doi.org/10.1038/s41419-019-1599-9

Täubel, J., Hauke, W., Rump, S., Viereck, J., Batkai, S., Poetzsch, J., Rode, L., Weigt, H., Genschel, C., Lorch, U., Theek, C.,

Levin, A. A., Bauersachs, J., Solomon, S. D., & Thum, T. (2021). Novel antisense therapy targeting microRNA-132 in patients with heart failure: Results of a first-in-human phase 1b randomized, double-blind, placebo-controlled study. *European Heart Journal, 42*(2), 178–188. https://doi.org/10.1093/eurheartj/ehaa898

van der Vaart, J. I., van Eenige, R., Rensen, P. C. N., & Kooijman, S. (2024). Atherosclerosis: An overview of mouse models and a detailed methodology to quantify lesions in the aortic root. *Vascular Biology, 6*(1), Article e230017. https://doi.org/10.1530/VB-23-0017

Wang, J., Li, Y., Wang, H., Meng, Q., Li, P., Wang, Y., Wang, K., & Yang, S. (2025). Harnessing miRNA therapeutics: A novel approach to combat heart and brain infarctions in atherosclerosis. *Cell Death Discovery, 11*, Article 482. https://doi.org/10.1038/s41420-025-02649-9

Wang, Y., Xu, Z., Wang, X., Zheng, J., Peng, L., Zhou, Y., Song, Y., & Lu, Z. (2021). Extracellular-vesicle containing miRNA-503-5p released by macrophages contributes to atherosclerosis. *Aging, 13*(8), 12239–12257. https://doi.org/10.18632/aging.103855

Wei, Y., Zhu, M., Corbalán-Campos, J., Heyll, K., Weber, C., & Schober, A. (2015). Regulation of Csf1r and Bcl6 in macrophages mediates the stage-specific effects of microRNA-155 on atherosclerosis. *Arteriosclerosis, Thrombosis, and Vascular Biology, 35*. https://doi.org/10.1161/ATVBAHA.114.304723

Yu, H., Douglas, H. F., Wathieu, D., Braun, R. A., Edomwande, C., Lightell, D. J., Jr., Pham, T., Klingenberg, N. C., Bishop, S. P., Khismatullin, D. B., & Woods, T. C. (2023). Diabetes is accompanied by secretion of pro-atherosclerotic exosomes from vascular smooth muscle cells. *Cardiovascular Diabetology, 22*, Article 112. https://doi.org/10.1186/s12933-023-01833-4

Zhu, J., Liu, B., Wang, Z., Wang, D., Ni, H., Zhang, L., & Wang, Y. (2019). Exosomes from nicotine-stimulated macrophages accelerate atherosclerosis through miR-21-3p/PTEN-mediated VSMC migration and proliferation. *Theranostics, 9*(23), 6901–6919. https://doi.org/10.7150/thno.37357

SUPPLEMENTARY MATERIAL S1. SEARCH STRINGS

PubMed (advanced search; run in August 2026):

(atherosclerosis[tiab] OR "coronary artery disease"[tiab] OR "Atherosclerosis"[MeSH] OR "Coronary Artery Disease"[MeSH]) AND (microRNA*[tiab] OR miRNA*[tiab] OR miR[tiab] OR "MicroRNAs"[MeSH]) AND (endothelial[tiab] OR "smooth muscle"[tiab] OR macrophage*[tiab] OR "foam cell*"[tiab] OR "cholesterol efflux"[tiab] OR antagomir*[tiab] OR nanoparticle*[tiab]) AND 2006/01/01:2026/08/31[dp]

Scopus (advanced document search; run in August 2026):

TITLE-ABS-KEY ((atherosclerosis OR "coronary artery disease") AND (microRNA* OR miRNA* OR miR) AND (endothelial OR "smooth muscle" OR macrophage* OR "foam cell*" OR "cholesterol efflux" OR antagomir* OR nanoparticle*)) AND PUBYEAR > 2005 AND PUBYEAR < 2027

ClinicalTrials.gov (searched August 2026): conditions atherosclerosis or coronary artery disease combined with microRNA terms, and the agents CDR132L, MRG-110, cobomarsen and miravirsen. The exact registry query is available from the author on request.