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Research Paper

Review: Recent Advances in Clinical Therapy for Cardiovascular Disease

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ABSTRACT
Cardiovascular disease (CVD) is one of the leading causes of death worldwide. Currently, many methods have been proposed by researchers for the prevention and treatment of CVD; among them, stem cell-based therapies, Gene therapy,antiplatelate therapy, anticoagulant, nanotechnology and 3D- printing. The goal of this analysis was to summarize the recent advances in therapy for cardiovascular disease.
KEY WORDS
Cardiovascular disease (CVD), stem cell, antiplatelate, Gene, nanotechnology, therapy

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I. Introduction

In all societies, cardiovascular disease (CVD) is the leading cause of morbidity and mortality, and it is expected that the incidence of CVD will increase in the future. Indeed, as a significant challenge to global health, the social and economic consequences of heart failure are now growing [1,2].

1. STEM CELLS THERAPY FOR CVD

A very exciting therapeutic strategy is to regenerate cardiac tissue by replacing lost cells or rejuvenating damaged cells. In fact, stem cell-based therapies for cardiac regeneration can be used to cure CVD in a manner that traditional medicines and newer biological therapies still cannot, even though they are used as established treatments for cardiac damage and heart failure [3]. However, due to a number of factors, such as the complexity of the heart, the inability for the heart to remodel after tissue damage, and the ineffectiveness of repair mechanisms, the usage of regenerative cell-based therapies is optimal, although effective cardiac repair strategies remain challenging. As mentioned above, it has long been believed that mammalian heart muscle cells, including those in humans, cannot proliferate. Nevertheless, recent studies have demonstrated a self-renewing resident cardiac stem cell population in the adult mammalian myocardium, and mature cardiomyocytes (CMs) have been shown to be capable of differentiation [4,5]. Interestingly, although there has been great enthusiasm regarding this discovery, it is now believed that the turnover rate of these cells is low in the absence of injury. Even in the case of the loss of a large number of cells, such as after myocardial infarction (MI), cardiac stem cells and progenitor cells that reside in the tissue are still unable to proliferate and regenerate fully, so proper heart function cannot be recovered to a pre-lesion level.

Cardiac cell-based therapy has been performed with a wide variety of cell types, including aspirated bone marrow cells, peripheral blood progenitor cells, stem cells, cells expanded through ex

vivo culture, pluripotent stem cells (PSCs), skeletal myoblasts, and endothelial progenitor cells, such as embryonic stem cells (ESCs) [6,7]. Moreover, different cell delivery pathways have been used, such as direct injection into the myocardium, introduction through the epicardial and coronary arteries, and introduction via intravenous infusion, and these routes have been studied in many clinical settings. In addition to the cell type and administration route, cell-based therapies may also be impacted by other factors. These mainly include the dose of cells being administered, the frequency of cell administration, the timing of administration in relation to the injury (chronic heart failure versus acute MI), the metabolic state of the transplanted cells (previously frozen and thawed cells versus new cells), and the simultaneous use of other drugs, initiation of revascularization and treatment with surgery [8,9,10]. Due to the heterogeneity of these methods, it is difficult to perform direct comparisons of clinical studies. In addition, most clinical trials of cell-based therapies for heart disease have only assessed medical endpoints, such as mechanical or clinical improvements in measurements, for example, the ejection fraction on echocardiography or other imaging methods, without reporting the ultimate benefits of such therapies. This study aimed to ultimately improve the patient survival ratio.

The stem cells studied in cardiovascular research ranged from bone marrow to adipose tissue to skeletal muscle stem cells[11].

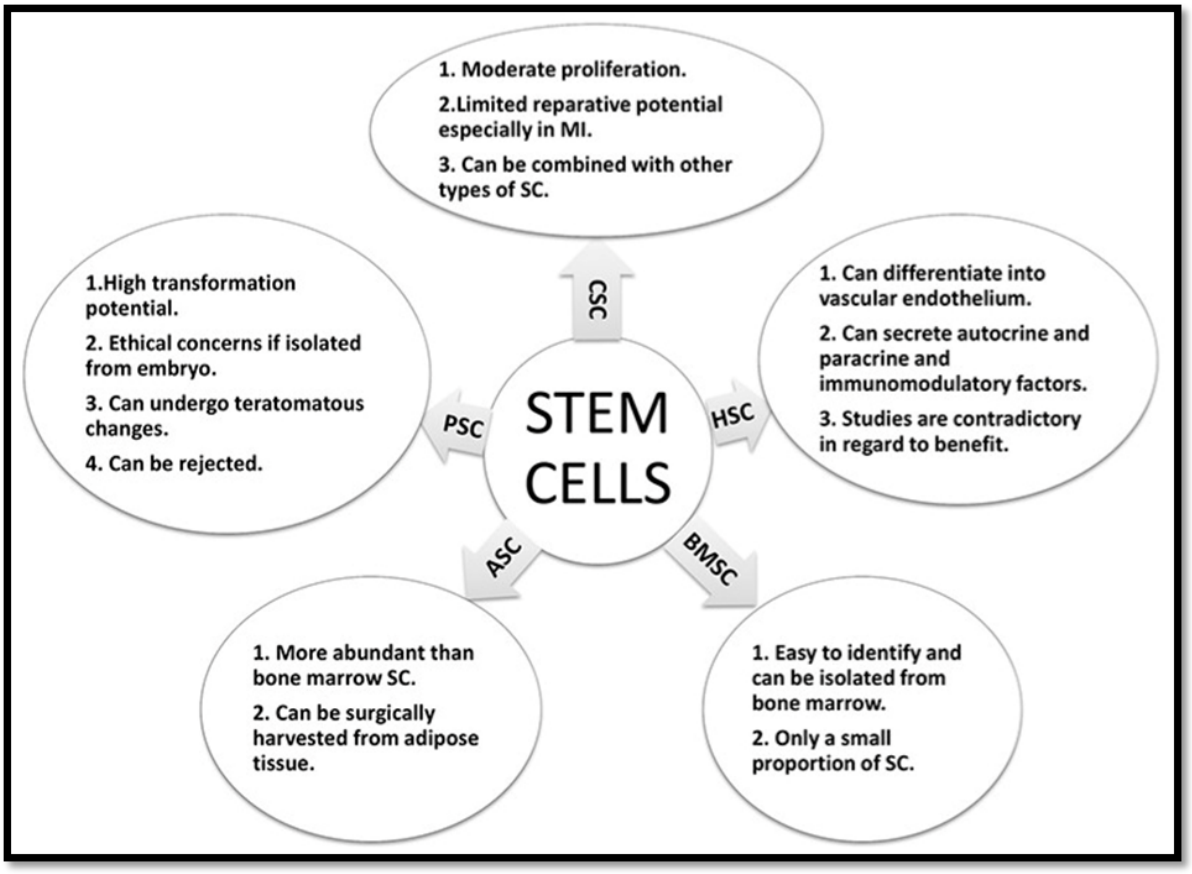

Figure 1: The schematic illustrates the potential of different types of stem cells in the treatment of CAD. Abbreviations: Adipose stem cells (ASC); bone-marrow stem cells (BMSC); cardiac stem cells (CSC); hematopoietic stem cells (HSC); pluripotent stem cells (PSC); stem cells (SC). [11]

2. GENE THERAPY IN CVD

Gene therapy describes the transfer of genes to a target cell or organ to treat or prevent disease. Successful delivery of a gene to the target is paramount to therapeutic efficacy. In some cases, this can be as simple as transduction of a few cells to secrete a hormone or growth factor; in more stringent cases, the requirement may be as extensive as transduction of most or all cells in the target organ. A number of gene delivery methods have been developed using both viral- and non-viral-based vectors. Nonviral methods include using naked DNA alone or complexed with liposomes.[12, 13] Naked DNA vectors are simple closed circular DNA plasmids that at a minimum contain a promoter driving a gene of interest and a polyadenylation site.[14] Naked DNA vectors are inefficient, as only a small percentage of target cells express reporter genes after

transfection.[13] They are easy to produce and are used extensively for applications that do not require high-density gene transfer. Importantly, the gene of interest does not need to encode a specific protein to be of therapeutic value. Mechanisms that use antisense oligonucleotides or short interfering RNA, which can reduce or eliminate protein function, have been uncovered. In the case of short interfering RNA, the promoter drives production of the effector RNA sequence rather than production of a messenger RNA that is then translated into an effector protein.

Viral vectors are more commonly used for cardiovascular applications because they transfer genes to cardiac myocytes much more efficiently than any of the non viral methods. Commonly used viral vectors include retroviruses (including the lentivirus family of which the human immunodeficiency viruses are members), adenoviruses (ADs) and adeno-associated viruses (AAVs). Retroviruses have been used for a number of noncardiac applications, but they do not efficiently transduce cardiomyocytes because they require active cell division for integration and function. Lentiviruses do not require active cell division, so they have been used extensively for cardiac applications. A limitation of lentiviral vectors has been the inability to generate sufficient concentrations of virus for delivery by coronary perfusion. Successful examples of lentiviral gene transfer to the heart predominantly use intramyocardial injection.

One of the limitations for widespread use of gene therapy is efficient delivery of the gene transfer vector to the target. Methods of reported cardiovascular gene delivery include intramyocardial injection, coronary perfusion, and pericardial delivery.[15-22]. All these techniques are moderately successful, but each is hindered by efficacy, tolerability, or access. See Table 1 for a list of positive and negative points regarding each delivery system.

Table 1. Delivery Techniques for Gene Therapy¶

Gene Delivery Technique	Pro	Con
Myocardial injection	●High density of gene transfer limited to cardiac muscle ●Simple and safe, able to inject percutaneously	●Small area of gene expression ●Multiple injection sites needed ●Acute inflammatory response and potential scarring from the injection
Coronary perfusion-anterograde and retrograde perfusion	●Delivers genes globally across the myocardium ●Distributes gene vector more homogeneously ●Cardiac specific	●Inefficient ●Delivered into systemic circulation
Aortic cross-clamp LV cavity infusion	●Increased gene transfer efficiency	●Accessibility, need open chest ●High risk of myocardial injury ●Not cardiac specific
Cardiopulmonary bypass perfusion and “closed-loop” system	●Specifically enhances coronary perfusion by separating it from systemic circulation ●Allows for temperature control of solution, cold increased transfection efficiency ●Increased contact time with gene vector through multiple-pass cardiac recirculation	●Significant morbidity risk from cardiopulmonary bypass procedure (CBP) ●Intended for patients undergoing CBP
Epicardial painting	penetration (atrial) ●High degree of	●Accessibility, currently needs open chest
Ultrasound and microbubbles	●Increased permeability of capillary and cell membrane	●Only slightly improved gene transfer efficiency from myocardial injection alone
Electroporation	●Enhanced transfer of naked DNA via myocardial injection and retrograde perfusion ●Cardiac specific	●Pulse needs to be delivered in sync or ventricular fibrillation occurs

LV, left ventricle.

Preclinical angiogenesis studies investigated a variety of angiogenic growth factors including VEGF, FGF, hepatocyte growth factor, platelet-derived growth factor, and hypoxia-inducible factor, among others [23-27]. Clinical trials have focused predominantly on VEGF and FGF. Preclinical work showed improved

myocardial function and perfusion by increasing angiogenesis after administration of the gene for either VEGF or FGF to ischemic tissue.[5] See Table 2 for a summary.

Table 2. Gene Therapy Targets for Coronary Heart Disease

Molecular Target	Stage in Development	Findings	Model Assessed	Reference
Vascular endothelial growth factor (VEGF)	Clinical trials, phase 2/3 Continued safety and efficacy	Safe but not consistently efficacious with increasing myocardial perfusion. Success with secondary end points, ie, increased exercise capacity and reduction in ischemic area	Human	Hedman et al, *Gene Ther*, 2009 Stewart et al, *Mol Ther,* 2009
Fibroblast growth factor (FGF)	Clinical trials, phase 2/3 Continued safety and efficacy	Safe but most trials have not increased myocardial perfusion. Some have improved exercise capacity and symptom alleviation	Human	Kukula et al, *Am Heart J*, 2011
Hepatocyte growth factor (HGF)	Clinical trial, phase 1 Preclinical	Safe with negligible side effects from ADs; HGF in serum not detected after 35 days Increased capillary density and end-diastolic volume Improved cardiac perfusion and reduced apoptosis	Human Rat Pig	Yang et al, *Mol Biol Rep*, 2009 Jin et al, *Gene Ther*, 2012 Yang et al, *Mol Biol Rep*, 2010
Platelet-derived growth factor (PDGF)	Preclinical	Increased capillary growth and collateral formation from single naked DNA injection	Rabbit	Li et al, *Microvasc Res*, 2010
Hypoxia-inducible factor (HIF1α)	Clinical trial, phase 1 Preclinical	Preliminary safety of ADs after 1 year Increased myocardial perfusion and improved LV function but no improvement in bioactivity end points	Human Pig	Kilian et al, *Circ J*, 2010 Heinl-Green et al, *Eur Heart J*, 2005

ADs indicate adenoviruses; LV, left ventricle.

Ongoing or completed clinical trials for heart failure gene therapy have included those testing the sarco endoplasmic reticulum calcium-ATPase 2a (SERCA2a), SDF-1, and adenylate cyclase-6 (AC6). Strategies to judge efficacy noninvasively include measuring ejection fraction on echocardiograms, measuring HF symptoms–6-minute walk test, New York Heart Association class, and quality-of-life questionnaire. In addition to these targets, numerous other transgenes have reported efficacy for heart failure in various mouse or other small mammalian models. Preclinical studies with multiple literature reports or with efficacy data in large mammalian models include the S100 calcium-binding protein A1 (S100A1), a c-terminal fragment of the β-adrenergic receptor kinase (βARKct), and parvalbumin (PVALB). See Table 3 for a summary.

Table 3. Gene Therapy Targets for Heart Failure

Molecular Target	Stage in Development	Findings	Model Assessed	Reference
Sarcoendoplasmic Reticulum calcium-ATPase 2a (SERCA2a)	Clinical trials, phase 2	Decreased HF symptoms, increased functional status, and reversal of negative LV remodelling	Human	Jessup et al, *Circulation*, 2011
Stromal-derived factor-1 (SDF-1)	Clinical trials, phase 1/2	Safe and improved 6-minute walk test, quality of life, and NYHA class	Human	Penn et al, *Circ Res*, 2013
Adenylyl cyclase 6 (ADCY6)	Preclinical	Increased LV function, increased cAMP levels, reversal of dysfunctional β-AR signaling, and increased survival Improved LV contractility	Mice Pig	Rebolledo et al, *Hum Gene Ther*, 2006 Roth et al, *Circulation*, 1999, 2002. Takahashi et al, *Circulation*, 2006. Lai et al, *Circulation*, 2000
βARKct-carboxy terminal peptide from GRK2	Preclinical	Heart failure rescue Improved β-AR signaling and contractile dysfunction	Rabbit Human cardiomyocytes	Shah et al, *Circulation*, 2001 Williams et al, *Circulation*, 2004
S100A1	Preclinical	Increased reuptake SR Ca^{2+}, lowered Ca^{2+} leak, enhanced cardiac function, and reversed LV remodelling	Rat cardiomyocytes	Most et al, *J Clin Invest*, 2004 Pleger et al, *Circulation*, 2007
Parvalbumin (PVALB)	Preclinical	Increased rate of Ca^{2+} removal and improved relaxation rate	Rat	Szatkowski et al, *J Clin Invest*, 2001

HF indicates heart failure; LV, left ventricle; NYHA, New York Heart Association; βARKct, β‑adrenergic receptor kinase; β‑AR, β‑adrenergic; SR, sarcoplasmic reticulum.

No arrhythmia gene therapy has entered human clinical trials as yet. Preclinical work is under way demonstrating the efficacy and feasibility of gene therapy to treat these arrhythmias. See Table 4 for a summary. To determine efficacy, noninvasive tests include ECG monitoring and electrophysiological studies.

Table 4. Gene Therapy Targets for Arrhythmia [28]

Molecular Target	Stage in Development	Findings	Model Assessed	Reference
KCNH2-G628S	Preclinical	Prolonged refractory period by shutting down I_{Kr}, eliminating arrhythmia inducibility	Pig Dog	Sasano et al, *Nat Med*, 2006 Amit et al, *Circulation*, 2010 Soucek et al, *Heart Rhythm*, 2012
Cardiac sodium channel 4a (SCN4a)	Preclinical	Reduced VT inducibility, increased V_{max} causing rapid conduction, and decreased electrogram fragmentation	Dog	Lau et al, *Circulation*, 2009
Connexin 32	Preclinical	Improved gap junctional conductance but no antiarrhythmic effect and larger infarct size	Dog	Boink et al, *J Am Coll Cardiol*, 2013
Connexin 40	Preclinical	Enhanced atrial conduction and prevented atrial fibrillation	Pig	Igarashi et al, *Circulation*, 2012
Connexin 43	Preclinical	Improved conduction and reduced arrhythmia susceptibility	Pig	Greener et al, *J Am Coll Cardiol*, 2012 Igarashi et al, *Circulation*, 2012 Bikou et al, *Cardiovasc Res*, 2011
Sarcoendoplasmic reticulum calcium-ATPase 2a (SERCA2a)	Preclinical	Reduced VT and VF during reperfusion Reduced premature ventricular contraction and nonsustained VT Decreased APD alternans	Pig Rat Guinea Pig	Prunier et al, *Circulation*, 2008 Lyon et al, *Circ Arrhythm Electrophysiol*, 2011 Cutler et al, *Circ Arrhythm Electrophysiol*, 2009
Adenylyl cyclase 1 (ADCY1)	Preclinical	Increased beating rate, provided stable pacemaker effects	Dog	Boink et al, *J Interv Card Electrophysiol*, 2011
Adenylyl cyclase 6 (ADCY6)	Preclinical	Provided biological pacing during catecholaminergic stimulation	Pig	Ruhparwar et al, *Tissue Eng Part A*, 2010
Kir2.1	Preclinical	Increased pacemaking	Guinea Pig	Miake et al, *Nature*, 2002, *J Clin Invest*, 2003

VT indicates ventricular tachycardia; VF, ventricular fibrillation; APD, action potential duration.

3. ANTIPLETES THERAPY IN CVD[29]

Platelets have a key role in normal hemostasis and in the pathogenesis of atherothrombotic events, such as acute coronary syndrome. Following plaque rupture, platelets adhere to the subendothelial matrix, become activated and then aggregate to form a prothrombotic surface that promotes clot formation and subsequently

vascular occlusion. Multiple pathways are involved in platelet activation, including those activated by adenosine diphosphate (ADP), thromboxane A2, epinephrine, serotonin, collagen, and thrombin.

Antiplatelet medications remain a cornerstone of therapy for atherosclerotic cardiovascular and cerebrovascular diseases. In primary prevention (patients with cardiovascular risk factors but no documented events, symptoms or angiographic disease), there is little evidence of benefit of any antiplatelet therapy, and such therapy carries the risk of excess bleeding. Where there is documented disease (secondary prevention), stable patients benefit from long-term antiplatelet monotherapy, aspirin being first choice in those with coronary heart disease and clopidogrel in those with cerebrovascular disease; moreover, recent evidence shows that low-dose rivaroxaban in combination with aspirin confers added benefit, in patients with stable cardiovascular and peripheral arterial disease. In patients with acute cerebrovascular disease, aspirin combined with clopidogrel reduces subsequent risk, while in acute coronary syndrome, dual antiplatelet therapy comprising aspirin and a $P2Y_{12}$ inhibitor (clopidogrel, prasugrel or ticagrelor) confers greater protection than aspirin monotherapy, with prasugrel and ticagrelor offering greater antiplatelet efficacy with faster onset of action than clopidogrel. Although greater antiplatelet efficacy is advantageous in preventing thrombotic events, this must be tempered by increased risk of bleeding, which may be a particular issue in certain patient groups.

Pharmacology of antiplatelet

The principal agents in clinical use are aspirin (acetylsalicylic acid) and the $P2Y_{12}$ receptor inhibitor drugs clopidogrel, prasugrel and ticagrelor (Figure 2).

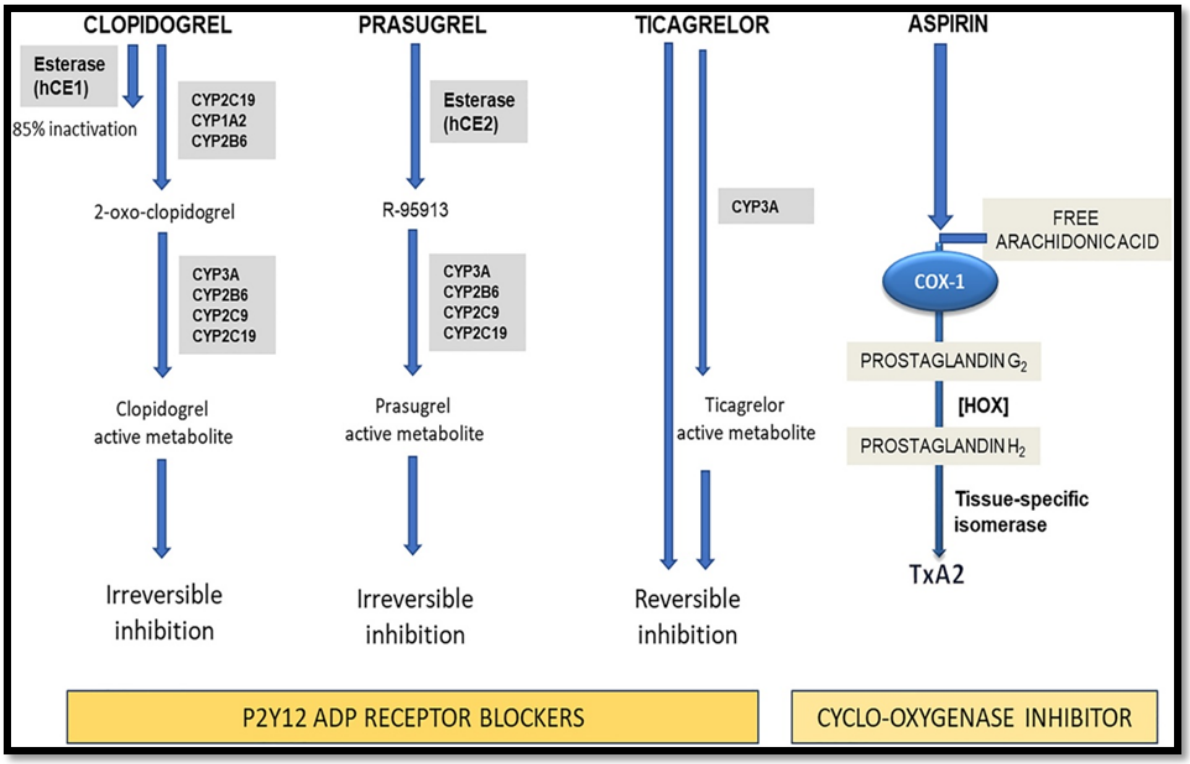

Figure :2 Antiplatelet drug mechanisms of action

Figure 2 shows Antiplatelet drug mechanisms of action. The thienopyridines clopidogrel and prasugrel prevent ADP from binding its specific $P2Y_{12}$ receptor and cause its irreversible inhibition; ticagrelor exerts reversible $P2Y_{12}$ receptor antagonism. While clopidogrel and prasugrel require hepatic metabolism to produce the active drug metabolite, ticagrelor is not a prodrug and has a direct inhibitory action, although additionally undergoing a cytochrome-dependent oxidation that also produces an active metabolite contributing to the pharmacological effect. Aspirin irreversibly blocks the enzymatic activity of cyclooxygenase-1 (COX-1), which is a key enzyme in the metabolism of arachidonic acid to produce prostanoids. COX-1 converts arachidonic acid to the unstable intermediate prostaglandin G2 (PGG2). Further metabolism of PGG2 by hydroperoxidases (HOX) leads to prostaglandin H2 synthesis that is finally converted into prostanoids by tissue-specific isomerases (platelets mainly contain thromboxane A2 [TxA2] synthase resulting in production and release of TxA2). By acting on COX-1, aspirin reduces TxA2-dependent platelet activation. CYP: cytochrome P450. hCE: human carboxylesterase

Because of much recent interest in the concomitant use of direct oral anticoagulants DOACs with antiplatelets for cardiovascular prevention, largely thanks to the results of the COMPASS trial (Table 5),[30] which will be discussed below.

TABLE 5. Major randomised controlled clinical trials testing antiplatelet strategies in the secondary prophylaxis of cardiac and peripheral arterial disease[30]

TRIAL	Study population	Study treatment (experimental treatment *vs.* control) and duration	Primary efficacy outcomes	NNT	NNH
MONOTHERAPY					
CAPRIE[7]	Patients with prior ischaemic stroke, MI or symptomatic atherosclerotic peripheral arterial disease (*n* = 19 185)	Clopidogrel *vs.* aspirin 1–3 y	Composite of ischaemic stroke, MI or vascular death	196 (104, 5720)	No significant effect
EUCLID[8]	Patients with symptomatic peripheral arterial disease (*n* = 13 885)	Ticagrelor *vs.* clopidogrel Median 30 mo	Composite of cardiovascular death, MI or ischaemic stroke	No significant effect	No significant effect
GLOBAL LEADERS[9]	Patients with stable coronary disease or ACS undergoing PCI (*n* = 15 968)	Aspirin + ticagrelor for 1 mo followed by ticagrelor monotherapy *vs.* aspirin + ticagrelor/clopidogrel for 12 mo followed by aspirin monotherapy	A composite of all-cause mortality or nonfatal centrally adjudicated new Q-wave MI at 2 y	No significant effect	No significant effect
TWILIGHT-ACS[10]	Patients undergoing PCI at high risk of ischaemic or bleeding events (*n* = 7119)	3 mo of aspirin + ticagrelor followed by ticagrelor monotherapy *vs.* 12 mo of aspirin + ticagrelor	Bleeding Academic Research Consortium type 2, 3, or 5 bleeding at 12 mo Secondary endpoint: a composite of death from any cause, nonfatal MI or nonfatal stroke at 12 mo	No significant effect	−32 (−22, −37)

TICO[11]	Patients with ACS treated with drug-eluting stents (n = 3056)	Ticagrelor monotherapy (90 mg twice daily) after 3-mo DAPT *vs*. ticagrelor-based 12-mo DAPT	1-y net adverse clinical event, defined as a composite of major bleeding and adverse cardiac and cerebrovascular events (death, MI, stent thrombosis, stroke or target-vessel revascularisation). Secondary endpoint: major adverse cardiac and cerebrovascular events.	50 (29, 222)	No significant effect
ANTIPLATELET PLUS ANTICOAGULANT THERAPY					
COMPASS[12]	Patients with history of peripheral artery disease of the lower extremities, of the carotid arteries or coronary artery disease (n = 7470)	Aspirin plus rivaroxaban *vs*. aspirin Mean 23 mo	Cardiovascular death, MI or stroke	52 (44, 131)	362 (151, 534)
ATLAS ACS 2-TIMI 51[13]	Patients with a recent ACS (n = 15 526)	Rivaroxaban either 2.5 mg or 5 mg twice daily *vs*. placebo (on top of standard antiplatelet therapy) Up to 31 mo (mean 13 mo)	Composite of death from cardiovascular causes, MI or stroke	63 (19, 453) for 2.5 mg twice daily 53 (43, 468) for 5 mg twice daily	83 (56, 254) for 2.5 mg twice daily 56 (48, 157) for 5 mg twice daily
VOYAGER PAD[14]	Patients with peripheral artery disease who had undergone revascularisation (n = 6564)	Aspirin plus rivaroxaban *vs*. aspirin Mean 28 mo	Composite of acute limb ischaemia, major amputation for vascular causes, MI, ischaemic stroke or death from cardiovascular causes	39 (23, 140)	No significant effect
DAPT					
CURE[15]	Patients with ACS with non-STEMI within 24 h from	Clopidogrel *vs*. placebo (on a background of aspirin)	Composite of cardiovascular death, nonfatal MI or stroke at 12 mo	48 (31, 88)	100 (56, 287)

	randomisation (*n* = 12 562)	3–12 mo			
CLARITY[16]	Patients with STEMI (*n* = 3491)	Clopidogrel *vs*. placebo (on a background of aspirin ranging 150–325 mg daily) Patients were to receive study medication daily up to and including the day of coronary angiography. For patients who did not undergo angiography, study drug was to be administered up to and including d 8 or hospital discharge, whichever came first	Death, recurrent MI At 30 d	16 (10, 19)	No significant effect
COMMIT[17]	Patients with MI (93% ST elevation MI, 7% non-ST elevation MI; *n* = 45 852)	Clopidogrel *vs*. placebo (on a background of aspirin 162 mg) Up to 4 weeks	Death, repeat infarction, stroke At 30 d	111 (71, 330)	No significant effect
DAPT[18]	Patients undergoing PCI with drug-eluting stent insertion (*n* = 9961)	Following 12 mo of treatment with clopidogrel or prasugrel plus aspirin, patients randomised to continue thienopyridine treatment *vs*. placebo for further 18 mo (on top of aspirin)	Stent thrombosis Major adverse cardiovascular and cerebrovascular events (a composite of death, MI or stroke)	100 (92, 146) 63 (42, 116)	111 (106, 127)
TRITON-TIMI 38[19]	Patients with ACS scheduled for PCI (*n* = 13 608)	Prasugrel *vs*. clopidogrel (on a background of aspirin 75–162 mg) 6–15 mo	Cardiovascular death, MI or stroke	45 (32, 87)	166 (89, 500)
PLATO[20]	Patients with ACS within 24 h from randomisation (*n* = 18 624)	Ticagrelor *vs*. clopidogrel (on a background of aspirin 75–100 mg) 12 mo	A composite of death from vascular causes, MI or stroke at 12 mo	53 (12, 115)	No significant effect
PEGASUS-TIMI 54[21]	Patients who had had a MI 1 to 3 y previously (*n* = 21 162)	Ticagrelor 90 mg twice daily *vs*. ticagrelor 60 mg twice daily *vs*. placebo Median 33 mo	Composite of cardiovascular death, MI or stroke	85 (49, 306) for 90 mg 82 (47, 245) for 60 mg	65 (48, 135) for 90 mg 80 (59, 191) for 60 mg

THEMIS-PCI [22]	Patients 50 y or older, with type 2 diabetes receiving antihyperglycaemic drugs for at least 6 mo, with stable coronary artery disease, and previous PCI (*n* = 11 154)	Ticagrelor *vs*. placebo (on a background of aspirin) Median 3.3 y	Composite of cardiovascular death, MI or stroke (median follow up 3.3 y)	77 (45, 389)	111 (51, 187)
HOST-EXAM [23]	Patients on DAPT without clinical events for 6–18 mo after PCI with drug-eluting stents or aspirin 100 mg once daily for 24 mo (*n* = 5438)	Monotherapy with clopidogrel 75 mg daily *vs*. aspirin 100 mg daily 24 mo	Composite of all-cause death, nonfatal MI, stroke, readmission due to ACS, and Bleeding Academic Research Consortium bleeding type 3 or greater at 24 mo	50 (32, 132)	- (harm from bleeding included in primary composite endpoint)

NNT: number needed to treat for primary efficacy outcome (with 95% confidence intervals). Negative value indicates control treatment more efficacious on primary outcome than experimental treatment.
Values for NNT and NNH are only given for clinical outcomes and if the difference in efficacy or harm attained statistical significance in the study.
ACS, acute coronary syndrome; MI, myocardial infarction; PCI, percutaneous coronary intervention.

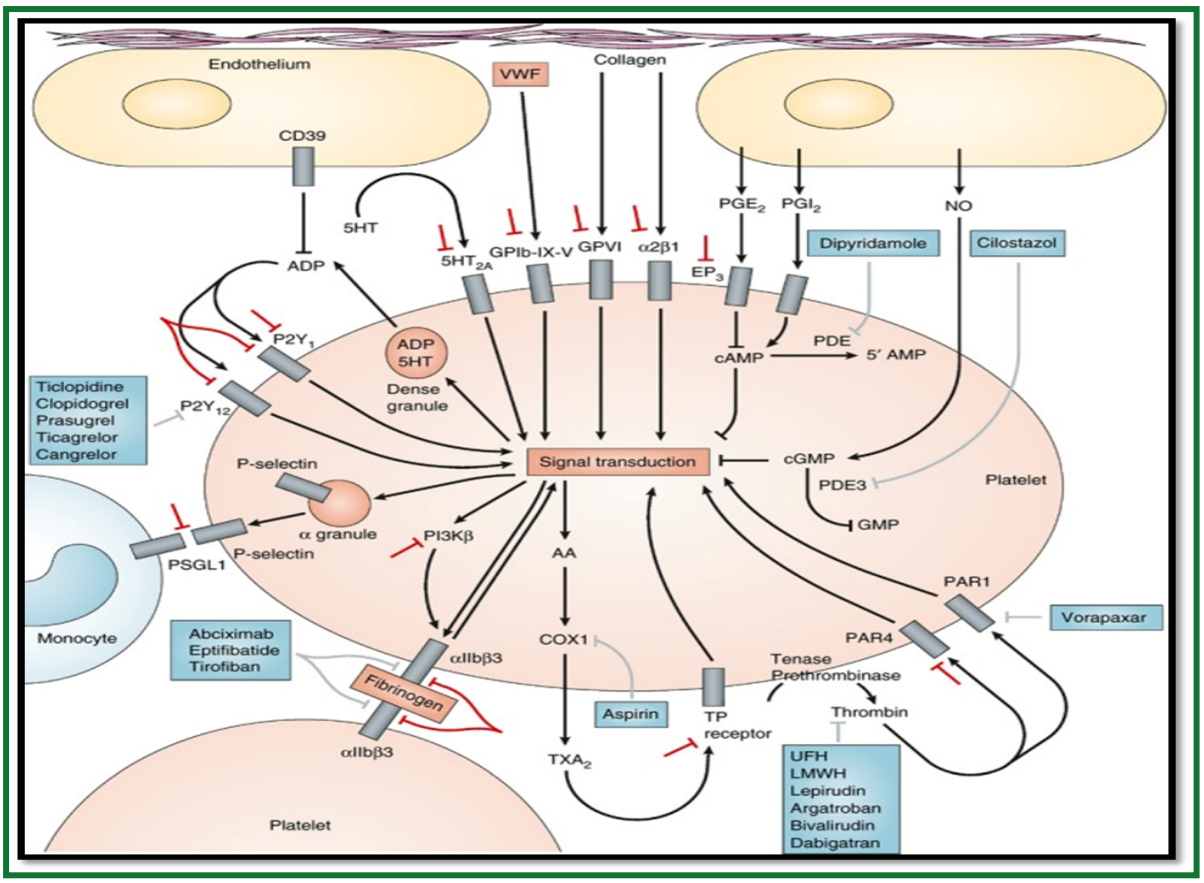

Figure:3 Platelet function and molecular targets of antiplatelet agents.

Initial platelet adhesion to damaged vessel walls is mediated by the binding of exposed collagen to platelet surface glycoprotein (GP) VI and integrin α2β1 and by the binding of von Willebrand factor (VWF) to the platelet surface GPIb-IX-V complex. This complex is also a receptor for other platelet ligands (thrombospondin, collagen and P-selectin), leukocyte integrin αMβ2, and procoagulant factors (thrombin, kininogen, factor XI and factor XII). Thrombin, generated by the coagulation cascade, is a potent activator of human platelets through two platelet surface receptors: protease-activated receptor (PAR)-1 and PAR-4. Three groups of platelet surface receptors provide important positive feedback loops for platelet activation: $P2Y_1$ and $P2Y_{12}$ are stimulated by ADP released from platelet dense granules; 5-hydroxytryptamine 2A receptors ($5HT_{2A}$) are stimulated by 5-hydroxytryptamine (5-HT; also known as serotonin) released from platelet dense granules; and the thromboxane prostanoid (TP) receptor is stimulated by thromboxane A_2 (TXA_2) generated by the platelet cyclooxygenase (COX)-1-dependent signaling pathway. Platelet-to-platelet aggregation is mediated by fibrinogen and, at high shear flow, by VWF binding to activated integrin αIIbβ3. Perpetuation of platelet-to-platelet aggregation is augmented by other receptors, including junctional adhesion molecule A (JAMA) and JAMC, growth-arrest specific gene 6 receptor, and ephrin. Platelet-monocyte adhesion is initially mediated by the binding of platelet surface P-selectin to its constitutively expressed cognate receptor, P-selectin glycoprotein ligand-1 (PSGL-1), on the monocyte surface. Activated platelets, monocytes and microparticles bind coagulation factors and provide a surface for the generation of a fibrin clot. Approved antiplatelet agents and their molecular targets are shown in boxes. Indirect inhibitors (unfractionated heparin [UFH], low-molecular-weight heparin [LMWH]) and direct inhibitors (lepirudin, argatroban, bivalirudin and dabigatran) of thrombin, unlike PAR-1 antagonists, are anticoagulants rather than specific antiplatelet drugs. However, their inhibition of thrombin results in reduced platelet activation. Investigational strategies for novel antiplatelet agents are shown by the symbols adjacent to: GPIb-IX-V, GPVI, α2β1, EP_3, $5HT_{2A}$, PAR-4, $P2Y_1$, $P2Y_{12}$, PSGL1, PI3Kβ, αIIbβ3 and the TP receptor. AA, arachidonic acid; EP_3, prostaglandin E2 receptor EP_3 subtype; NO, nitric oxide; PDE, phosphodiesterase; PG, prostaglandin; PI3Kβ, phosphoinositide 3-kinase β-isoform. Modified from Michelson AD. Nat Rev Drug Discov. 2010 with permission[31]

Based on the results of the TRA 2P-TIMI 50 (Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events – Thrombolysis in Myocardial Infarction) trial in patients with stable atherosclerotic disease,[32] vorapaxar may be used in addition to standard antiplatelet therapy in the secondary prophylaxis of ischemic events in patients with a history of MI or symptomatic peripheral artery disease (PAD; Table 6).

Table 6: Approved antiplatelet agents in cardiovascular disease

Agent	Structure	Administration	Mechanism	Indication
Aspirin	Acetylsalicylic acid	Oral	COX-1 inhibition	CAD, PAD, CVD, CABG, CEA, coronary and peripheral stents
Ticlopidine	Thienopyridine	Oral	$P2Y_{12}$ inhibition	CVD, coronary stents
Clopidogrel	Thienopyridine	Oral	$P2Y_{12}$ inhibition	Prior MI, stroke or symptomatic PAD, as monotherapy; ACS or coronary stenting, in combination with aspirin
Prasugrel	Thienopyridine	Oral	$P2Y_{12}$ inhibition	ACS patients undergoing PCI with stenting, in combination with aspirin

Ticagrelor	Triazolopyrimidine	Oral	$P2Y_{12}$ inhibition	ACS patients, in combination with aspirin
Cangrelor	Adenosine triphosphate analog	Intravenous	$P2Y_{12}$ inhibition	$P2Y_{12}$ inhibitor naïve PCI patients
Abciximab	F_{ab} fragment of mouse human chimeric antibody 7E3	Intravenous	GPIIb-IIIa inhibition	PCI
Tirofiban	Non-peptide mimetic based on RGD	Intravenous	GPIIb-IIIa inhibition	ACS, PCI
Eptifibatide	KGD-containing cyclic heptapeptide	Intravenous	GPIIb-IIIa inhibition	ACS, PCI
Vorapaxar	Tricyclic himbacine derivative	Oral	PAR-1 inhibition	Prior MI, PAD

Recently, we synthesized a series of new diadenosine tetraphosphate (Ap_4A) analogs and evaluated these Ap4A derivatives as platelet aggregation inhibitors, and with respect to their effects on platelet $P2Y_1$, $P2Y_{12}$, and P2X1 receptors.[33,34] Based on the results of these experiments, 1 compound (GLS-409) that synergistically inhibited $P2Y_1$ and $P2Y_{12}$ without affecting P2X1 was selected for studies on antiplatelet efficacy (Table 7).[33]

Table 7: Potential future antiplatelet agents in cardiovascular disease

Agent	Structure	Administration	Mechanism	Possible field of application
GLS-409	Diadenosine tetraphosphate derivative	Intravenous	Synergistic inhibition of $P2Y_1$ and $P2Y_{12}$	ACS, PCI
PZ-128	Cell-penetrating lipopeptide	Intravenous	PAR-1 inhibition	ACS, PCI
BMS-986120	2-methoxy-6-[6-methoxy-4-[[5-methyl-2-(4-morpholinyl)-4-thiazolyl]methoxy]-2-benzofuranyl]-imidazo[2,1-b]-1,3,4-thiadiazole	Oral	PAR-4 inhibition	CAD, PAD, CVD
Troα6, Troα10	Hexa- and deca-peptides derived from the C-terminal region of trowaglerix	Intravenous	Glycoprotein VI inhibition	ACS, PCI
BI1002494	(R)-4-{(R)-1-[7-(3,4,5-trimethoxy-phenyl)-[1,6]naphthyridin-5-yloxy]-ethyl} pyrrolidin-2-one	Oral	Spleen tyrosine kinase inhibition	CAD, PAD, CVD
ML-355	*N*-(benzo*[d]*thiazol-2-yl)-4-((2-hydroxy-3-methoxybenzyl)amino) benzenesulfonamide	Oral	12-lipoxygenase inhibition	CAD, PAD, CVD

ACS-acute coronary syndrome; CAD-coronary artery disease; CVD- cerebrovascular disease; PAD- peripheral artery disease; PAR-protease‑activated receptor; PCI-percutaneous coronary intervention.

4. NANOTECHNOLOGY IN CVD THERAPY[35]

Generally, smart nanocarriers encapsulate two parts: targeting moieties and therapeutic drugs. Therefore, targeting moieties, including peptides, antibodies, ligands, and cell membranes, could drive the nanoplatforms to the lesion microenvironment and target the components of interest (Figure 4). Owing to their high capacity and easy modification, diverse therapeutic drugs, such as chemicals, proteins, peptides, and nucleic acids, have previously been loaded into nanocarriers. Tables 8 summarize recently reported nanocarriers to deliver different drugs in detail.

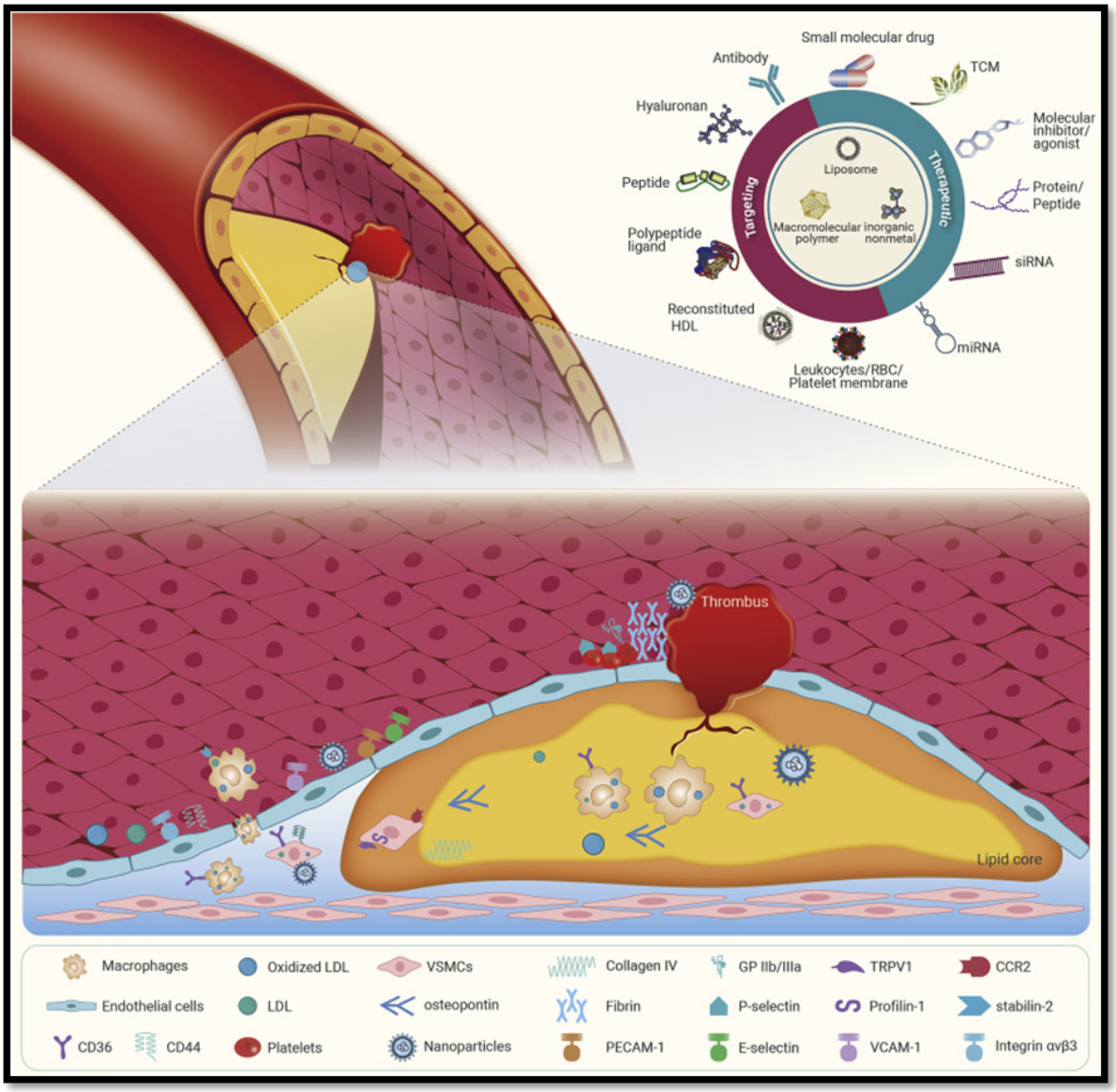

Figure 4. Multiple smart nanoplatforms targeting the lesion in the progression of atherosclerosis

The surface modification of nanoplatforms via peptides, antibodies, ligands, and cell membranes could target different cells or components in the plaque to achieve precise delivery of chemicals, proteins, peptides, or nucleic acids and finally release these cargos to exert therapeutic effects.

Table 8. Novel nanoplatforms for delivery of different drugs to the sites of CADs

Empty Cell	Loaded drug	Nanoplatforms	Disorders	Mechanism of action	Surface modifications	Model of use/animal	Administration route

Statins	atorvastatin	HA-ATV-NP	atherosclerosis	suppression of inflammation	hyaluronan	*in vitro*; *in vivo*, Apoe−/− mice	intravenous injection
	atorvastatin	Oxi-COS/MM-AT-nps	atherosclerosis	suppression of inflammation	proteins derived from macrophages membrane	*in vitro*; *in vivo*, Apoe−/− mice	intravenous injection
Rapamycin	rapamycin	PFN1-CD-mnps	atherosclerosis	suppression of inflammation	profilin-1 antibody	*in vitro*; *in vivo*, Apoe−/− mice	intravenous injection
	rapamycin	liposome	atherosclerosis	suppression of inflammation	membrane protein from leukocytes	*in vivo*, Apoe−/− mice	retro-orbital injection
Traditional Chinese medicine	Sal B, PNS	RGD-S/P-lpns	AMI		RGD peptide ligand	*in vivo*, SD rats receiving experimental MI	intravenous injection
Small molecule agonists/inhibitors	SMI 6877002	rHDL NPs	atherosclerosis	inhibition of monocyte recruitment; suppression of plaque inflammation	Apoa-I	*in vitro*; *in vivo*, Apoe−/− mice, cynomolgus monkeys	intravenous injection
Small molecule agonists/inhibitors	SNO	SNO-HDL NPs	atherosclerosis		Apoa-I	*in vitro*; *in vivo*, Apoe−/− mice	intravenous injection
siRNA	siCamk2g	G0-C14 PLGA NPs	atherosclerosis	promotion of efferocytosis	S2P peptide (CRTLTVRKC)	*in vitro*; *in vivo*, Ldlr−/− mice	intravenous injection
miRNA	miR-145	PAM	atherosclerosis	promotion of the contractile VSMC phenotype	MCP1/CCL2	*in vitro*; *in vivo*, Apoe−/− mice	intravenous injection

miRNA switches	miRNA switches	mRNA-p5RHH nanoparticle	Restenosis	specific inhibition of the VSMCs and inflammatory cells		*in vitro*; *in vivo*, C57BL6/J mice undergoing femoral artery wire injury	intravenous injection

HA-ATV-NP, hyaluronan-atorvastatin nanoparticle; Oxi-COS/MM-AT-nps, oxidation-sensitive chitosan oligosaccharide nanoparticles of amphiphilic/macrophage membrane-coated and atorvastatin-loaded nanoparticles; PFN1-CD-MNPs, low ph-sensitive cyclodextrin paramagnetic iron oxide nanoparticles conjugated with profilin-1 antibody; Sal B, salvianolic acid B; PNS, panax notoginsenoside; RGD-S/P-lpns, arginyl-glycyl-aspartic acid modified, Sal B and PNS co-loaded lipid-polymer hybrid nanoparticles; SMI 6877002, lipophilic small-molecule inhibitor of the CD40-TRAF6 interaction; rHDL NPs, reconstituted high-density lipoprotein nanoparticles; SNO, S-nitrosylated phospholipid, an NO donor compound; SNO-HDL NPs, S-nitrosylated phospholipid (1,2-dipalmitoyl-*sn*-glycero-3-phosphonitrosothioethanol) assembled with S-containing phospholipids and apolipoprotein A-I; G0-C14, a cationic lipid–like material; S2P peptide (CRTLTVRKC), a peptide recognizing the macrophage receptor stabilin-2; PS, phosphatidylserine; PAM, peptide amphiphile micelle; MCP1/CCL2, monocyte chemoattractant protein-1/C-C motif chemokine ligand 2; miRNA switches, modified mRNA encoding for the cyclin-dependent kinase inhibitor p27Kip1 that contains one complementary target sequence of miR126 at its 5′UTR.

5. ROBOTICS IN CVD THERAPY [36]

Robots have been in place in mass production industries for many years. However, their introduction in medicine was fairly recent and started in the fields of surgery and radiotherapy. In cardiology, they have been in use for more than a decade for surgeries like mitral valve repair, coronary artery bypass graft and septal defect closure. The technology is fast evolving with reports emerging about their potential applications in percutaneous coronary intervention and atrial fibrillation ablation . Robotics provide the operator with advantages such as improved ergonomics, precision and sometimes shortening of intraoperative time (Figure 5) . There have been reports that robot-assisted surgery can shorten patient hospital stay and improve patient perception (Figure 5) .
This schematic illustrates the potential applications by which nanotechnology, stem cells, robotics, new drugs and 3-D printing can be used in the treatment of coronary artery disease. Abbreviations: coronary artery bypass graft (CABG), coronary artery disease (CAD), percutaneous coronary intervention (PCI). The upward arrow represents an increase of blood flow.

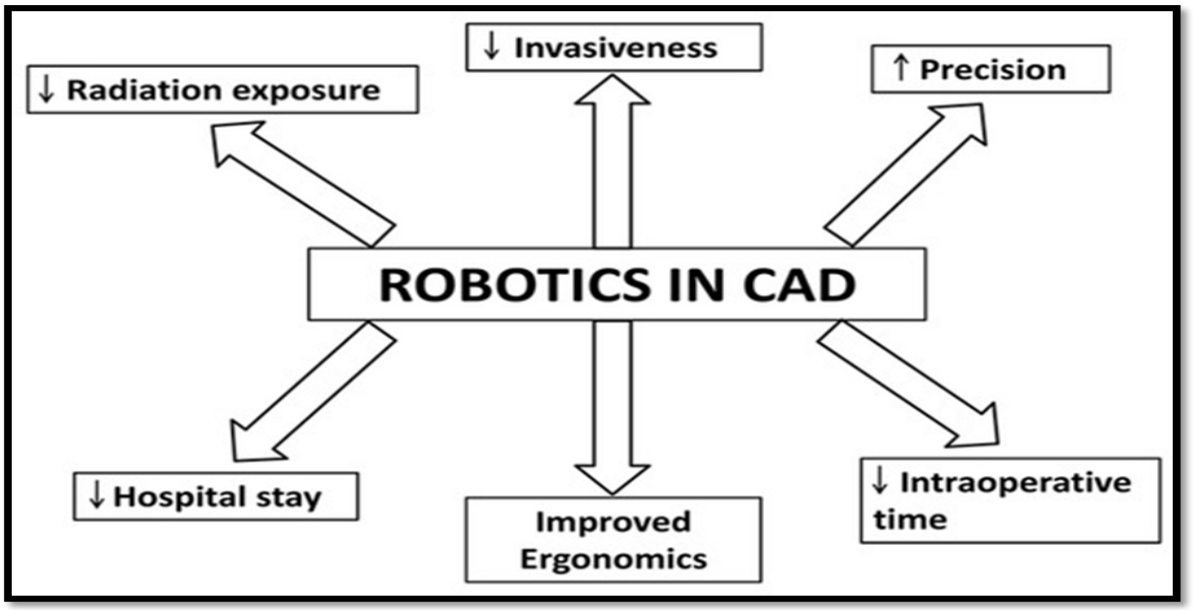

Figure 5: The schematic illustrates the potential advantages of using robotics in the treatment of CAD. The upward or downward arrows represent an increase or a decrease of blood flow, respectively.

In the field of interventional cardiology, robotics are being used for catheter-based surgical procedures. Conventional angiography radiation exposure for CAD patients is estimated at 7 mSV, and this exposure can be increased by up to 5 times in complicated surgeries . Robotic guided surgery has potential to limit this radiation exposure. In addition, they can also reduce contrast induced nephrotoxicity and associated mortality in patients (Figure 5) . In terms of patient related outcomes, the robotic assisted surgery has potential benefits as it can accurately measure the size of the lesions (which can be miscalculated using 2D angiography) which could improve long-term health. Hence, they reduce radiation exposure for the surgeon and the patient as well as improve precision by rendering accurate measurements of lesions (Figure 5) . Granada et al. published the first robotic interventions for cardiac patients . They performed coronary angioplasty and reported 100% success rate (measured in terms of less than 30% residual stenosis along with the absence of major cardiac complications) in all of their patients (80 subjects). In a multicenter study published by Weisz et al., a percutaneous coronary intervention was performed for patients with coronary artery disease . They used similar success criteria (measured in terms of less than 30% residual stenosis along with absence of major cardiac complications) and reported a 97.6% rate of success (164 patients). They also reported a significant reduction (95%) in operator radiation exposure .

Robotics has also been used to perform coronary artery bypass grafting in CAD patients. The procedure, including the harvesting of the mammary arteries and anastomosis, can be performed endoscopically . The results of the clinical studies are summarized in Table 9. Although there are reported benefits for robotically assisted bypass grafting, high costs and long learning curves have slowed down its progress towards becoming used routinely . Robotically assisted hybrid coronary revascularization, which involves coronary artery bypass graft as well as percutaneous coronary intervention, has also been developed as a treatment modality for CAD. There have been reported benefits such as reduced morbidity and shortened hospital stays due to the minimally invasive nature of the procedure .

Table 9: Summary of clinical studies for robotic assisted coronary artery bypass grafting.

S. No.	Author's Name	Results	Additional Comments
1.	Dogan et al.	They reported a patency rate of 100%.	TECAB was performed on hearts arrested intraoperatively.
2.	Kappert et al.	Reduced duration of surgery (down from 280 to 186 minutes); All of them had normal wound healing	TECAB was performed on a beating heart. 3 patients had to undergo re-exploration due to bleeding.
3.	Mohr et al.	Successful procedure in 22 patients (5 of them had to be converted to manual procedure); At discharge, patency was 100% and 95.4% at 3 months; In the TECAB group, success rate was 50%.	TECAB was performed on beating (n = 8) and arrested (n = 27) heart.

TECAB: Totally endoscopic coronary artery bypass graft; S. No: Serial number.

The current state of robotic surgery is promising in the treatment of CAD. These systems are of excellent quality with high-end technology. Their proposed benefits in the form of improved precision, increased visibility, improved ergonomics and reduced radiation exposure have been documented, which have translated into improved patient recovery times with reduced hospital stays. They also provide a distinct advantage for procedures that are difficult to be performed using endoscopy or catheters . However, their translation into full-fledged clinical usage is inhibited by high cost and the learning curve needed to master these procedures. It remains to be determined, with further technological advancement, whether this technology will be accepted into routine clinical practice and replace conventional technologies.

6. 3D- PRINTING IN CVD THERAPY [37]

Three-dimensional (3D) printing is a novel imaging modality which involves creating patient-specific models of cardiovascular structures. As percutaneous and surgical therapies evolve, spatial recognition of complex cardiovascular anatomic relationships by cardiologists and cardiovascular surgeons is imperative. Handheld 3D printed models of cardiovascular structures provide a facile and intuitive road map for procedural and surgical planning, complementing conventional imaging modalities. Moreover, 3D printed models are efficacious educational and communication tools.

Three-dimensional (3D) printing is at the crossroads of printer and materials engineering, noninvasive diagnostic imaging, computer-aided design, and structural heart intervention. Cardiovascular applications of this technology development include the use of patient-specific 3D models for medical teaching, exploration of valve and vessel function, surgical and catheter-based procedural planning, and early work in designing and refining the latest innovations in percutaneous structural devices[38]

II. CONCLUSION

Despite great progress in cardiovascular research, CAD remains one of the most common causes of morbidity and mortality worldwide. However, significant inter-collaborative efforts between researchers, clinicians and other related professionals have led to multi-faceted and novel strategies to be developed to treat CAD and its associated conditions. Though some of these strategies have strong evidence supporting their clinical use, some others are still in the experimental stage. Despite only early evidence being available on some of these novel treatment modalities, the results are promising and hold the potential to become alternatives to current treatment options in the future.

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