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Hydrogel-Coated Coronary Stents for Vascular Healing: Design Strategies, Controlled Drug Delivery, Endothelialization and Translational Challenges

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Abstract : *Hydrogel-coated coronary stents represent one strategy to conjugate mechanical support with a hydrated interface capable of modulating thrombosis, inflammation, endothelial recovery, smooth-muscle proliferation and vascular remodelling. This review covers hydrogel composition, network architecture, cross-linking, surface chemistry, mesh size, porosity, mechanical compatibility, coating durability, fabrication and controlled delivery of molecules, proteins, nitric oxide and nucleic acids. Mechanism-guided design: Antithrombotic, endothelializing, antirestenotic, nitric oxide-mediated, and immunomodulatory effects. The focus is on correlating material properties and release kinetics with cellular, molecular, flow, tissue and in vivo outcomes. A staged validation framework of in vitro, dynamic flow, ex vivo, and large-animal studies is proposed to enable translational development and identify thrombogenicity, delayed healing, delamination, particulates, and late lumen loss.*

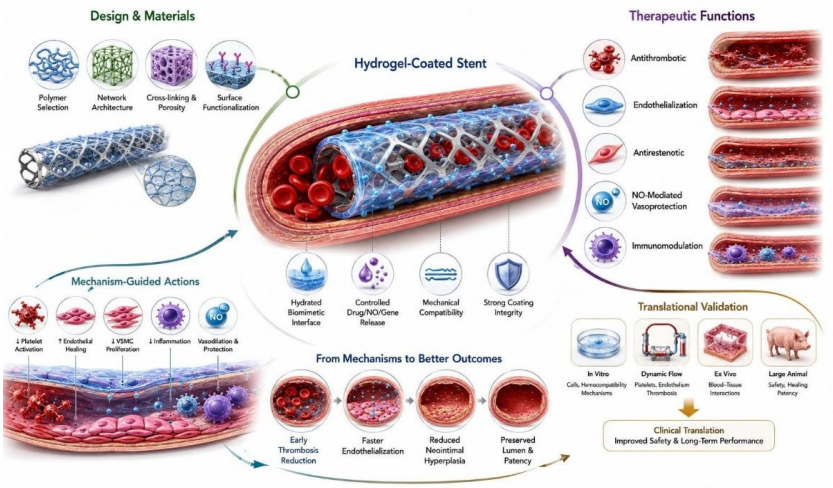

Fig no 1: Graphical abstract.

Keywords: Hydrogel-coated stents, Coronary stents, Vascular healing, Biomaterials, Endothelialization, Antithrombotic therapy, Antirestenotic therapy, Nitric oxide, Controlled drug delivery, Vascular smooth muscle cells, Immunomodulation, Drug-eluting stents, Translational validation and Cardiovascular biomaterials.

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I. INTRODUCTION

Coronary stents have revolutionised percutaneous coronary intervention by restoring and maintaining vessel patency but in-stent restenosis, delayed endothelial healing, stent thrombosis and persistent vascular inflammation remain important limitations to long-term outcome [1]. The mechanical mismatch of rigid stent platforms and compliant arterial tissue can disturb local biomechanics, favouring abnormal shear stress, inflammation and neointimal hyperplasia. Drug-eluting stents have greatly reduced restenosis, but there are still concerns about delayed endothelialization and long-term exposure to metallic and polymeric components [2].

These challenges have spurred the development of advanced stent platforms that meld mechanical support with biologically active interfaces [3]. Hydrogels offer a hydrated, tunable surface that can influence protein adsorption, platelet activation, inflammation and cell behaviour [4]. Their three-dimensional networks can also enable localised delivery of therapeutic agents such as drugs, peptides, genes, nitric oxide donors and growth factors [5].

Here, we review how hydrogel composition and design influence mechanical compatibility, hemocompatibility, endothelial regeneration, smooth muscle proliferation, inflammation and vascular remodelling, focusing on material-biology relationships and translational potential.

II. HYDROGEL ARCHITECTURE AND STRUCTURE PROPERTY RELATIONSHIPS

The therapeutic function of vascular hydrogels is ultimately controlled by the chemistry of the polymers, the architecture of the network, the density of cross-linking, the kinetics of degradation, and the mechanical properties, which collectively influence hydration, swelling, molecular transport, tissue adhesion, cellular responses, and the spatiotemporal release of cargo [6]. Therefore, the selection of polymers should be based on the functional needs of the vascular environment, not solely on biocompatibility. Natural polymers provide ECM-like bioactivity, whereas synthetic polymers offer more control over mechanical properties, degradation, reproducibility, and network structure. These complementary features can be combined in hybrid systems [7].

Polymer Chemistry

Alginate forms hydrated, ionically cross-linked networks, typically with Ca^{2+}, in which cross-link density governs porosity, swelling, mechanical stability, and solute diffusion. Its anionic carboxyl groups also influence interactions with proteins and charged therapeutics [8].

Gelatin is a denatured collagen that contains cell-interactive sequences for enhanced cell adhesion and ECM-like properties. Nevertheless, it typically needs further cross-linking or polymer blending to enhance its mechanical stability under physiological conditions [9].

Hyaluronic acid (HA) is a highly hydrophilic glycosaminoglycan that interacts with cellular receptors involved in migration, proliferation, inflammation and tissue remodelling, and promotes water retention and viscoelasticity. These properties are determined by the molecular weight and chemical modification of it [10].

Chondroitin sulphate (CS) is an anionic polysaccharide present in nature, providing a hydrated environment, modulating protein binding, ionic interactions, and cell material responses, and potentially improving ECM mimicry.

Polyethylene glycol (PEG) imparts hydrophilicity and low fouling behaviour by limiting non-specific protein adsorption. Functionalisation or incorporation in hybrid networks enables combination with bioactive polymers [11].

Cross-Linking and Network Density

Cross-linking controls polymer-chain connectivity and therefore hydrogel mesh size, swelling, mechanical strength, viscoelasticity, degradation, and molecular transport. Increasing the cross-link density generally reduces the mesh size and swelling, while improving the mechanical stability and limiting the therapeutic diffusion. Conversely, loosely cross-linked networks are more hydrated and more mobile at the molecular scale, but they may swell excessively, degrade rapidly and lack structural stability. Accordingly, the network density should be optimised based on the therapeutic cargo, required release duration, vascular mechanical environment and degradation profile [12]. The performance of the hydrogel is also affected by cross-linking chemistry, bond reversibility, polymer architecture, and network heterogeneity.

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Ionic cross-linking, such as Ca^{2+}-cross-linked alginate, enables mild fabrication conditions suitable for sensitive biomolecules but may show reduced stability under physiological ion exchange. Covalent cross-linking leads to more robust and stable networks, but too much cross-linking can limit the swelling and diffusion of molecules. Physical cross-linking is based on reversible interactions, offering flexibility and viscoelasticity but usually lower mechanical strength [13]. Double-network, interpenetrating, and self-healing hydrogels can improve toughness, structural stability, and resistance to cyclic vascular deformation, which are attractive for stent interfaces [14].

Surface Charge, Hydrophilicity, and Protein Adsorption

Surface characteristics of hydrogels are important in their interactions with blood and vascular tissues, affecting thrombogenicity, inflammation, and endothelialization. Platelets and leukocytes responses and cellular attachment are governed by a combination of surface charge, hydrophilicity, interfacial hydration and protein adsorption [15].

The surface charge influences the electrostatic interactions with plasma proteins and cell membranes. Highly cationic surfaces can increase protein adsorption and platelet activation. Anionic surfaces can result in charge-dependent changes in protein adsorption. Zwitterionic groups with co-localized positive and negative charges create highly hydrated interfaces that reduce nonspecific protein and cellular interactions. Similarly, hydrophilic polymers such as PEG and polysaccharide based materials can retain surface hydration and suppress nonspecific adsorption. However, excessive antifouling activity can inhibit endothelial-cell attachment, which points out the necessity of balancing hemocompatibility with selective bioactivity [16].

When in contact with blood, proteins rapidly adsorb onto the hydrogel to form the biological interface sensed by the cells. Surface chemistry and architecture influence the amount, composition, orientation and conformation of adsorbed proteins. Excess fibrinogen and fibronectin adsorption may facilitate platelet adhesion and inflammatory signalling. Thus, the incorporation of antifouling domains with selective presentation of extracellular matrix ligands may minimise thrombosis and support endothelialization simultaneously.

Mesh Size, Porosity, and Diffusion

Mesh size (ξ) is the average distance between polymer chains or cross-linking points in a hydrated hydrogel. It acts as a molecular sieve and is an important determinant of drug transport. The effective diffusion coefficient in hydrogel is lower than in water because of steric hindrance, tortuosity, limited porosity and polymer-drug interactions:

$$D_{\text{eff}} = D_0 \frac{\varepsilon}{\tau} K$$

where D_0 is the diffusion coefficient in water, ε is accessible porosity, τ is tortuosity, and $K$is the partition or hindrance factor. Diffusion decreases as the ratio of drug hydrodynamic radius (r_h) to mesh size (ξ) approaches unity. Molecules larger than the mesh experience severely restricted transport [17].

The mesh size depends on the polymer concentration, molecular weight, cross-linking density, swelling and the network structure. In general, the mesh size and molecular mobility decrease with increasing polymer concentration or cross-linking density. While theoretical network models relate mesh size to polymer volume fraction and molecular weight between cross-links, real hydrogels exhibit heterogeneity, nonideal cross-linking, and time-dependent swelling.

Large meshes allow for quick diffusion, and may cause burst release. Smaller meshes increase drug retention, allowing for sustained release. However, highly restrictive networks may limit the transport of proteins, nucleic acids and nanoparticle-based therapeutics . Other factors affecting the release are drug charge, hydrophobicity, binding, swelling and degradation, and polymer-drug interactions [18].

Fick's first law describes transport by concentration:

$$J = -D_{\text{eff}} \frac{\partial C}{\partial x}$$

where J is molecular flux and C is drug concentration. Time-dependent diffusion is described by:

$$\frac{\partial C}{\partial t} = D_{\text{eff}} \nabla^2 C$$

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Porosity is the volume available for diffusion and tortuosity is the complexity of the transport path. High porosity does not necessarily guarantee rapid diffusion, pore interconnectivity, pore size distribution, mesh size and tortuosity also need to be taken into consideration. Degradation may induce swelling and increase the effective mesh, which may accelerate drug release [19].

The mesh size, porosity, tortuosity, cross-linking, swelling and degradation of the hydrogel coated stents should be optimised in conjunction with each other. The ideal network minimises burst release, maintains adequate drug exposure at the injured vessel wall, preserves mechanical integrity and supports sustained anti-restenotic therapy.

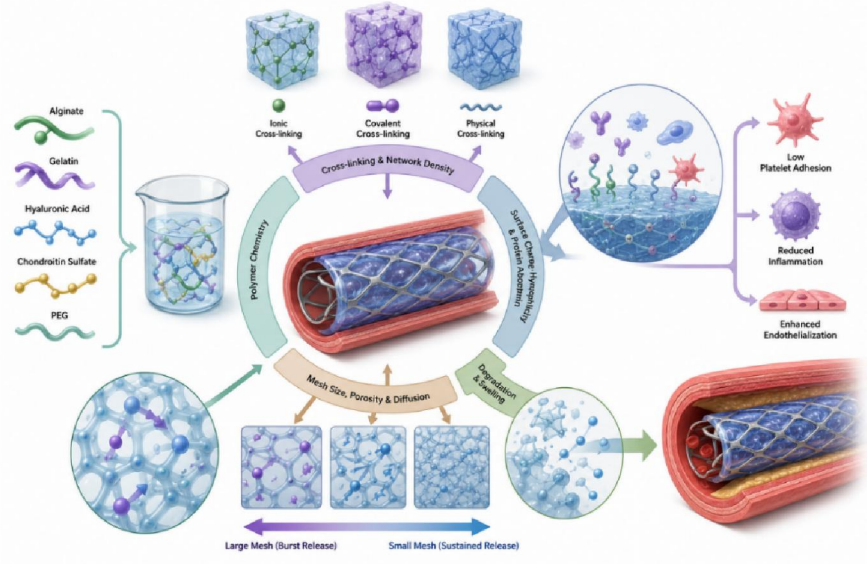

Fig no 2: Hydrogel Architecture Property Function Relationships Governing Stent Performance.

III. HYBRID STENT DESIGN AND MECHANICAL MECHANISM

Rationale for Hybrid Stents

Hydrogels have high hydration, tunable biology and localised drug delivery, but lack the stiffness and swelling stability needed for radial strength, deployment and fatigue resistance. Hybrid stents separate these functions: a metal or polymer backbone for structure and a hydrogel for a compliant biological interface and therapeutic reservoir [20].

Backbone (mechanical) Gives radial strength, lumen support, flexibility, deliverability, deployment stability and fatigue resistance. This allows the hydrogel to focus on its biological and therapeutic roles, while carrying the main mechanical load, without compromising the vascular support [21].

Hydrogel (biological/therapeutic) A hydrated interface between stent, blood and vessel wall. Reduces nonspecific interactions, promotes endothelialization and enables local delivery of sirolimus, paclitaxel, NO, siRNA or miRNA. Mesh size and crosslink density control loading and release as well as swelling, degradation and polymer-drug interactions. Uniformity and adhesion are important in deployment.

Mechanical matching The main difficulty is to combine a rigid backbone with a soft hydrogel. Interfacial stresses, arising from modulus, deformation, swelling and strain mismatches, develop during deployment and during physiological loading, risking cracking or delamination. Co-optimization of coating thickness, cross-linking, adhesion chemistry, interfacial architecture and stent geometry is required [22].

This functional separation allows the integration of mechanical stability, localised therapy, hemocompatibility and improved vascular healing in hybrid stents.

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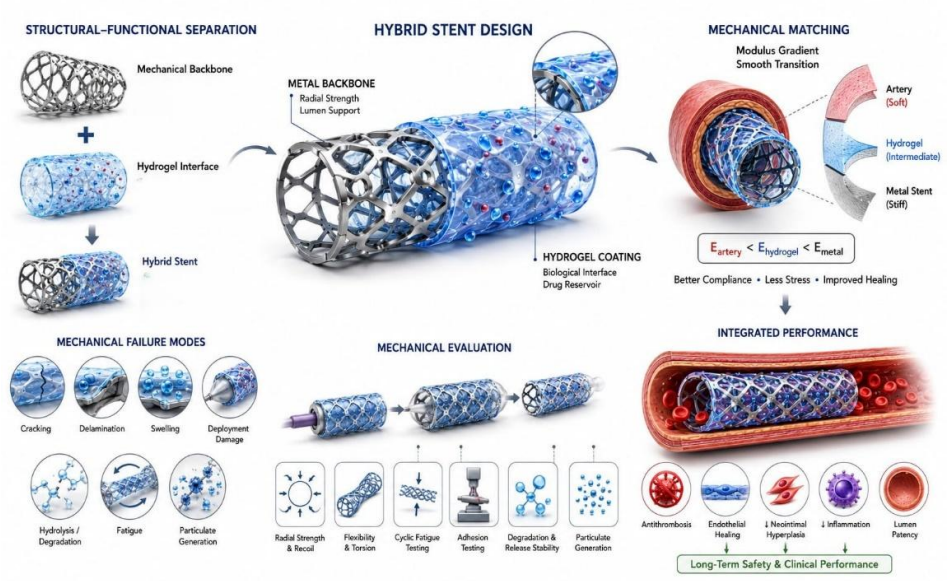

Fig no 3 : Hybrid Stent Architecture and Mechanochemical Integration of the Stent–Hydrogel Interface.

Compliance Matching

Compliance matching is the ability of a stent-artery system to undergo physiological deformation with minimal stress at the device-tissue interface. Metallic stents are much stiffer than arteries, leading to decreased local vascular compliance, disruption of wall mechanics and flow, and contributing to endothelial injury and neointimal formation.

For linear elastic deformation:

$$\sigma = E\varepsilon$$

where σ is stress, E is elastic modulus, and $\varepsilon$is strain. Compliance must be optimized alongside radial strength, flexibility, fatigue resistance, and deployment performance [23].

Role of the hydrogel interface: A compliant hydrogel coating provides a mechanical transition between rigid stent and deformable arterial wall:

$$E_{\text{artery}} < E_{\text{hydrogel}} < E_{\text{metal}}$$

This intermediate compliance may help to reduce stress concentrations and enhance conformal contact during cyclic deformation. The hydrogel mechanics can be adjusted by the polymer composition, water content, cross-linking density, network structure and coating thickness.

Performance is also affected by adhesion, viscoelasticity, swelling, strain compatibility and fatigue resistance. Coatings that are too soft or poorly adherent crack or delaminate . Well-designed hydrogels act as both compliant biointerfaces and localised drug-delivery systems [24].

Mechanical Failure Mechanisms

Durability depends on backbone integrity and hydrogel stability. Crimping, deployment, swelling, cyclic loading, blood exposure, and degradation generate stresses that can compromise coating integrity and therapeutic performance [25].

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Table no 1: Major mechanical failure modes of hydrogel-coated coronary stents, their causes, and potential consequences.

Sr.no.	Failure mode	Major cause	Potential consequence
1	Cracking	Tensile/shear stress; insufficient fracture resistance	Coating defects; altered drug release
2	Delamination	Weak adhesion; interfacial stress; differential deformation	Coating detachment; loss of function
3	Swelling	Water uptake; osmotic effects	Buckling; debonding; dimensional instability
4	Deployment damage	Rapid radial expansion; balloon–coating interaction	Surface defects; coating disruption
5	Hydrolysis/degradation	Cleavage of susceptible polymer chains or cross-links	Mechanical weakening; accelerated drug release
6	Fatigue	Repeated cyclic deformation	Progressive cracking; delamination
7	Particulate generation	Mechanical degradation; coating fragmentation	Potential inflammatory and thrombotic responses

Evaluation should include adhesion, deployment integrity, fatigue, degradation, release stability, and particulate generation under physiologically relevant conditions.

Mechanical Evaluation

Testing should evaluate the complete stent–hydrogel system during crimping, delivery, deployment, physiological deformation, and long-term implantation, following ISO 25539-2, ASTM radial-loading methods, and pulsatile-fatigue protocols [26].

Radial strength/stiffness determine resistance to vessel compression and lumen patency. Elastic recoil:

$$\text{Recoil} = \frac{D_{\max} - D_{\text{final}}}{D_{\max}} \times 100\%$$

where $D_{\max}$is maximum expanded diameter and $D_{\text{final}}$is diameter after force removal. The hydrogel should not substantially reduce radial strength, collapse resistance, or final expanded diameter.

Assess bending, torsion, longitudinal deformation, and cyclic loading alongside coating cracking, wrinkling, peeling, and delamination. Tensile/compression tests determine modulus, strength, elongation, failure strain:

$$E = \frac{\sigma}{\varepsilon}$$

For hydrated hydrogels, report temperature, hydration state, strain rate, loading frequency, and test duration [27].

Coating must remain adherent during crimping, delivery, expansion, and cyclic loading. Perform peel, pull-off, or shear tests before and after deployment, assessing coating integrity, exposed stent area, release, and particulates.

Monitor mechanical stability during degradation: changes in radial strength, modulus, adhesion, swelling, coating integrity, and release should remain within predefined limits throughout the therapeutic period.

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IV. MECHANISMS OF VASCULAR HEALING

Vascular healing after stent implantation involves thrombosis, inflammation, endothelial recovery, VSMC activation, matrix remodeling, and neointimal formation. Hydrogel-coated stents can influence these responses through hydration, chemistry, compliance, and localized drug or NO delivery.

Antithrombotic Mechanism

An interfacial water layer can reduce protein adsorption on hydrated polymer layers. Zwitterionic or PEG-based coatings can be useful, but effectiveness depends on surface density, chain conformation, hydration stability, and coating integrity after deployment [28].

Nitric oxide has an active antithrombotic effect by inhibiting platelet activation and aggregation. NO-releasing hydrogels can thus combine passive antifouling with direct thromboresistance. However, performance depends on flux, duration and coating stability [29].

The antithrombotic performance should be evaluated by haemolysis, protein adsorption, platelet adhesion/activation, thrombin generation, fibrin deposition, complement activation, thrombus formation under flow and whole blood loop testing. Flow-based testing is especially important as stent geometry and deployment may alter blood compatibility [30].

Endothelialization Mechanism

Rapid endothelialization is essential for restoring the natural antithrombotic, anti-inflammatory, and barrier functions of the vessel. Hydrogel coatings can support this process by providing endothelial-selective adhesion sites, controlled delivery of VEGF or nitric oxide (NO), and extracellular-matrix-like cues. RGD promotes cell adhesion but is not endothelial-specific, whereas REDV may provide greater endothelial selectivity. Controlled VEGF and NO delivery can further enhance endothelial migration and recovery while limiting platelet activation, inflammation, and VSMC proliferation [31].

The hydrogel surface should therefore balance cell adhesion with antifouling properties to promote endothelial coverage without excessive nonspecific cellular interactions. Functional recovery should be evaluated using endothelial markers such as CD31, VE-cadherin, eNOS, and KLF2, together with cell migration, barrier formation, and NO production. Importantly, simple cell attachment or viability is insufficient to demonstrate functional endothelialization; assessment should also consider thrombosis, inflammation, and neointimal formation [32].

Nitric Oxide–Mediated Vascular Protection

Nitric oxide (NO) is a key endogenous regulator of vascular homeostasis, inhibiting platelet adhesion and activation, suppressing vascular smooth muscle cell (VSMC) proliferation and migration, and reducing leukocyte–endothelium interactions via the sGC–cGMP–PKG pathway. Its biological effect depends on local flux, cumulative delivery, release duration, and bioavailability rather than total NO loading alone [33]. Cumulative NO delivery is expressed as:

$$M(t) = \int_0^t J_{\mathrm{NO}}(\tau) \cdot A \, d\tau$$

where $M(t)$ is the cumulative amount released, J_{NO} is NO flux, $A$is surface area, and t is time. NO-release studies should therefore be paired with functional assays for platelet inhibition, endothelial recovery, VSMC proliferation, inflammatory signaling, and oxidative stress, aiming for sustained local bioactivity without excessive or rapid release [34].

Antirestenotic Mechanisms

Restenosis involves VSMC phenotypic switching, migration, proliferation, extracellular-matrix deposition, and neointimal growth after vascular injury . Hydrogel-mediated local delivery seeks to interrupt this cascade while limiting systemic exposure. Sirolimus inhibits mTORC1 via FKBP12, paclitaxel stabilizes microtubules, NO activates sGC–cGMP–PKG, miR-145 promotes a contractile VSMC phenotype, and siRNA enables RISC-mediated gene silencing.

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Antirestenotic performance should be assessed using VSMC proliferation/migration assays, cell-cycle markers (Ki-67, PCNA), contractile markers (α-SMA, SM22α, calponin), and in vivo endpoints including neointimal area, lumen area, endothelial coverage, inflammation, and late lumen loss (LLL):

$$\mathrm{LLL} = \mathrm{MLD}_{\mathrm{post}} - \mathrm{MLD}_{\mathrm{follow-up}}$$

Lower LLL indicates better lumen preservation. Efficacy depends on local concentration, release kinetics, target engagement, and long-term remodeling, not drug loading alone [35].

Immunomodulatory Mechanisms

Stent implantation triggers inflammation involving platelets, endothelial cells, monocytes/macrophages, and VSMCs. Hydrogel-mediated immunomodulation aims to promote resolution of excessive inflammation rather than broadly suppress immune responses. Surface chemistry, protein adsorption, degradation products, and particulates can influence this response.

Macrophage behavior can be assessed using CD68, iNOS/CD86, CD206/Arg1, cytokine profiles, and functional assays, interpreted as complementary indicators rather than rigid M1/M2 categories. Persistent inflammatory signaling, including TNF-α, IL-1β, and IL-6, may promote endothelial dysfunction, oxidative stress, and VSMC activation, while TGF-β can contribute to fibrosis [36, 37].

Therefore, effective hydrogel design should promote balanced immune resolution, endothelial recovery, and controlled vascular remodeling while limiting excessive inflammation, fibrosis, and neointimal formation.

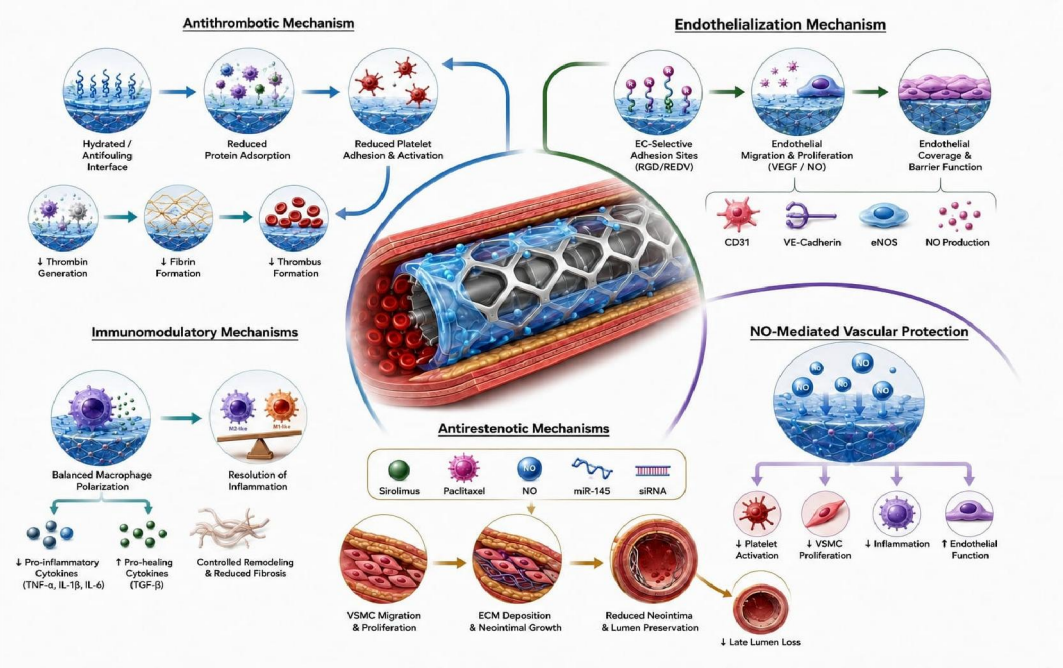

Fig no 4: Integrated Mechanisms of Vascular Healing Mediated by Hydrogel-coated Coronary Stents.

V. CONTROLLED DELIVERY FROM HYDROGEL STENTS

Stents coated with hydrogel act as tunable therapeutic reservoirs that optimise drug retention, transport and bioactivity. They allow localised delivery of small molecules, proteins and nucleic acids, reducing premature release and systemic exposure by controlling mesh size, cross-linking density, swelling, thickness, degradation and drug polymer interactions.

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Small-Molecule Delivery

Hydrogels can deliver sirolimus, paclitaxel, statins, antifibrotics, anti-inflammatories, and NO donors. Each agent differs in size, hydrophobicity, solubility, and polymer affinity, requiring tailored hydrogel architectures. Sirolimus inhibits mTOR to suppress VSMC proliferation; paclitaxel stabilizes microtubules to arrest mitosis. For both, the goal is sustained local exposure without early concentration spikes or excessive retention that limits tissue penetration [38].

NO delivery is distinct: because NO is reactive and short-lived, local flux and duration matter more than total loading:

$$J_{\mathrm{NO}} = -D_{\mathrm{eff}} \frac{dC}{dx}$$

Release involves overlapping mechanisms diffusion through the hydrated network, swelling-induced mesh expansion, degradation-driven permeability increases, and drug–polymer interactions (hydrophobic, electrostatic, hydrogen bonding, affinity). Stimulus-responsive hydrogels further modulate release via pH, enzymes, or redox cues [39]. The design target is an optimal local concentration–time profile, not maximal loading or longest release.

Protein and Growth-Factor Delivery

Hydrogels enable localized delivery of proteins such as VEGF and SDF-1/CXCL12 to promote endothelialization and recruit progenitor cells. Proteins are fragile: they denature, aggregate, oxidize, degrade enzymatically, and adsorb nonspecifically during fabrication and release. Thus, efficacy depends not only on release but on retained structural integrity and bioactivity [40].

VEGF creates a transient pro-endothelial niche; SDF-1 recruits $CXCR4^{+}$ regenerative cells. Both require appropriate local concentration, exposure duration, spatial distribution, and receptor engagement. Evaluation should include structural integrity post-release, aggregation/degradation, burst release, receptor activation, and cell-based functional assays. Detecting protein in release media does not confirm bioactivity; affinity retention, protective phases, or nanoparticle encapsulation can enhance stability and control [41].

Gene and Nucleic-Acid Delivery

Hydrogels can deliver siRNA, miRNA, plasmid DNA, mRNA, or nucleic-acid-loaded nanoparticles to modulate VSMC proliferation, inflammation, and matrix remodeling. siRNA enables sequence-specific gene silencing; miRNAs regulate multiple targets but risk off-target effects. Plasmid DNA requires carriers due to size and charge; mRNA offers transient expression but faces RNase degradation, poor uptake, endosomal trapping, immune activation, and instability.

The hydrogel governs local retention; the nanoparticle shields cargo and facilitates uptake. Efficacy must be proven by target-gene modulation, protein-level changes, and functional outcomes not just prolonged release. Polymer chemistry strongly influences siRNA retention and activity, highlighting the need to optimize hydrogel–cargo interactions [42].

Release Models and Therapeutic Window

Release kinetics reflect diffusion, swelling, polymer relaxation, degradation, erosion, and drug–polymer interactions. Models aid comparison but require physicochemical validation:

Higuchi: diffusion-dominated, stable networks.

Korsmeyer–Peppas: diffusion + polymer relaxation; interpret exponent with geometry and swelling data.

Degradation-based: cleavage-driven release.

Mechanistic diffusion–degradation: time-varying mesh size and diffusivity in biodegradable systems.

No single model proves mechanism; selection must match dominant transport and be validated by swelling, mesh size, degradation, and drug distribution data [43].

The therapeutic goal is a concentration–time profile that matches vascular healing phases: early anti-thrombotic/anti-inflammatory action, intermediate VSMC suppression, and late endothelial recovery. Multifunctional systems demand coordinated release because cargos differ in size, stability, diffusivity, and target. Optimal design prioritizes predictable, bioactive, clinically relevant exposure not maximal loading or slowest release [44].

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VI. FABRICATION STRATEGIES AND THEIR BIOLOGICAL CONSEQUENCES

Fabrication defines coating thickness, architecture, surface chemistry, cross-linking, porosity, mechanics, drug distribution, and degradation parameters that collectively govern hemocompatibility, endothelialization, release, and durability. These must be optimized together, not in isolation.

Dip Coating

Dip coating immerses the stent in polymer/precursor solution, withdraws it at controlled speed, then dries or cross-links. Thickness follows Landau–Levich–Derjaguin (LLD) theory for ideal Newtonian fluids:

$$h = 0.94\,\ell_c\,\mathrm{Ca}^{2/3},\ \mathrm{Ca} = \eta U/\gamma$$

but hydrogel precursors often deviate due to non-Newtonian behavior, evaporation, entanglement, and in situ cross-linking. Excessive viscosity/speed causes strut buildup, dripping, and gradients; too low yields poor coverage. Thickness must be mapped at multiple sites mean values are insufficient. Optimal coatings balance therapeutic capacity with mechanical and biological compatibility [45].

Covalent and Ionic Cross-Linking

Cross-linking controls swelling, mesh size, mechanics, degradation, and drug diffusion. Covalent networks offer stability and predictability but risk residual reagents and restricted diffusion. Ionic systems (e.g., alginate–Ca^{2+}) form under mild conditions but are reversible and sensitive to pH, ionic strength, and ion exchange [46].

Table no 2: Comparison of Covalent and Ionic Cross-Linking Strategies in Hydrogel Stent Coatings.

Sr.no.	Property	Covalent	Ionic
1	Stability	High	Reversible
2	Swelling/diffusion	Predictable	Ion-sensitive
3	Mechanics	Stable	Dynamic
4	Processing	Reactive chemistry	Mild, aqueous
5	Main concern	Residual reagents	Physiological weakening

Cross-link density (ν) governs mesh size (ξ) and diffusivity (D_{eff}): $\nu \propto \xi^{-3} \propto D_{\mathrm{eff}}^{-1}$. Optimal networks balance durability, transport, degradation, and biological access.

Layer-by-Layer Assembly

LbL enables functional compartmentalization into distinct stent-adhesive, drug-reservoir, and blood-facing barrier layers. Each layer can be tuned for adhesion, drug loading/release, hemocompatibility, and endothelial interaction. Advantage: drug loading, protection, and blood compatibility are decoupled. Risk: excessive barrier thickness impedes diffusion and endothelialization [47].

3D Printing and Photolithography

These methods enable precise control of geometry, porosity, and spatial drug placement. Porosity and spatial organization influence permeability, release, cell infiltration, mechanics, and degradation. Strategic placement:

Blood-facing: antithrombotic/NO.

Tissue-facing: antiproliferative/anti-inflammatory.

Endothelial-supportive: VEGF, SDF-1, ligands.

Resolution, sterilization, and reproducibility must be validated via critical quality attributes (thickness, cross-link density, pore structure, drug distribution, mechanics, degradation, residuals, post-sterilization performance) [48, 49].

Defects and Scale-Up

Defects (voids, incomplete polymerization, weak interfaces, stresses) concentrate load and promote cracking, delamination, or particle release. Testing must be on final, sterilized devices not bulk hydrogel.

Printing/photolithography offer precision but face scale-up challenges: throughput, monitoring, consistency, sterilization, QC, and cost. Final strategy must balance precision with reproducibility, validation, manufacturability, and regulatory feasibility [50].

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VII. MECHANISM-BASED PERFORMANCE EVALUATION

Hydrogel-coated stent evaluation should link each design feature to a defined mechanism, quantitative readout, and clinically relevant outcome. A hierarchical validation strategy comprising physicochemical characterization, mechanistic in vitro testing, flow and ex vivo assessment, and in vivo validation can distinguish intrinsic material properties from their biological effects and clarify their contribution to vascular healing.

Evidence Framework

Table no 3: Integrated Evaluation Framework for Hydrogel-Coated Coronary Stents: Functional Claims, Assessment Methods, and Expected Outcomes.

Sr.no.	Claim	Evaluation	Outcome
1	Antithrombotic	Protein adsorption, platelet activation, thrombin/fibrin, whole-blood flow	Reduced thrombosis
2	Endothelialization	Adhesion, migration, phenotype, barrier function, flow	Functional endothelial coverage
3	Antirestenotic	VSMC proliferation/migration, pathway activation, histology	Reduced neointimal hyperplasia
4	Immunomodulatory	Macrophage phenotype, cytokines, infiltration, histology	Controlled inflammation
5	Drug delivery	Release, tissue distribution, PK/PD, target engagement	Local efficacy, no delayed healing
6	Coating durability	Deployment, adhesion, fatigue, degradation, particulates	Long-term integrity

Antithrombotic Performance

Link hydrophilicity/charge to blood–material interactions: fibrinogen adsorption, platelet adhesion/activation, thrombin generation, fibrin deposition, complement activation, and whole-blood flow testing. Direct thrombus quantification under flow is more informative than static platelet counts. Hydrated coatings reduce fibrinogen adsorption, platelet adhesion, and fibrin formation [51].

Endothelialization Performance

Endothelialization should be evaluated as a sequential functional process involving cell attachment, spreading, migration, proliferation, maturation, monolayer formation, and restoration of barrier function. Assessment should include CD31, VE-cadherin, vWF, eNOS, and KLF2, together with nitric oxide production, permeability, and junctional integrity [52]. In vivo endothelial recovery should be confirmed by appropriate histological and imaging analyses. Endothelialization should be interpreted alongside thrombosis, inflammation, and neointimal formation, as excessive antiproliferative activity may delay endothelial recovery [53].

Antirestenotic Performance

Antirestenotic efficacy should be established by linking inhibition of VSMC proliferation and migration to specific molecular mechanisms. Relevant endpoints include DNA synthesis, cell-cycle progression, Ki-67, PCNA, α-SMA, SM22α, and calponin, with pathways such as PDGF–PDGFR, PI3K–AKT–mTOR, MAPK–ERK, TGF-β–SMAD, Wnt/β-catenin, and RhoA/ROCK considered where appropriate. In vivo efficacy should be assessed by neointimal area, percentage stenosis, lumen area, late lumen loss, endothelial coverage, and vascular inflammation. Evidence of target engagement is important because suppression of pathways such as mTOR may reduce neointimal growth while simultaneously impairing endothelial recovery [54].

Immunomodulatory Performance

Demonstrate changes in immune-cell behavior and signaling: CD68, iNOS/CD86, CD206/Arg1, cytokines (TNF-α, IL-1β, IL-6, TGF-β). Interpret with morphology, oxidative stress, and tissue histology not as strict M1/M2. In vivo:

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inflammatory infiltration, macrophage accumulation, injury, fibrosis, collagen, neointima. Goal: resolve excessive inflammation without impairing repair [55, 56].

Drug-Release and Pharmacodynamic Validation

Integrate release with tissue distribution and PD:

$$F_{\text{rel}} \rightarrow C_{\text{tissue}} \rightarrow \text{Target engagement} \rightarrow \text{PD effect}$$

For sirolimus: link arterial exposure to mTOR inhibition, VSMC suppression, neointimal reduction. In vitro release ≠ in vivo exposure; release and retention differ across platforms. Aim for therapeutic window, not maximal accumulation [57].

Mechanical Durability and Coating Integrity

Test under crimping, delivery, expansion, pulsatile flow, cyclic deformation. Coating must remain adherent without cracking, delamination, thinning, or particle generation. Assess:

- Deployment compatibility, post-expansion morphology.
- Adhesion (peel/shear/pull-off).
- Cyclic fatigue.
- Degradation and mechanical retention.
- Release stability post-loading.
- Particulate generation.

Test mechanics before and after degradation. Particulates can alter delivery or trigger inflammation/thrombosis. Coating inspection and particulate characterization are standard for drug-eluting stents [58,59].

Integrated Evidence Framework

An integrated evidence framework should establish a continuous relationship between physicochemical properties, molecular mechanisms, cellular responses, tissue-level effects, drug exposure, and coating durability. This approach enables material characteristics to be directly linked to biological outcomes and long-term vascular performance.

Examples:

↓ fibrinogen → ↓ platelet activation → ↓ thrombus.
↑ eNOS/KLF2 → ↑ NO → ↑ barrier function.
mTOR inhibition → ↓ VSMC → ↓ neointima.
Macrophage modulation → ↓ cytokines → controlled inflammation.

No single endpoint proves success: antiproliferative potency may coexist with delayed endothelialization; efficient release may coexist with delamination/thrombogenicity [60].

Minimum Translational Evidence Package

A minimum translational package should integrate blood compatibility, endothelialization, antirestenotic activity, immunomodulation, controlled drug delivery, and mechanical durability. Strong evidence requires interconnected physicochemical, molecular, cellular, tissue, pharmacological, and durability endpoints rather than isolated performance metrics [61].

VIII. IN VITRO, EX VIVO, AND IN VIVO VALIDATION

Hydrogel-coated stents should be evaluated through a staged strategy encompassing in vitro, dynamic flow, ex vivo, and large-animal studies. Because no single model captures the complex blood–cell–tissue–mechanical–drug interactions, integrated testing is essential to link hydrogel properties and drug exposure with biological mechanisms, coating integrity, and vascular healing.

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In Vitro Testing

Isolate individual mechanisms under controlled conditions.

Material and release: Characterize thickness, uniformity, morphology, wettability, charge, swelling, mesh size/porosity, cross-linking, degradation, mechanics, adhesion, drug loading/distribution, particulates. Quantify cumulative/burst release, duration, stability, bioactivity; link to local concentration and biological effect.

Hemocompatibility: Protein adsorption, platelet adhesion/activation, thrombin/fibrin, complement, hemolysis, thrombus under flow. Static assays screen; dynamic whole-blood flow loops are essential for physiologically relevant thrombogenicity.

Endothelial response: Adhesion, spreading, viability, proliferation, migration, monolayer, barrier, NO. Markers: CD31, VE-cadherin, vWF, eNOS, KLF2. Viability ≠ function; assess junctions, phenotype, permeability under static and flow.

VSMC/macrophage: VSMC proliferation/migration, cell cycle, Ki-67, PCNA, α-SMA, SM22α, calponin, ERK, AKT–mTOR. Macrophage: CD68, iNOS/CD86, CD206/Arg1, cytokines, morphology, function interpret contextually, not as strict M1/M2.

Co-culture/flow: Endothelial + VSMC + macrophage co-cultures reveal paracrine interactions; dynamic flow adds shear, evaluating alignment, barrier, platelet adhesion, drug transport, NO. Report shear, flow, blood composition, temperature, duration [62, 63].

Ex Vivo Testing

Bridge cell culture and animal implantation.

Whole-blood loops: Coating interacts with plasma proteins, platelets, leukocytes, erythrocytes, coagulation, complement. Endpoints: platelet activation, fibrin, thrombin/complement, hemolysis, thrombus. Control collection, anticoagulation, temperature, flow, preactivation.

Arterial tissue/flow: Representative vessel-wall environment for endothelial/VSMC responses, inflammation, degradation, coating attachment, tissue drug penetration/distribution. Patient-derived cells can assess variability (age, disease, injury); incorporate donor variability into design/statistics [64,65].

Large-Animal Testing

Assess integrated performance under clinically relevant anatomy, flow, mechanics, injury, thrombosis, inflammation, remodeling. Porcine models are standard for coronary stents; rabbits complement for endothelialization/neointima [66].

Key endpoints: endothelial coverage/phenotype (CD31, VE-cadherin, eNOS), neointimal/lumen area, stenosis %, late lumen loss, thrombosis (platelet/fibrin), inflammation (cells, cytokines, fibrosis, injury), coating integrity (cracks, delamination, degradation), particulates (number, size, embolization), tissue drug distribution, degradation–response relationship [67].

The desired sequence is controlled degradation, sustained drug release, vascular healing, and tissue integration. Rapid degradation may cause premature burst release and loss of protective function, whereas excessively slow degradation may prolong material persistence and local inflammation [68].

Integrated Validation

Lumen patency is the principal outcome, assessed via angiography/intravascular imaging:

$$\mathrm{LLL} = \mathrm{MLD}_{\mathrm{post}} - \mathrm{MLD}_{\mathrm{follow-up}}$$

Table no 4: Sequential Preclinical Evaluation Strategy for Hydrogel-Coated Coronary Stents.

Sr.no.	Stage	Purpose	Endpoints
1	In vitro	Define mechanisms	Release, cytocompatibility, signaling, proliferation
2	Dynamic in vitro	Add flow	Platelet adhesion, endothelial response, thrombus
	Ex vivo	Blood–tissue	Whole-blood compatibility, tissue distribution

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3		interactions	
4	Large animal	Integrated performance	Endothelialization, neointima, thrombosis, inflammation, integrity, patency

Each stage should validate findings from the preceding level, linking in vitro mechanisms to flow, ex vivo, and in vivo outcomes. This sequential approach connects material design with vascular performance while identifying key risks, including thrombogenicity, delayed endothelialization, inflammation, uncontrolled release, delamination, particulates, and late lumen loss [69].

IX. CONCLUSION

Hydrogel-coated coronary stents provide a multifunctional platform that can integrate structural support with localised biological regulation and therapeutic delivery. The performance of such systems hinges on the synergistic optimisation of polymer chemistry, network architecture, cross-linking, surface hydration, mechanical compatibility, degradation, coating adhesion, and drug–polymer interactions. Ideal designs should simultaneously inhibit thrombosis and inflammation, promote functional endothelialization, inhibit pathological VSMC activity, and maintain lumen patency. More importantly, drug loading or good in vitro cytocompatibility alone are not sufficient to guarantee translational success. Evidence should link physicochemical properties with mechanism, flow-dependent blood compatibility, tissue response, pharmacodynamic exposure, coating integrity, and large-animal vascular outcomes. Future development should target reproducible manufacturing, standardised testing, controlled degradation, optimisation of the therapeutic window, particulate safety, and clinically relevant preclinical validation to enable durable, biologically integrated coronary stent technologies.

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