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Review Paper

A Comprehensive Review: Plaque Targeted Implantable Therapies in Atherosclerosis

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ABSTRACT

Atherosclerotic cardiovascular disease (CVD) is one of the most significant global health problems today. Current standard therapies for cardiovascular disease and revascularization do not eliminate plaque locally nor alleviate residual risk of developing future cardiovascular events. Implantable cell-based therapeutic approaches provide a method for delivering therapeutic cells/cell-derived products directly to the plaque, increasing local retention and limiting systemic side effects from these therapies. This review discusses advances in bioengineered vascular interfaces and delivery technologies and immune-metabolically-mediated modulation of atherosclerotic plaque to establish a framework of precision implantable therapies. The approaches outlined in this review regulate macrophage polarization, smooth muscle cell phenotype, and endothelial repair to stabilize and reduce plaque size. Engineered exosomes and biomimetic nanovesicles are two approaches enhancing the targeting and effectiveness of precision implantable therapies. Clinical trials have demonstrated good safety and moderate effectiveness for implantable cell-based therapies used for peripheral and coronary artery disease, highlighting the need to establish biomarkers that can guide identification and selection of appropriate patients for treatment and to optimize delivery of these therapies. Several systemic factors, including but not limited to age, diabetes, and clonal haematopoiesis may affect integration of implanted cells within the atherosclerotic plaque and patient outcomes and demonstrate the value of considering both systemic elements as well as implant design in future development of implantable cell-based therapeutic modalities. Future directions emphasize, there is a need to establish standardized methods for evaluation, scalable manufacturing processes, and regulatory pathways, to provide a continued and long-term clinical benefit beyond current systemic therapies

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INTRODUCTION

1.1. Mechanistic Insights and Rationale

The burden of atherosclerotic cardiovascular disease (CVD) worldwide continues to grow significantly; however, the decline in the age-standardized rates makes it difficult to determine how much of this increase is due to improvements in medical care versus an increase in population age or size. In fact, the global prevalence of CVD has increased by approximately two-fold (271 million cases in 1990 vs. 523 million cases in 2019). The two largest contributors of CVD mortality are ischemic heart disease (IHD) (49.2% of total deaths due to CVD) and stroke (approximately 25% of total deaths due to CVD), with approximately half of the strokes due to ischemic causes. Incidence trends are heterogeneous, with the number of incident CVD cases increasing by 77% globally from 1990 to 2019, but age-standardized incidence only declining by 1.6% in the most recent decade. Peripheral artery disease (PAD) incidence has also declined globally, although the rate of decline has slowed in the recent decade. The implications of this increasing absolute burden of atherosclerotic CVDs are significant for health systems and resource availability globally.^[1]

1.2 Limitations of Current Therapies for Local Plaque Control

The key limitations of current therapies for local plaque control are that systemic administration of drugs often leads to off-target effects and low local drug concentrations at the plaque site, post-stenting restenosis induced by vascular injury response and non-specific therapeutic drugs limits the effectiveness of stent-based approaches.

Mechanical trauma from balloon angioplasty can cause endothelial damage, platelet deposition, and smooth muscle cell hyperplasia, leading to restenosis, and surgical approaches like bypass grafting, while effective, are highly invasive and carry risks of complications.^[2]

Administration of pharmacological agents in the clinical context, statins are central to atherosclerosis treatment but often fail to sufficiently lower LDL or are poorly tolerated due to side effects. Alternative therapies such as fibrates, ezetimibe, bile acid Sequestrants and niacin provide only limited benefit, while PCI and drug-eluting stent (DESs) re-establish blood flow but expose the endothelium to injury due to the DESs obstructing re-endothelialization. This creates a greater risk for stenting and neo atherosclerosis. These treatments leave a significant residual risk of disease and surgery has done nothing to prevent disease from progressing. Current treatments do not adequately treat the local plaque pathology creating an urgent need for new and improved therapies.^[3, 4]

1.3 Rationale for Plaque-Directed Implantable Cell Therapies

Cell therapy is designed to implant therapeutic cells or derived products directly into their intended delivery site to enhance the concentration, retention, and management of the cells in this specific area while reducing the risk of systemic toxicity. While the use of implantable cell therapies has significant potential for improving the treatment of systemic diseases or conditions, it may also provide unique advantages for treating focal pathologic conditions such as atherosclerotic plaques, tumours, fractures, infarcts, periodontitis, etc.^[5, 6, 7].

Table 1: Local versus Systemic Delivery of Therapeutic Cells: Mechanistic and Clinical Considerations

Sr. No.	Dimension	Plaque directed/Local delivery	Systemic delivery	Citations
1	Primary goal	Targeted retention and tissue regeneration	Natural homing and minimally invasive	[5,6]
2	Typical routes	Intraplaque, intracoronary, intramyocardial	Peripheral IV, as systemic approach	[5,6]
3	Cell retention at target	High retention	Low retention	[5,6]
4	Regenerative efficacy	Local delivery and better retention	Systemic therapy and less effective repair	[5,6]
5	Targeting	Local,site-specific(plaque)	Whole body distribution	[5,7]
6	Dependence on homing signals	Less dependent	Strongly dependent	[6,7]
7	Off-target distribution	Lowersystemic exposure	High off-target trapping	[5,6]
8	Invasiveness/procedural risk	More invasive (procedural/implant)	Less invasive (IV/Injection)	[6,7]
9	Technical complexity	Specialized procedure, operator skills required	Technically simple	[6,7]
10	When preferred	Accessible lesions and local targeting	Inaccessible lesions and non-invasive approach	[5,6]

Implantable cell therapies—whether delivered as live cells, cell-seeded scaffolds, or cell-derived products like exosomes—offer a strategic advantage for localized, plaque-directed therapy by providing sustained, targeted, and controlled therapeutic effects while minimizing systemic exposure [5, 6, 7].

1.4 Objectives and Novel Contributions of this review

This purpose of this review is to give a focused assessment of therapeutic devices that can be used for atherosclerosis treatment. The review has been structured in such a way that it combines information on the many disciplines relevant to the study; including engineering, plaque biology, and clinical data acquisition. Thus, the true value of this review lies in the explanation of how bioengineered vascular devices (bioengineered Vascular Interfacing Systems - BVI) and implantable cell therapies can provide a precisely targeted and sustained stabilization and regeneration of atherosclerotic plaques, which

relate directly to the methodology for developing a clinical translation pathway. This review then proposes design principles for therapeutic devices based upon biomechanical and biological limitations, methods of delivering drugs via a therapeutic device and techniques of using imaging to evaluate a therapeutic device. Furthermore, this review provides a roadmap for conducting clinical trials in which the use of a biomarker will guide the selection of patients for participation and will be used to stratify patients as either a responder or non-responder. This roadmap will maximize both the safety and efficacy of precision implantable therapeutic devices for patients with atherosclerotic cardiovascular disease. [1,2,3,4,5,6,7]

2. Cellular and Molecular Landscape of Atherosclerotic Plaques

2.1 Cellular Composition of the Atherosclerotic Plaque



Atherosclerotic plaques are made up of a heterogeneous population of cells, including ECs, VSMCs, macrophages and immune cells. Endothelial dysfunction, as seen in patients with hypercholesterolemia, hypertension, and/or diabetes, stimulates lipid deposition and results in inflammation within the plaque. VSMCs undergo phenotypic transitions, including through endothelial mesenchymal transition and converting into foam cells; this process increases the size of the plaque and contributes to the calcification of the plaque. Macrophages, deriving both from resident sources as well as monocyte sources, can take on pro-inflammatory (M1) or pro-resolution (M2) phenotypes, which influence the stability and progression of the plaque. The recruitment of pro-atherogenic T cells through the release of chemokines increases the overall inflammatory process within the plaque and contributes significantly to atherosclerotic progression [3, 8].

2.2 Targetable Pathobiological Processes in Atherosclerosis

The principal target areas for therapeutic intervention in atherosclerosis include: (i) Endothelial dysfunction, (ii) oxidative stress (iii) chronic inflammation, (iv) impaired efferocytosis and (v) plaque instability/erosion. Endothelial cell injury is responsible for increasing low-density lipoprotein (LDL) penetration into the vessel wall and leukocyte adherence to endothelial cells. Oxidation of LDL and the presence of proinflammatory cytokines are both driving forces behind subsequent plaque development. Impaired efferocytosis leads to the formation of necrotic cores, which further destabilise the plaque, rendering it susceptible to rupture and resulting in acute coronary syndrome. Continued plaque expansion will also impede blood flow and facilitate thrombosis. Therefore, nanoparticle-based therapies aim to modulate these pathways

through improving endothelial function, reducing oxidative stress, controlling inflammation, enhancing efferocytosis and stabilising plaques. [4, 8].

2.3 Plaque Reprogramming as an Emerging Therapeutic Paradigm

The concept of plaque reprogramming in atherosclerosis involves the therapeutic modification of the following three important cell types associated with plaque development: macrophages, vascular smooth muscle cells (VSMCs) and endothelial cells (ECs). This concept has the following three therapeutic implications to inhibit disease progression: 1) shift macrophages from pro-inflammatory (M1) to anti-inflammatory (M2) phenotypes to increase cholesterol efflux and efferocytosis, 2) shift VSMCs towards a contractile/functionally quiescent phenotype to stabilize the fibrous cap, and 3) restore the balance of ECs to their homeostatic state. The mechanisms used to achieve these responses in macrophages, VSMCs and ECs will utilize cell- and exosome-based therapies, such as engineered exosomes from macrophages exhibiting anti-inflammatory and pro-efferocytosis properties, mesenchymal stem cell therapy to enhance EC function and increase VSMC quiescence, and nanoparticle-based delivery of miRNAs (e.g., miRNA-146a for macrophages and miR-145 for VSMCs) to reprogram cellular functioning. Finally, the use of biomimetic nanoparticles and extracellular vesicles derived from endothelial progenitor cells to promote vascular repair/angiogenesis and the use of immunomodulatory therapies, such as engineered regulatory T cells and senolytic CAR-T cells, to target inflammation and senescence of plaque, will expand the therapeutic approaches for plaque reprogramming. [9, 10, 11]

There are multiple ways in which stem cell-derived exosomes can positively impact the



treatment of atherosclerosis. They can influence macrophage polarization to the anti-inflammatory M2 phenotype by altering cellular signaling through the following miRNAs: miR-let7, miR-182 and HMGA2/NF-κB. They can also inhibit VSMC mineralization by inhibiting the expression of genes that drive VSMC mineralization (e.g., RUNX2, BGLAP, BMP2) and through the inhibition of the NFATc3-osteocalcin pathway.

Additionally, stem-cell-derived exosomes from multiple sources (e.g., MSCs, CPCs, and EPCs)

can restore endothelial cell function by delivering miRNAs (e.g., miR-342-5p, miR-512-3p, and miR-10a) that protect against oxidative stress and ox-LDL-induced endothelial cell dysfunction. They may further stimulate angiogenesis. As demonstrated by their diverse actions, stem cell-derived exosomes are a potentially comprehensive therapeutic option for treating atherosclerosis. [8]

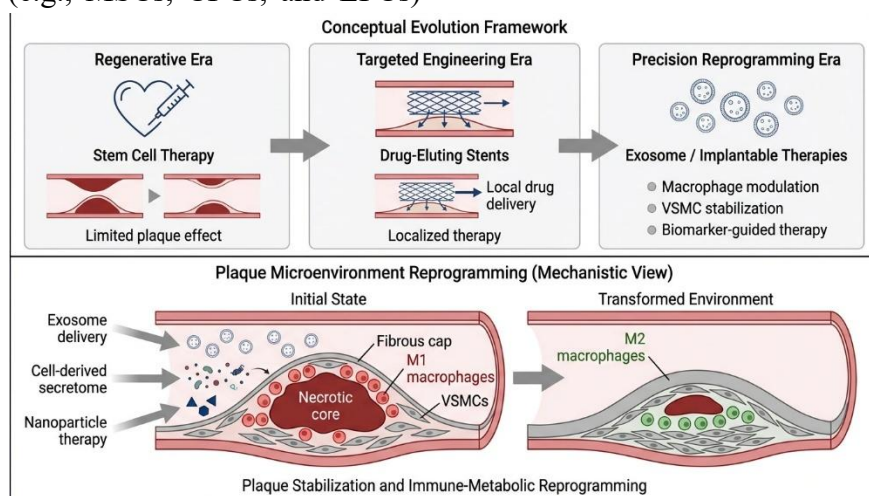


Figure 1. The Advancement of Implantable Therapies for Precision Reprogramming of the Plaque Microenvironment in Atherosclerosis

3. Clinical Status of Cell-Based Therapies in Atherosclerotic CVD

3.1 Clinical Evidence in Peripheral Atherosclerotic Disease

Several meta-analyses have evaluated the clinical evidence for autologous cell therapy in patients with peripheral artery disease (PAD) and chronic limb-threatening ischemia (CLTI):

Table 2: Key clinical trial findings [12]

Author(s) of trial/ meta-analysis	Key findings
Rigato et al. [13]	A meta-analysis of 19 randomized clinical trials (involving 837 patients) found that autologous cell therapy may improve amputation-free survival, limb perfusion, and functional capacity. However, the studies had significant heterogeneity and were underpowered.
Gao et al. [14]	An analysis of 27 randomized trials (with 1186 patients) revealed that autologous stem cell therapy improved ulcer healing compared to standard treatments, but limb salvage outcomes were similar. The authors noted that many studies had small sample sizes and there was considerable variation among trials.

Pu et al. ^[15]	A meta-analysis of 12 randomized controlled trials (involving 630 patients with CLTI) showed significant improvements in amputation rates, ankle-brachial index, transcutaneous oxygen tension, and rest pain scores when compared to placebo or standard care. The findings suggest autologous stem cell therapy is a promising treatment for “no-option” candidates.
Arango-Rodríguez et al. ^[16]	A randomized, double-blind, controlled study in diabetic patients with CLTI compared auto-BM-MNC and allo-WJ- MSCs. Both cell types demonstrated potential therapeutic benefits, indicating stem cell therapy could be a promising alternative treatment.

Meta-analyses reveal that studies on autologous cell therapy s for PAD/CLTI, mostly have small sample sizes and considerable heterogeneity with respect to study design, characteristics of the disease, types and doses of cells, and length of follow-up, resulting in limited statistical power and clarity of results. Primary outcomes evaluated were amputation-free survival (AFS), perfusion of the limb (e.g., ABIs and TcPO₂), and functional ability (e.g., rest pain and pain-free walking distance). All of the above outcomes had considerable variability; however, autologous cell therapy has generally demonstrated some potential for improving these outcomes, particularly in patient’s ineligible for revascularization. Thus, these data suggest a promising avenue for limb salvage and an improved quality of life; although, more well-designed studies are needed to determine their safety and effectiveness. ^[12]

3.2 Coronary and cardiac cell-therapy trials

Over 200 clinical trials have examined stem cell therapies—including MSCs, EPCs, and BM-MNCs—for acute MI, chronic ischemic cardiomyopathy, CAD, and IHD. The results of these trials confirm safety but show modest, inconsistent efficacy, with some improvements in LVEF, perfusion, and function lacking statistical significance. Key insights highlight optimizing cell dose, delivery route, timing, and patient selection, alongside advanced imaging to track cell

fate and assess outcomes. These findings can guide the development of targeted, plaque-directed cell therapies addressing CAD pathophysiology more precisely. ^[108, 109, 110, 110]

3.3 Therapeutic Potential of Adipose-Derived MSC-Derived Exosomes

Adipose-derived mesenchymal stem cells (ADSCs) and their exosomes show promise for stabilization in atherosclerosis plaque by modulating lipids, reducing inflammation, and promoting repair via paracrine factors. ADSC exosomes assist the process of cholesterol exit from cells through the upregulation of the cholesterol transporters ABCA1 and ABCG1. A challenge to clinical translation of ADSC exosomes is variability among donors, such as type 2 diabetes and/or obesity. Ongoing trials will assess the safety and efficacy of ADSC exosomes from patients with diabetes and/or obesity; however, additional research is warranted with regard to donor variables influencing ADSC exosome product quality. ^[8]

4. Shifting from Regeneration to Plaque Reprogramming

4.1 Limitations of Regenerative Strategies in Atherosclerosis

Current evidence suggests that fully “regenerating” normal arterial wall in advanced

atherosclerosis is unlikely, but reprogramming plaque cells and microenvironment toward a stable, regressive state is increasingly plausible. [19, 20]

There are several significant limitations in the "regenerative" paradigm of the treatment of atherosclerosis and heart disease; even with 20 years of research into this area, stem cell therapies have yet to achieve clinical success; one factor contributing to the failure of stem cell therapies is a disconnect between the mechanisms of tissue repair and the mechanisms of disease. The clinical trial results obtained so far have demonstrated that stem cells can exhibit dysfunction and have genetic defects which underlie the conditions associated with atherosclerosis and heart disease; therefore, the authors of this article recommend an increased understanding of mechanisms through enhanced computational data analysis, through a common data repository, and through collaboration at a scientific/clinical level (clinical trial/longitudinal studies and integration of basic research with clinical trials and long-term). The existence of cardiovascular risk factors such as hypertension, diabetes, hyperlipidaemia, and smoking has a significant detrimental effect on the number and functionality of EPCs; therefore, there is a loss of therapeutic potential for autologous EPC therapies because of this factor, and the use of allogeneic EPCs will continue to be limited due to immunological incompatibility. Currently, no effective interventions exist to overcome EPC dysfunction caused by these risk factors. [19, 20]

Complete vascular regeneration in established atherosclerosis is limited, especially in patients with multiple risk factors. However, reprogramming plaque cells and their microenvironment—targeting macrophages, endothelium, innate immunity, and surrounding tissue—provides a mechanistic, scalable approach for plaque regression and stabilization, now the leading therapeutic framework. [19, 20]

4.2 Immunometabolic Modulation by Implanted Cellular Products

Novel findings from recent advances confirm the therapeutic potential of exosomes produced from stem cells to change the polarization of macrophages leading to alleviation of several inflammatory diseases.

Exosomes derived from mesenchymal stem cells (MSCs) can reduce the development of atherosclerosis through the induction of M2-type polarization of macrophages and decrease the presence of M1-type macrophages present within plaque by upregulating M2 candidate markers and downregulating M1 candidate markers via miR-21a-5p. This miRNA enhances expression of the M2 marker, Arg-1, while reducing expression of the M1 marker, iNOS, and decreasing expression of the transcription factor KLF6 resulting in a greater concentration of M2 macrophages [21]. Metabolically engineered stem cell-derived exosomes (DS-EXOs) can also affect macrophage heterogeneity within rheumatoid arthritis by promoting the ability of macrophages to convert from an M1-type to an M2-type macrophage. In-vitro, DS-EXOs will decrease expression of iNOS and increase expression of CD206 via miRNA let-7b-5p and miRNA-24-3p through modulation of the JAK-STAT pathway. Systemic DS-EXO treatment shifts joint macrophages toward M2, reducing proinflammatory M1 cells and synovial fibroblast activity, reprogramming the synovial microenvironment early in disease [22].

Implanted cells and engineered exosomes act as immune-metabolic modulators across models, coordinating macrophage polarization, autophagy, endothelial repair, and VSMC phenotype/calcification. This frames therapies as programmable tools that rewire plaque and vascular microenvironments along interconnected pathways rather than simple regenerators. [22]



4.3 Representative Engineered Cell-Derived Therapeutic Platforms

Table 3: Engineered Stem Cell-Derived Therapeutic Platforms

Engineered Stem Cell-derived Product	Modification / Feature	Mechanism/ Effect	Therapeutic outcome	Citation
MSCs overexpressing Akt	Akt protein overexpression	Promotes angiogenesis	Improved cardiac function	[8]
Platelet membrane - coated exosome-mimetic nanovesicles	Platelet membrane coating	Upregulates cholesterol transporters ABCA1 and ABCG1	Reduces intracellular cholesterol accumulation	[8]
MSC-ExoP	Platelet- membrane fusion	Enhances plaque targeting, activates VSMC autophagy	Reduces VSMC proliferation, migration, foam-cell formation	[23]
Platelet- mimetic exosomes for restenosis (PM-Exo)	Platelet- membrane fusion	Improves injured artery homing, promotes endothelial repair	Limits neointimal hyperplasia	[24]
Platelet- MSC hybrid exosomes for myocardial infarction	Platelet- membrane fusion	Boosts uptake by endothelial cells and cardiomyocytes	Enhances cardiac targeting and post-MI functional recovery	[25]

These case studies show that platelet-membrane-engineered exosomes/nanovesicles greatly improve vascular and myocardial targeting, enhancing uptake by endothelial cells, cardiomyocytes, and plaque regions. Across models of atherosclerosis, restenosis, and myocardial infarction, they reprogram plaque and vascular cells [8, 8, 23, 24, 25].

4.4 Relevance of Plaque Reprogramming for Clinical Evaluation

Atherosclerosis therapy is shifting from a limited “regeneration” view to plaque reprogramming, where implanted cells and exosomes are designed as immune-metabolic modulators that tune macrophage polarization, efferocytosis, autophagy, endothelial repair, VSMC phenotypic switching and anti-calcific pathways to shrink

necrotic core and thicken fibrous cap, thereby stabilizing plaques and reducing events [26,27,28,29]. By engineering mesenchymal stem cells (MSCs) and their exosomes to provide mechanistic therapy tailored to individual patients—rather than simply a broad regenerative response—targeted therapy can be achieved. For example, through use of exosomes released from MSCs that overexpress Akt, angiogenesis is enhanced and cardiac function is improved post-myocardial infarction by acting through the PDGF-D/Akt pathway.

Exosome-mimetic nanovesicles (P-ENVs) derived from platelets are directed toward atherosclerotic plaque sites, activate ABCA1/ABCG1, enhance cholesterol efflux, and decrease both lipid- and necrotic-core volume. Exosomes derived from MSCs that fuse with platelet membranes (MSC-ExoP) concentrate at the site of plaques, activate autophagy in vascular smooth muscle cells

(VSMCs), and inhibit VSMC proliferation, migration, and foam-cell formation, thereby promoting stabilization of these lesions. Platelet-mimetic exosomes for restenosis (PM-EXOs) show fourfold higher uptake in injured arteries, promote endothelial repair, shift macrophages to anti-inflammatory phenotypes, and prevent VSMC phenotypic switching, reducing neointimal hyperplasia without systemic toxicity [23,24]. Platelet–MSC hybrid exosomes for MI exploit platelet homing to enhance uptake by endothelial cells and cardiomyocytes, improving exosome accumulation in injured myocardium and post-MI functional recovery [25]

5. Bioengineered Vascular Interfaces for Plaque-Targeted Therapy

Bioengineered vascular interfaces have evolved from bare-metal and drug-eluting stents to bio-functional, cell-interactive devices designed to stimulate endothelialisation and site-specific repair. Injectable/implantable scaffolds of PBMNC for CLTI and plaques are intended to improve cell retention, survival, local therapeutic-genetic effects with safety. New biomimetic approaches such as membrane-guided nanoparticles and exosome-loaded devices also offer the potential for specific cutting-edge of plaque targeting and signal-oriented vascular regeneration. Together, these approaches straddle the line between promise and delivery in terms of translation, scaling, regulation and established long-term safety [4, 23, 24, 25, 30, 31, 32, 33, 34].

Table 4: Mapping bioengineered vascular interface examples

Bioengineered vascular interface	Examples	Citations
Cell-interactive stents	Platelet-membrane-coated rapamycin DES; exosome-eluting stents; exosome-functionalized stent surfaces	[30,31,32]
Resorbable scaffolds (ICS-001)	PBMNC-loaded ICS-001 intramuscular scaffold for CLTI; exploratory trial data	[33]
Biomimetic nano/exosome hybrids	Platelet-decorated exosomes for restenosis; platelet-exosome hybrids for plaques and MI; hybrid membrane NPs for CVD	[24,4,34, 23,25]

6. Delivery Science and Design Principles for Arterial Implants

Therapeutic arterial implants face distinct mechanical and biological constraints in coronary vs peripheral beds, which shape feasible delivery routes, drug/cell dosing, and imaging readouts. Existing stent, liquid-drug, and graft technologies provide a practical “design window” for new cell or gene-based arterial implants [48, 49, 50].

6.1 Physical constraints of coronary and peripheral delivery

Shear stress & geometry: Coronary and peripheral stenting produce localized low and high shear stress forces at the edges of struts and in relation to the anastomotic connection. Variables that significantly influence the recirculation zones and risk of restenosis include curvature; the anastomotic angle; the material stiffness; and ratio of graft diameter to recipient artery diameter. [35,36,37]

Access routes: Contemporary practice spans femoral, radial/ulnar, axillary, carotid, and transcaval access, chosen by sheath size,



tortuosity, and comorbidities. These limit device profile and support for bulky cell/gene systems. [38]

Microvasculature: CABG and peripheral graft modelling show downstream resistance and uncertain peripheral hemodynamic substantially affect wall stress and strain predictions, underscoring the need for robust design margins. [39,37]

The major mechanical constraint and an associated design consideration for each of the four procedures were collectively described as follows: For coronary percutaneous coronary interventions (PCIs) employing drug-eluting stents, shear stress disturbances due to the curvature of blood vessels and the forces acting on the edges of the stent are primarily localized. Therefore, the design must have thin, flexible, conformable struts that preserve radial strength while minimizing poor positioning to reduce both the risk of restenosis and stent thrombosis. [40,41, 42]

The presence of repetitive flexion, compression, and torsion combined with complicated plaque in superficial femoral and femoropopliteal interventions with low shear or oscillatory shear mean that fatigue-resistant structural supports as well as optimizing drug delivery are required to maintain patency during these procedures and prevent fracture or an excessive amount of neointimal growth following these interventions. [41,43,44]

Designs for femoral bypass grafts, including peripheral vascular bypass grafts and tissue-engineered femoral grafts, focus on mechanical matching, long-term durability when loaded with physiologic loads, and promotion of arteriogenesis rather than intimal hyperplasia in order to drive failure due to a lack of compliance and disturbed shear at the anastomoses [45, 41, 46, 47]

6.2 Insights from Existing Trials to Define Design Windows

Endovascular drug devices: Drug-eluting stents, balloons, and local liquid-drug delivery (LLD) catheters (Bullfrog, ClearWay, OPC, TAPAS) reliably deliver high local doses over 10–150 mm segments with favourable safety, supporting “leave-nothing-behind” concepts. [48, 49, 50]

Imaging-guided PCI: IVUS/OCT guidance reduces target lesion failure, MACE, restenosis, and stent thrombosis vs angiography alone across 15,000–18,000 patients. This defines a practical imaging backbone for arterial implant trials. [51,52,53,54,55,36]

Peripheral imaging: In femoropopliteal disease, IVUS/OCT detect more dissections, calcification, and under expansion than angiography and are associated with lower restenosis when used to guide therapy. [56, 57]

Imaging Endpoints for Plaque Stabilisation / Implant Performance

Intravascular imaging (core for “design rules”):

IVUS: Vessel size, plaque burden, stent expansion, edge dissections; prognostic for TLR, TVR, MACE. [51, 52, 53, 54, 55]

OCT: High-resolution neointimal thickness, malposition, tissue protrusion, microcalcification, and healing; useful for mechanistic readouts of endothelialisation and drug/cell distribution. [51, 54, 55, 50]

For peripheral implants: IVUS/OCT in femoropopliteal arteries refine sizing and correlate with incidence of restenosis and reintervention. [56, 57]

Non-invasive / systemic: MRI/CT angiography for lumen and remodelling, PET for inflammatory activity, and clinical endpoints (TVF, limb salvage, CLTI improvement) are established as logical higher-order outcomes variables extrapolated from endovascular drug-device literature. [58, 49, 50, 59]



6.3 Design Principles for Optimizing Retention, Homing, and Viability

From drug-eluting and liquid-delivery platforms, key transferable principles:

6.3.1 Matching of the mechanical characteristics of devices to local haemodynamic should attempt to avoid extremes of shear stress and oscillation index value, both of which stimulate neointima formation and thrombosis. [35, 55, 37]

6.3.2 Lesion-specific delivery: Drug/cell type and formulation (polymeric capsules, reservoirs); Coating method will be determined by the plaque morphology (fibrotic vs lipid rich and calcific), as determined by IVUS/OCT/VH. [55, 50, 57]

6.3.3 Uniform intramural distribution: LLD catheters and microneedle/adventitial devices show that penetrating beyond the lumen (adventitial, intramural) can improve homogeneity and reduction in systemic spillover. [48, 49, 50]

6.4.4 Chronic support vs leave-nothing-behind: Reservoir implants and intravascular pumps maintain stable therapeutic windows for years but at the cost of device complexity; “leave-nothing-behind” LLD and balloons prioritize vessel natural history and future re-intervention options. [58, 48, 49, 59]

7. Systemic Modifiers and Precision Context for Implantable Therapies

Implant integration and cardiovascular cell therapies are strongly shaped by systemic factors such as ageing, obesity, diabetes, clonal haematopoiesis, and baseline inflammatory tone. Emerging work also links anti-inflammatory biologics and colchicine with outcomes, suggesting shared pathways that could guide precision patient selection [60, 66, 67, 68].

7.1 Impact of Systemic Risk Factors on Implant Response

Systemic factors critically shape both cell product quality and host responses to implants. Aging and immunosenescence skew macrophage polarization, delay resolution, and prolong mesh-induced inflammation in an organ-specific manner, indicating that “biocompatibility” is age- and context-dependent [60, 61, 62]. Obesity and diabetes sustain peri-implant inflammation and impair tissue and bone integration (e.g., titanium), characterized by excess neutrophils/M1 macrophages, reduced MSC recruitment, and dysfunctional regenerative cells [63,64,65]. Obesity-driven inflammation also accelerates clonal expansion of CHIP-mutant hematopoietic stem/progenitor cells [66]. Clonal haematopoiesis amplifies inflammatory signalling and vascular risk, while IL-1 pathway blockade (e.g., anakinra) and other agents can suppress mutant clone growth in preclinical models [67, 68, 69, 70].

7.2 Responder and Non-Responder Phenotypes in Cell-Therapy Trials

Baseline clinical factors predict response to intracoronary CD34+ therapy in end-stage CAD: prior smoking (positive), female sex, lower angina class, and milder diastolic dysfunction (negative predictors: male sex, severe angina, higher diastolic grade) [71]. After MI, responders to BM-MNC therapy have broadly higher baseline cytokine/growth factor levels (e.g., stem cell factor, PDGF-BB, IL-15), suggesting a “primed” reparative inflammatory milieu [72]. In NIDCM, genotype strongly stratifies response to MSCs: patients without pathogenic variants gain EF and survival benefit, whereas those with pathogenic variants may not and have worse outcomes [73]. Reviews emphasize that age, diabetes, heart failure, and overall risk profile reduce autologous bone marrow cell quality and may underlie non-response [74, 75].



7.3 Integration with Anti-Inflammatory Therapeutic Strategies

Inhibition of IL-1 β in the CANTOS study and low-dose colchicine in the COLCOT study demonstrate that targeting the NLRP3-IL-1-IL-6 axis reduces recurrent events in atherosclerotic cardiovascular disease (CVD) and establishes residual inflammatory risk as an exploitable modifiable risk factor [76, 77, 78, 3]. High sensitivity CRP and IL-6 can serve to identify patients who may benefit from anti-inflammatory therapies to better allocate precision medicine resources in the treatment of atherosclerosis [76, 79, 77, 78, 3]. The purpose of the upcoming CADENCE trial will be to determine if FDG-PET imaging of arterial inflammation and biomarker levels (hs-CRP, IL-6, IL-1 β , TNF- α , MCP-1) can identify patients who responded to colchicine treatment after recent vascular events and with diabetes/prediabetes [80].

7.4 Framework for precision implantable therapy in atherosclerosis

An Implantable Therapy Precision Framework for the treatment of Atherosclerosis can be achieved through a comprehensive profile for the patient, which includes their systemic inflammatory state, their metabolic state, their presence of Clonal Haematopoiesis, and their immune phenotype. As such, this will enable the clinician to select potential candidates for implants in a tailored manner and also optimise the design of those implants by, if necessary, combining cell therapy with targeted, anti-inflammatory agents. Using biomarkers to monitor the patient prior to, and after, implanting their device, the clinician will be able to dynamically adjust the patient's therapy to ensure maximum efficacy and minimise adverse effects. Ultimately, integrating systemic context with implant design and patient management will

provide the basis for precision medicine in atherosclerotic treatment [81, 82, 83, 84].

8. Unmet gaps in Current Reviews and Proposed Clinical Roadmap for Implantable Therapies in Atherosclerosis

Most regenerative reviews emphasize systemic stem/cell therapy and generic tissue regeneration, which are often in bone or dental models, with limited attention to vascular implants or ischemic limb salvage [85, 86, 87, 88, 89, 90].

8.1 Key gaps:

8.1.1. Implantable/localised platforms (drug-eluting or cell-loaded scaffolds, nano-engineered surfaces) although there is an increasing amount of information on implantable/localised platforms are under-represented despite emerging data in CLTI and dental implants [33, 91, 92, 93, 94].

8.1.2. Engineering–plaque biology–trial design integration is weak: biomaterial advances (scaffolds, nanocarriers, antimicrobial/therapeutic coatings) frequently exceed the development of in-vivo plaque-relevant models, sterility/packaging standards, and clinical translation frameworks [91, 92, 9, 94].

8.1.3. Responder biology and systemic modifiers (age, diabetes, inflammation, immune milieu) are rarely built into inclusion criteria or analysis, despite having significant effect on cell function and outcomes in PAD/diabetic foot and PBMNC-based CLTI therapy [13, 86, 87, 95, 15, 96].

8.2 Current Clinical Signal; across ASO/CLI/diabetic foot, autologous cell therapy provides moderate, realistic, and achievable benefits in limb salvage, perfusion (ABI, TcPO₂), ulcer healing, pain and walking distance, with no mortality benefit and effect sizes attenuating in



higher-quality RCTs. Safety is generally favourable; serious cell-related adverse events are rare, but there is still insufficient long-term monitoring of cellular therapies [13, 86, 95, 15, 96].

8.3 Proposed Clinical Roadmap

(I)CLTI scaffold-assisted cell implants: adequately powered RCTs using injectable or resorbable scaffolds plus PBMNCs/stem cells, with primary endpoints of major amputation/limb salvage and perfusion [33, 13, 86, 91, 92, 93].

Previous plaque-stabilisation trials: localized, implant or nanocarrier-based therapies with imaging and patency endpoints, modelled on BTK scaffold studies and targeted delivery platforms [91, 9, 92, 93].

Biomarker/immunophenotype-guided

inclusion: enrich for likely responders using inflammatory, perfusion, and immune markers (e.g., PBMNC signatures, TcPO₂, diabetes status) and stratify analyses accordingly [86, 87, 9, 95, 15, 96].

9. Future Directions and Translational Perspectives

Cell based implants are progressing towards engineered, mechanism driven localized implants that provide prolonged localized therapy and are synergistic with systemic treatments and not to replace systemic treatments. Future success will depend on a rational association of cell type with device, indication, and standardized end points to each regulatory pathways' definition. Currently implantable strategies designs emphasize: (i) type/source of implanted cells (primary, iPSC-derived, immune or stroma) selected for targeted type of paracrine, immune, or replacement function; [97, 98, 99]. (ii) Engineering of allergenic cells or substrates for survival and immune evasion via encapsulation, scaffold design, large devices or modifying membranes / or local substrates for controllable delivery [97, 100, 101, 102,

103, 84]. (iii) Delivery of cell-based therapies via pre-existing scaffold(s), hydrogels, or large encapsulating devices, locally applied to the disease site or resection site(s); [97, 101, 102, 84]. (iv) Target mechanisms expansion shift from engraftment to create paracrine, immunomodulatory, or drug carrier function; [97, 104, 105, 99]. (v) Ideal patient for implantation has focal, high risk, or refractory disease where sustained local therapy complements systemic therapy; [97, 101, 84, 106]. (vi) Key Endpoints for determination will include safety (fibrosis, immune response), device performance (release of drug / biomaterial or continuing percutaneous or per se), and clinical outcomes (organ function, reduction of clinical events) and standardized measures to determine these endpoints [107, 102, 104, 103].

Strategic 5–10-year priorities include harmonizing development/assessment; analysing mechanisms which underpin the paracrine & immune interactions; developing scalable GMP production facilities; and providing bespoke, modular biomaterials [107, 101, 98, 102, 104, 103, 99]. For cardiometabolic disorders, implantable cellular deposits can supplement the use of systemic lipid lowering & anti-inflammatory medicines by providing local plaque or myocardial conditioning; sustained anti-inflammatory/paracrine signals; and reduced levels of systemically active products [97, 104, 103, 99]. Ultimately, the successful clinical implementation & regulatory acceptance of these complex products will depend on demonstrating robust mechanism-related efficacy; reproducible manufacturing; long-term safety (tumorigenicity, device failure, immune responses); and establishing that these complicated implants are superior to optimum systemic pharmacotherapy in terms of long-term & consistent overall benefit [107, 101, 102, 104, 103, 99, 106].



Bibliometric Analysis

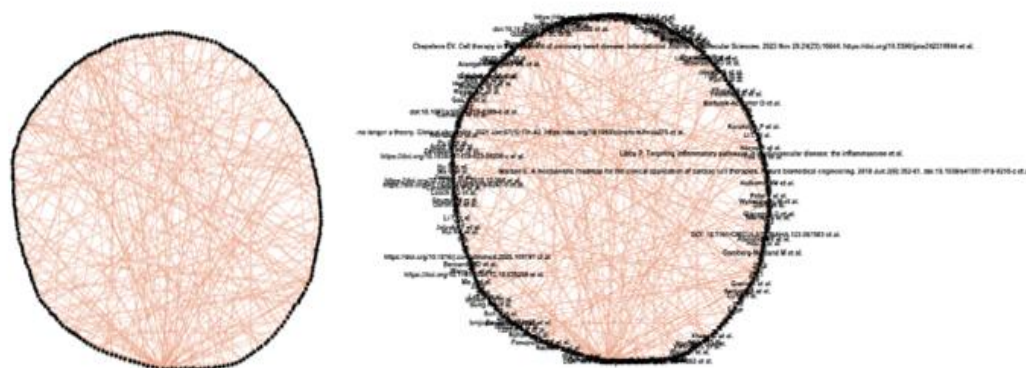


Figure 2. Bibliometric Network Visualization Depicting the Evolution Over Time of Research on Implantable Therapies for Atherosclerosis. Nodes in This Network Represent Key Authors or Documents, and Edges Represent Co-Citation Relationships That Are Weighted by the Year of Publication. The transition from early, foundational work on delivery of cells and stenting technologies, to contemporary science on plaque reprogramming, exosome engineering, and precision bio interfaces is evidenced by clusters indicating the increasing multidisciplinary integration of bioengineering, immunology, and clinical translation. These clusters also highlight the new rise in targeted implantable systems as primary therapeutic leads in the treatment of cardiovascular disease.

CONCLUSION

Cell-based implant therapies provide an innovative localized strategy for modifying the progression of atherosclerosis through sustained targeted interventions to overcome the limitations of systemic approaches. In addition, bioengineered vascular interfaces and exosome delivery systems enhance an aggregate of plaque biology through immune/exocytic metabolic reprogramming (i.e., repopulation of endothelial cells along with plaque stabilization). Maximizing therapeutic benefit will depend on integrating delivery science, imaging, and systemic modifiers (e.g., inflammation, age, and metabolic comorbidities). Although clinical studies in PAD and limb ischemia have shown promise, large, rigorously designed biomarker-based trials with standardized endpoints must be performed to assess long-term safety and efficacy. Future advances toward establishing implantable therapies as adjunctive agents to systemic medications for the management of chronic atherosclerotic disease will require ongoing collaboration between scientists, engineers, and regulators to create scalable manufacturing, refine

the designs of devices, and develop appropriate regulatory pathways.

Declaration of Conflict of interest

The authors confirm that there is no conflict of interest related to this manuscript. No funding was received for this study.

Abbreviation list

- ADSC: Adipose-Derived Mesenchymal Stem Cells
- ABI: Ankle-Brachial Index
- BM-MNC: Bone Marrow Mononuclear Cells
- CAD: Coronary Artery Disease
- CANTOS: Canakinumab Anti-inflammatory Thrombosis Outcomes Study
- CD34+: Cluster of Differentiation 34 Positive Cells
- CHIP: Clonal Haematopoiesis of Indeterminate Potential
- CLTI: Chronic Limb-Threatening Ischemia
- CVD: Cardiovascular Disease
- EC: Endothelial Cells



- EF: Ejection Fraction
- EPC: Endothelial Progenitor Cells
- HDL: High-Density Lipoprotein
- HMGA2: High Mobility Group AT-Hook 2
- IL-1 β : Interleukin-1 Beta
- IVUS: Intravascular Ultrasound
- LLD: Local Liquid-Drug Delivery
- LVEF: Left Ventricular Ejection Fraction
- M1: Pro-inflammatory Macrophage Phenotype
- M2: Anti-inflammatory Macrophage Phenotype
- MSC: Mesenchymal Stem Cells
- MSC-ExoP: Platelet-Membrane Fused MSC Exosomes
- NIDCM: Non-Ischemic Dilated Cardiomyopathy
- OCT: Optical Coherence Tomography
- PAD: Peripheral Artery Disease
- PBMNC: Peripheral Blood Mononuclear Cells
- PCI: Percutaneous Coronary Intervention
- PDGF: Platelet-Derived Growth Factor
- PM-Exo: Platelet-Mimetic Exosomes
- RUNX2: Runt-Related Transcription Factor 2
- TcPO₂: Transcutaneous Oxygen Tension
- TLR: Target Lesion Revascularization
- VSMC: Vascular Smooth Muscle Cells

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