Chapter 6
Evolution of Angioplasty Devices

Keywords Angioplasty device · Balloon catheter · Stent · Drug-eluting stent · Resorbable stent · Cell-based therapy · FDA-approved devices · Commercial devices · Drug polymer coating · Antiproliferative drugs · Experimental devices

It is estimated that over 600,000 to 1 million cardiac catheterizations (CC) are performed annually in the United States. This exceeds the number of coronary artery bypass graft procedures (CABG) which are growing at an annual growth rate of about 1–5% in the United States. Percutaneous coronary intervention (PCI) is the treatment to open the blocked coronary artery using a transcatheter intervention that involves the insertion of a catheter through the femoral or radial artery and then guiding it to the site of stenosis and opening the blocked artery by inflating the angioplasty device such as a balloon catheter, bare metal stent or drug-eluting stent procedure, as classified in Fig. 6.1 [6, 86].

After Dr Mason Sones discovered selective coronary angiography accidentally in 1958, Andreas Gruentzig, a German-born physician in Zurich, Switzerland, performed the first balloon angioplasty procedure using a fixed-wire catheter in a coronary artery in 1977, and eventually the first stent implantation was performed in a patient by Sigwart and colleagues 1 year later [87–89]. Figure 6.2 shows the developments in angioplasty devices over the last 40 years [90].

During the development and evolution of these PCI devices, restenosis and thrombosis are the two major clinical complications that have been observed, and both conditions are due to the type of material used for the implanted scaffold along with other mechanical and biological risk factors. In simple terms, restenosis is a gradual re-narrowing of the stented segment that occurs most often between 3 and 12 months after stent placement. It usually presents as recurrent angina, but it can present as an acute myocardial infarction, which should be managed by repeat percutaneous revascularization. In contrast, stent thrombosis is an abrupt thrombotic occlusion of the vessel because of impaired or delayed healing, and this results in a catastrophic complication that presents either as a large myocardial infarction or as sudden death.

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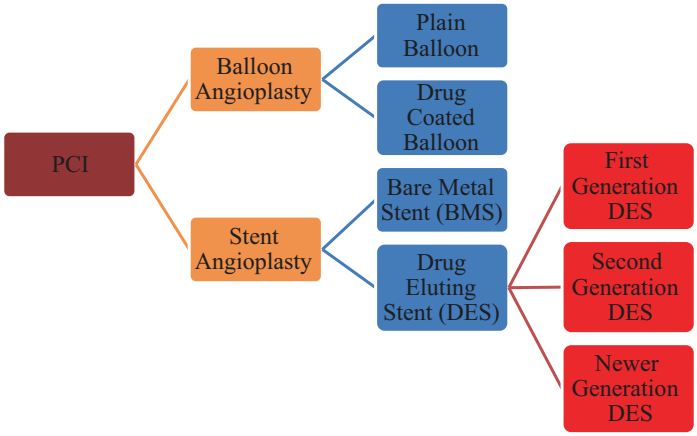

Fig. 6.1 Percutaneous coronary intervention (PCI) angioplasty procedure classification

There are several additional risk factors for late stent thrombosis, such as the penetration of the necrotic core, malapposition, overlapping stent placement, excessive stent length and bifurcated lesions. These factors represent additional barriers to healing, during drug-eluting stent (DES) implantation as mentioned in Fig. 6.3. They should be avoided so as to minimize the risk of thrombosis. Four categories of stent thrombosis have been defined as acute (0–24 h), early or subacute (within 30 days), late (between 30 days and 1 year) and very late (more than 1 year). We will discuss in this chapter how in the last three decades, starting from balloon angioplasty to the latest novel stent platform, there has been progress to diminishing restenosis, thrombosis and other limitations for each generation of device [91–94].

Balloon Catheter System for Angioplasty

Balloon catheters are used for primary percutaneous transluminal angioplasty (PTA) either with or without a stent that is crimped to it and are available in a wide variety of sizes, lengths, shapes and material compositions. The first generation of balloon catheters had a fixed-wire catheter-based balloon which then transitioned to an over-the-wire and exchangeable system (Rapid Exchange) over the last decade, which now allows the guide wire and balloon to move independently. An inflation device with an attachment hub is used at the proximal end of the balloon catheter near the site of insertion to inflate the balloon as shown in Fig. 6.4.

For any balloon catheter device, there are three clinical goals: deliverability, crossability and dilatation. But two major limitations of bare balloon catheter devices led to the development of the next generation of drug-eluting balloons and the first generation of a stent angioplasty scaffolds. The first limitation was the over-the-wire exchangeable system, which led to early closure of the treated vessel within a few hours to days that required repeated dilatation or emergency coronary artery bypass

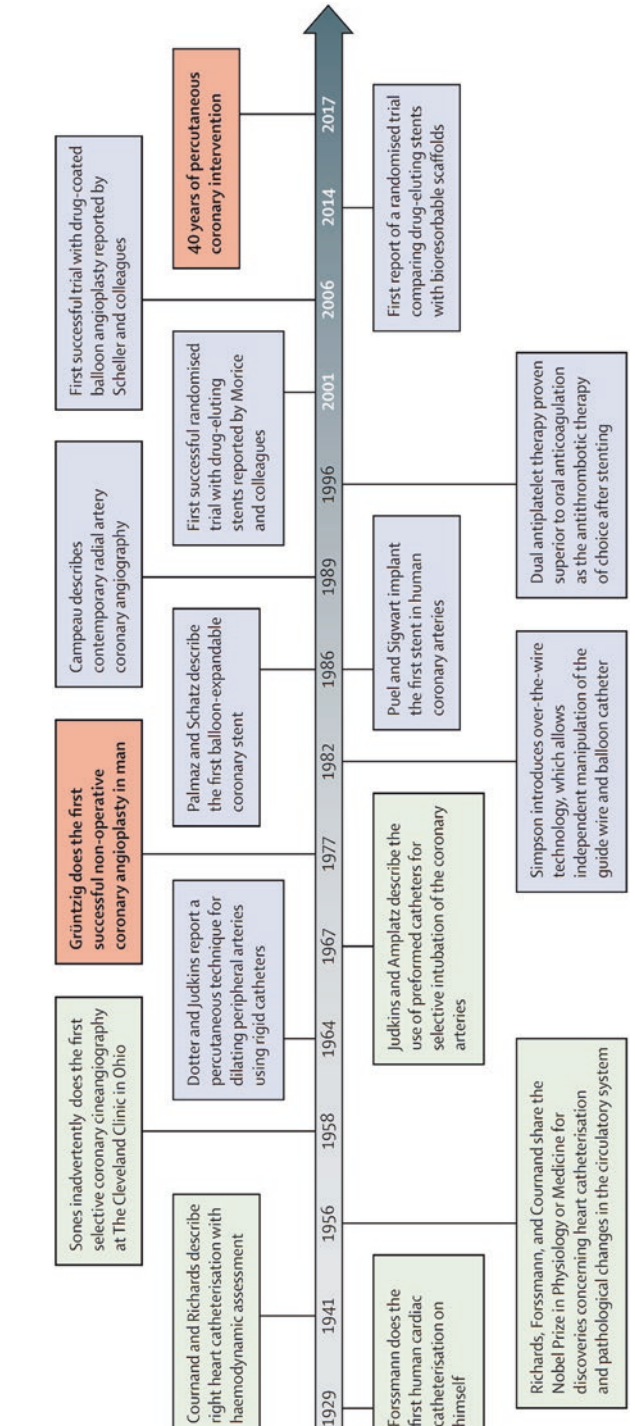

Fig. 6.2 Timeline of diagnostic cardiac catheterization, coronary balloon angioplasty, stent and scaffold implantation as contributors make improvements to reduce cardiovascular deaths. Developments in diagnostic catheterization are shown in green, coronary angioplasty in red and catheter therapeutics in blue [90]

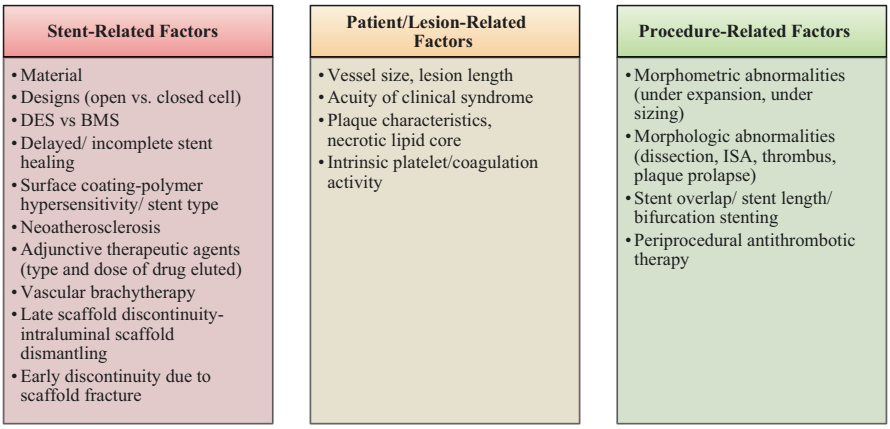

Fig. 6.3 Precipitants of stent thrombosis [94] *BMS* bare metal stent, *CHF* congestive heart failure, *DES* drug-eluting stent, *ISA* incomplete stent strut apposition

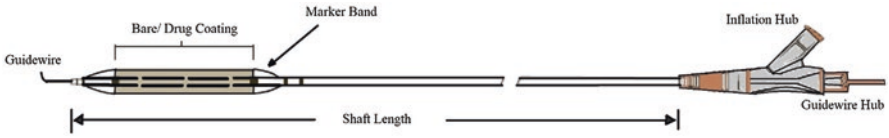

Fig. 6.4 Illustration of over-the-wire (OTW) balloon catheter

grafting (CABG) in about 3–5% of cases. The second limitation was the high rate of restenosis resulting in the recurrence of symptoms in about 20–30% of patients, mainly due to plaque prolapse, vessel recoil and constrictive remodelling. Table 6.1 contains the list of polymers utilized in the fabrication of the balloons [95, 96].

The first balloon used by Dr Gruentzig was made from polyvinyl chloride (PVC) film, but it had a thick wall. Over time balloon materials and technologies evolved to use improved thinner polymer materials such as polyethylene (PE), polyethylene terephthalate (PET) and nylon. PET offers the advantages of tensile strength and maximum pressure rating, while nylon is softer. There have been developments over the years in terms of surface coatings of angioplasty balloons to improve lubrication, trackability and abrasion resistance and to deliver an antirestenotic/anticoagulatory drug. A variety of different balloon coatings that either modify the surface properties or release an active pharmaceutical ingredient (API) have been reported. They include lubricious coatings, both hydrophilic and hydrophobic, abrasion and puncture resistant coatings, tacky or high friction coatings, conductive coatings, antithrombogenic coatings, drug release coatings, as well as reflective and selective coatings [96, 98].

A drug-coated balloon (DCB) or a drug-eluting balloon (DEB) is used to release an active pharmaceutical ingredient at the implantation site during the short duration of contact between the balloon surface and the site of injury without using a permanent metal stent. An early generation of balloon catheter systems utilized drugs such as paclitaxel and sirolimus. Among these drugs, paclitaxel is the

Table 6.1 Basic materials and properties of balloons [95, 97]

Balloon material	Compliance (%)	Burst pressure	Balloon selection based on compliance	Scratch resistance	Max. rated pressure	
					ATM	PSI
Polyvinyl chloride	High (>10)	Moderate	Pre-dilatation	Unknown	6–8	88–117
Polyethylene	Moderate (>10)	Moderate	Pre-dilatation	Low-moderate	10	147
Polyolefin copolymers	High (>10)	Moderate	Pre-dilatation	Unknown	Unknown	Unknown
Polyethylene terephthalate	Non (<5)	Highest	Post-dilatation of stents, resistant lesion	Low	20	294
Nylon	Low (5–10)	High	Pre-dilatation/ post-dilatation of stents	Moderate	16	235
Nylon-reinforced polyurethane	Non (<5)	High	Post-dilatation of stents, resistant lesion	High	10	147
Polyurethane	Low (5–10)	High	Pre-dilatation/ post-dilatation of stents	Unknown	10	147

preferred API due to its hydrophobicity, rapid drug uptake and retention. The mechanism of action of the drugs used to coat balloon and stent systems is discussed later. DCB's have not been approved for patients with a myocardial infarction; however, the FDA has approved the use of DCB's for peripheral artery disease (PAD) as mentioned in Table 6.2.

Clinically, data from 23 clinical trials involving a total of 2712 patients have compared drug-coated balloons with drug-eluting stents for the treatment of CAD. The data shows that DCB is equivalent to DES in terms of safety for managing CAD. Some other clinical trials have confirmed that the DCB leads to fewer incidents of in-stent restenosis and the occlusion of small coronary vessels [103–107]. A list of some CE-mark approved drug-coated balloon (DCB) devices is mentioned in Table 6.3. The use of DCB's for the treatment of bare metal stents-in-stent restenosis (BMS-ISR) or DES-in-stent restenosis (DES-ISR) has proven to be superior to plain balloon's and the first generation of DES angioplasty. The 2014 European Society of Cardiology (ESC)/European Association for Cardio-Thoracic Surgery (EACTS) guidelines recommended this approach for myocardial revascularization [108, 109].

Stent Angioplasty

This section will discuss the progress of stent angioplasty from the bare metal stents to newer stent platforms over the last two decades for improving healing and patient outcomes.

Table 6.2 US FDA-approved drug-eluting/drug-coated balloon catheter devices (DEB/DCB) for peripheral artery disease (PAD) [99–102]

Sr. no.	Balloon catheter	Year approved	Drug	Dose	Polymer
1	C.R. Bard's Lutonix 035 DCB catheter	2014	Paclitaxel	2 μg/mm^2	Specialized nonpolymer formulation with polysorbate, sorbitol as inactive ingredient
2	IN.PACT™ Admiral™ paclitaxel-coated percutaneous transluminal angioplasty (PTA) balloon catheter, Medtronic Inc.	2014	Paclitaxel	3.5 μg/mm^2	Proprietary FreePac™ coating solution of hydrophilic excipient (urea)
3	Stellarex OTW drug-coated balloon PTA catheter	2017	Paclitaxel	2 μg/mm^2	Proprietary coating of hydrophilic polymer excipient (polyethylene glycol 8000)

Bare Metal Stent (BMS) Angioplasty

Early limitations of balloon catheters encouraged the development of bare metal stents that enabled the widespread utilization of percutaneous coronary intervention (PCI) therapy worldwide. The biggest advantage of a bare metal stent over the balloon catheter was its mechanical strength that helped to overcome the effect of vessel recoil and constrictive remodelling and a reduction in the rate of restenosis [110]. Consequently, the design and development of new bare metal stent platforms had arrived with advanced medical therapies including dual antiplatelet therapy which had previously been limited early stent thrombosis and bleeding complications associated with thrombolytic therapy. The first licensed bare metal stent was made from 316L stainless steel which was subsequently replaced by an improved cobalt chromium metal alloy by Guidant Corporation. The advantage of this Guidant stent is its capability to produce a lower strut thickness with increased radial strength. Stent strut thickness is a key factor that plays an important role to reduce restenosis. The results of the ISAR-STEREO-2 clinical trial on a total of 611 patients indicated that the incidence of angiographic restenosis was 17.9% in the thin-strut stent group (50 micron) and was 31.4% in the thick-strut stent group (140 micron) [111]. Table 6.5 shows that stents are now available with different metal alloys, polymers and drugs with different strut thicknesses [112].

As a result of research and development of various metal alloys in the selection of modern stent materials, three basic properties have been taken into account. They are elasticity or plasticity for expansion, rigidity for the control of dilatation and resistance to elastic recoil. As shown in Table 6.5, various materials have been utilized for balloon expandable stents. They include 316L stainless steel, tantalum, martensitic nitinol, polymers, cobalt alloy, cobalt chromium alloy, hybrid tantalum with stainless steel, hybrid platinum with stainless steel and platinum chromium

Table 6.3 Drug-coated balloon (DCB) catheter devices available for percutaneous coronary intervention (PCI) [108]

Device	Company	Drug	Dose	Excipient
PACCOCATH®	Bayer, Germany	Paclitaxel	3 μg/mm^2	Iopromide
SeQuent® Please Neo	B. Braun Melsungen, Germany	Paclitaxel	3 μg/mm^2	Iopromide
DIOR I	Eurocor, Germany	Paclitaxel	3 μg/mm^2	Shelloic acid
DIOR II	Eurocor, Germany	Paclitaxel	3 μg/mm^2	Shelloic acid
Biostream	Biosensors International Group, Ltd., Switzerland	Paclitaxel	3 μg/mm^2	Shellac
Agent®	Boston Scientific, USA	Paclitaxel	2 μg/mm^2	Citrate ester
Essentia®	iVascular, S.L.U., Spain	Paclitaxel	3 μg/mm^2	Organic ester
IN-PACT Falcon™	Medtronic, USA	Paclitaxel	3 μg/mm^2	Urea
Genie™	Acrostak, Switzerland	Nanoporous	10 μmol/L	None
Pantera Lux®	Biotronik, Switzerland	Paclitaxel	3 μg/mm^2	Butyryl-tri-hexyl citrate
Elutax®	Aachen Resonance, Germany	Paclitaxel	2 μg/mm^2	Dextrane
Danubio®	Minvasys, France	Paclitaxel	2.5 μg/mm^2	Butyryl-tri-hexyl citrate
RESTORE® DEB	Cardionovum, Germany	Paclitaxel	3 μg/mm^2	Safepax
Protégé® and Protégé® NC	Blue Medical, Netherlands	Paclitaxel	3 μg/mm^2	Butyryl-tri-hexyl citrate
Virtue® DCB	Caliber Therapeutics, Inc., USA	Sirolimus nanoparticles	3 μg/mm^2	Porous balloon
Selution® DCB	M.A. Med Alliance SA, Switzerland	Sirolimus nanoparticles	1 μg/mm^2	Cell adherence technology (CAT)
MagicTouch™ Xtreme Touch™ DCB	Concept Medical, Surat, India	Sirolimus + nanocarriers	1.27 μg/mm^2 3 μg/mm^2	Phospholipid
Kanshas DCB	Terumo Corporation	Paclitaxel + Unicoat™ microcrystal coating	3.2 μg/mm^2	L-Serine Ethyl Ester HCl

alloy. For the development of self-expanding stents, alternate metals such as nickel titanium, nitinol, cobalt alloy, as well as novel biodegradable magnesium, iron (Fe), zinc (Zn) and their alloys have been used [113–116]. As thinner struts have been developed, the additional property of radio-opacity has become a major concern. Various methods, such as gold coating, radio-opaque dye coating or attachment of

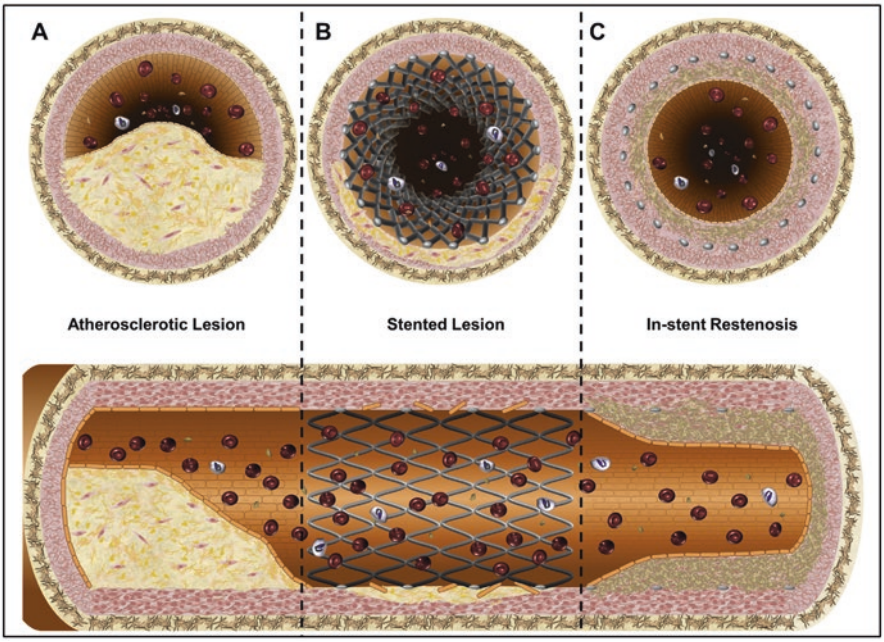

Fig. 6.5 Progression of in-stent restenosis. Cross-sectional and longitudinal views of an artery depicting the chronological progression of in-stent restenosis. (**a**) Obstructive atheromatous plaque causing flow-limiting stenosis of the arterial lumen with reduced luminal diameter. (**b**) After percutaneous endoluminal stenting which restores the native vessel diameter by compressing the atheromatous plaque into the vessel wall with resultant denudation of the endothelial layer. (**c**) In-stent restenosis after inappropriate neointimal hyperplasia in response to percutaneous stent insertion resulting in recurrence of flow-limiting stenosis [119]

a radio-opaque marker at the proximal and distal ends of the stent have been utilized [117]. One additional parameter that has been considered during metal stent development is the need to reduce the amount of metal ion release from the metal alloy, specifically nickel ions, after implantation. Strategies to reduce the release of metal ions have included using a nickel-free alloy or by using various coatings through chemical or physical vapour deposition methods such as diamond-like carbon coating, silicon carbide coating, carbon coating, titanium oxide coating, titanium-nitride-oxide coating or an iridium oxide coating [118].

Despite these advanced developments in bare metal stent technology, neointimal accumulation of plaque has remained the major limitation of bare metal stents, resulting in the development of in-stent restenosis (ISR) in 20–30% of cases as shown in Fig. 6.5. This restenosis limitation of the bare metal stent (BMS) has been referred to as the "Achilles' heel" of PCI and has led to the development of the first-generation drug-eluting stent system [109, 119].

Table 6.4 Three generations of drug-eluting stents (DES) [120, 121]

Generation	Device examples	Specifications	Advantage and limitations
First-generation DES	Cypher, Taxus	Drug: sirolimus, paclitaxel Platform: stainless steel, slotted tube design Polymer: durable	Superior to BMS in reducing the magnitude of neointimal proliferation and clinical restenosis Limitation: late stent thrombosis is more likely to occur with these stents
Second-generation DES	Endeavor, Xience V	Drug: zotarolimus, everolimus Platform: cobalt chromium, thin-strut stents Polymer: persistent	Superior to first-generation DES, exhibiting lower thrombosis rates Limitation: drugs delayed re-endothelialization
Newer generation DES	Axxess Stent, Nevo Stent	Drug: biolimus, sirolimus, everolimus Platform: platinum chromium, nickel-titanium Polymer: bioresorbable polymer coating, polymer free coating	Superior biocompatibility and controlled release drug profile

First-Generation Drug-Eluting Stent (DES) Angioplasty

Limitation of restenosis of the bare metal stent (BMS) led to the development of a drug-eluting stent (DES) which involved the controlled release of antiproliferative drugs incorporated within a polymer coating. At the same time as the development of bare metal stents and medical therapies, an early generation DES was developed that released sirolimus (e.g. the Cypher stent) or paclitaxel (e.g. the Taxus stent) from the relatively thick struts (120–140 μm) of a stainless steel stent platform coated with a polymer. To facilitate the controlled release of the drug, DES's utilized permanent synthetic polymer coating materials, known as biostable polymers, such as polyethylene-co-vinyl acetate, poly-n-butyl methacrylate and the tri-block copolymer poly(styrene-b-isobutylene-b-styrene). Tables 6.4 and 6.5 give an overview of all three generations of drug-eluting stents and list some of the US FDA-approved stents with their unique structural characteristics [120].

The first-generation DES was successful in reducing the angiographic and clinical restenosis by 50–70% compared to the bare metal stents, but it also increased the risk of late and very late stent thrombosis. As a result, the use of the first-generation DES was limited to certain conditions [122]. According to the research reported by Bønaa et al., the 6-year rate of repeat revascularization was less than about 16.5% in the drug-eluting stent group compared to 19.8% in the bare metal stent group ($p < 0.001$) [123]. Meta-analysis of a clinical trial comparing the 5-year follow-up

Table 6.5 Drug-eluting stents with durable or biodegradable polymer coatings [112, 121]

Sr. no.	Device	Platform	Drug	Strut thickness	Polymer type	Polymer material	Coating distribution	Polymer thickness	Additional coating
1	Taxus	SS	Paclitaxel	132 μm	Durable	SIBS	Circumferential	22	–
2	Cypher	SS	Sirolimus	140 μm	Durable	PEVA/PBMA	Circumferential	13	–
3	BioMatrix Nobori	SS	Biolimus	120 μm	Biodegradable	PDLLA	Abluminal	10	–
4	Endeavor	CoCr	Zotarolimus	91 μm	Durable	MPC/LMA/ HPMA/3-MPMA	Circumferential	6	–
5	Yukon PC	SS	Sirolimus	87 μm	Biodegradable	PDLLA	Circumferential	5	–
6	Xience Promus	CoCr PtCr	Everolimus	81 μm	Durable	PBMA/PVDF-HFP	Circumferential	8	–
7	Resolute	CoCr	Zotarolimus	91 μm	Durable	PBMA/PHMA/PVP/ PVA	Circumferential	6	–
8	Synergy	PtCr	Everolimus	74 μm	Biodegradable	PLGA	Abluminal	4	–
9	Orsiro	CoCr	Sirolimus	60 μm	Biodegradable	PLLA	Circumferential	7	Silicon carbide
10	DESyne	CoCr	Novolimus	81 μm	Biodegradable	PLLA	Circumferential	<3	–
11	Combo	SS	Sirolimus	100 μm	Biodegradable	PDLLA/PLGA	Abluminal	5	Anti-CD34 antibodies
12	Mistent	CoCr	Sirolimus	64 μm	Biodegradable	PLGA	Circumferential	10	–
13	Ultimaster	CoCr	Sirolimus	80 μm	Biodegradable	PDLLA-PCL	Abluminal	15	–

SS stainless steel, *CoCr* cobalt chromium, *PtCr* platinum chromium, *SIBS* poly(styrene-b-isobutylene-b-styrene), *PEVA* poly-ethylene-co-vinyl acetate, *PBMA* poly n-butyl methacrylate, *PVDF-HFP* co-polymer of vinylidene fluoride and hexafluoropropylene, *MPC* methacryloyloxyethyl phosphorylcholine, *LMA* lauryl methacrylate, *HPMA* hydroxypropyl methacrylate, *3-MPMA* trimethoxysilylpropyl methacrylate, *PVP* polyvinyl pyrrolidinone, *PHMA* polyhexyl methacrylate, *PVA* polyvinyl acetate, *PLGA* poly-lactic co-glycolic acid, *PLLA* poly-L-lactic acid, *PDLLA* poly-D, L-lactic acid

Table 6.6 First- and second-generation drug-eluting stent platforms showing year of FDA approval [121, 126–128]

Stent	Year	Manufacturer	Stent alloy	Drug
Cypher	2003	Cordis	Stainless steel	Sirolimus
Taxus	2004	Boston Scientific	Stainless steel	Paclitaxel
Xience V	2007	Abbott Vascular	Cobalt chromium	Everolimus
Promus	2008	Boston Scientific	Cobalt chromium	Everolimus
Endeavor	2008	Medtronic	Cobalt chromium	Zotarolimus
Xience Prime	2011	Abbott Vascular	Cobalt chromium	Everolimus
Promus Element	2011	Boston Scientific	Platinum chromium	Everolimus
Taxus Ion	2011	Boston Scientific	Cobalt chromium	Paclitaxel
Resolute	2012	Medtronic	Cobalt chromium	Zotarolimus
Promus Premier	2013	Boston Scientific	Platinum chromium	Everolimus
Synergy	2015	Boston Scientific	Platinum chromium	Everolimus
Resolute Onyx	2017	Medtronic	Platinum iridium core-cobalt alloy shell	Zotarolimus
EluNIR	2017	Medinol Ltd (Cordis)	Cobalt chromium	Ridaforolimus
ORSIRO	2019	Biotronik, Inc.	Cobalt chromium	Sirolimus

of the first-generation DES and bare metal stent implantations in 1414 patients showed a significant reduction in target vessel revascularization (TVR) (8.7% vs 14.8%), but an increase in very late stent thrombosis in the first-generation DES (3.0%) compared to the bare metal stent group (1.0%) [124].

Second-Generation Drug-Eluting Stent (DES) Angioplasty

The US FDA approved several second-generation drug-eluting stent devices, such as zotarolimus-eluting (e.g. Resolute), everolimus-eluting (e.g. Xience V) and ridaforolimus-eluting (e.g. EluNIR) stents (ZES, EES and RES) [125–127]. Table 6.6 mentions the first- and second-generation DES's along with the FDA year of approval. The newer DES stents have a platform of a cobalt chromium or platinum chromium alloy and are thinner, easier to deliver and are more biocompatible than the first-generation DES's as shown in Table 6.5. Advanced biostable and biodegradable polymers with advanced design features and metal alloys have been utilized in the second-generation DES to limit polymer-induced in-stent restenosis (ISR) and stent thrombosis (ST). Currently, drug-eluting stents are recommended over bare metal stents for any PCI, irrespective of the clinical presentation, lesion type, planned noncardiac surgery, anticipated duration of dual antiplatelet therapy (DAPT), concomitant anticoagulant therapy or radial access [122].

Drugs Used in DES's

There are several limus family members, such as everolimus, zotarolimus, biolimus A9, tacrolimus, novolimus and pimecrolimus, that have been researched for drug-eluting stent applications and taxus family members, such as cytotoxic paclitaxel, that have been used for PCI applications. Sirolimus, also called rapamycin, is a macrocyclic lactone, a chemical derivative of soil microorganisms. Sirolimus and other members of the limus family are active pharmaceutical ingredients (APIs) that inhibit the cell cycle progression between the late "Growth1" to "Synthesis" phase and thus prevent the proliferation and migration of vascular smooth muscle cells that is known to induce neointimal and restenosis development as shown in Fig. 6.6 [129, 130]. Pimecrolimus and tacrolimus are calcineurin inhibitors. At the cellular level, these drugs bind to the FK-binding protein 12 and subsequently inhibit the mammalian target of rapamycin (mTOR) which leads to increased tissue factor expression. Zotarolimus and everolimus are analogues of sirolimus and have similar immunosuppressant properties like sirolimus, but they have enhanced lipophilic properties due to their high log P values that prevent drug loss through blood flow.

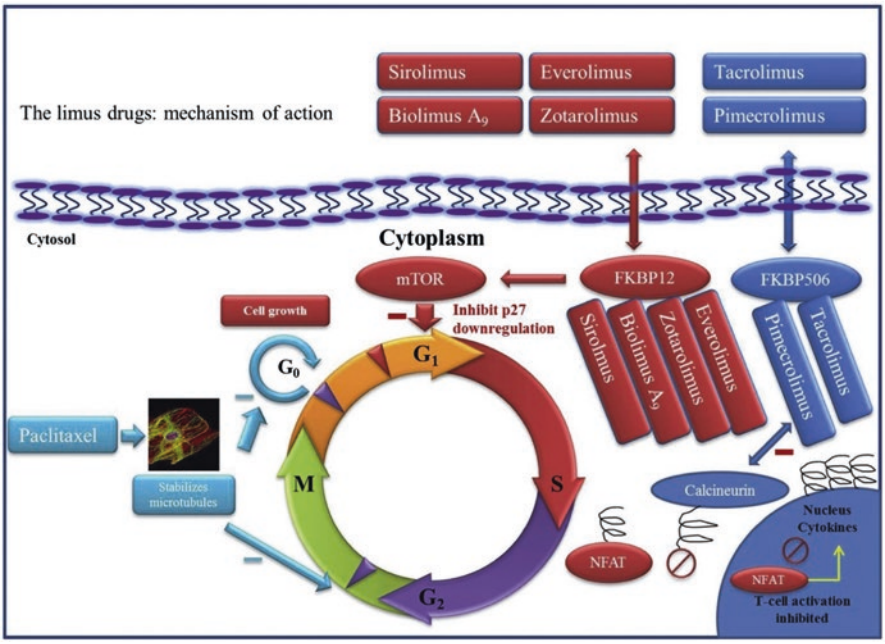

Fig. 6.6 Mechanisms of action of sirolimus, everolimus, biolimus A9, zotarolimus, tacrolimus and pimecrolimus [130] *FKBP* FK binding protein, *G* growth, *M* mitosis, *S* synthesis, *NFAT* nuclear factor of activated T cells, *mTOR* mammalian target of rapamycin

Note that tacrolimus has a less inhibitory effect on smooth muscle cell proliferation compared to sirolimus [131–134].

Paclitaxel is a potent cytostatic agent which inhibits cell proliferation and migration by disrupting the delivery of cellular microtubules. Paclitaxel interupts the cell cycle through stabilizing longer microtubules during mitosis by preventing the transition from the "Growth2" to the "Mitosis" phase which leads to the inhibition of smooth muscle cell proliferation and neointimal formation. The clinical trial KAMIR compared the paclitaxel- versus sirolimus-eluting stents for the treatment of STEMI patients and concluded that Paclitaxel is the preferred drug for angioplasty balloons due to its lipophilic properties that enable the drug-coated balloon to deliver the drug to the vessel wall during a shorter contact time. However, it was found that sirolimus was superior to paclitaxel with regards to the occurrence of a major adverse cardiac event (MACE) and target lesion revascularization (TLR) [135, 136].

Polymers Used in DES's

During the stages of DES development, one of the major factors affecting the in-vivo performance of the stent is the biocompatibility and in-vivo behaviour of the polymer when releasing the drug [137]. The purpose of the polymer is to modulate the elution of the drug into the arterial wall at the site of implantation. Over the years, polymers such as biostable/durable permanent polymers for the first-generation stents and biodegradable polymers for the second-generation stents have been optimized to provide a nonthrombotic, noninflammatory, nontoxic and re-endothelialisable performance [138].

Biostable or durable polymers, such as nonerodable polyethylene-co-vinyl acetate (PEVA) and poly-n-butyl methacrylate (PBMA) (Cypher Stent) and soft elastomeric polymers such as poly(styrene-bisobutylene-b-styrene) (SIBS) (Taxus, Promus and ION Stent), phosphorylcholine (ZoMaxx, Endeavor ZES), Biolinx polymer (Endeavor Resolute), polyvinylidene fluoride co-hexafluoropropylene (PVDF-HFP), poly-n-butyl methacrylate (Xience V and Promus stent), methacrylated phosphorylcholine based (PC) (Endeavor stent), a combination of poly(butyl methacrylate-co-vinyl acetate) (C10), poly(hexyl methacrylate-co-vinyl pyrrolidone-co-vinyl acetate) (C19) and poly(vinyl pryrrolidone) (PVP) (Resolute stent), have to date been used on devices approved by the US FDA [120, 121, 139, 140].

Some of the latest generation of stents with a biodegradable polymer coating have shown improvement in the efficacy of DES's with a lower rate of late in-stent thrombosis. The presence of late in-stent thrombosis for durable polymer-coated stents depends on the polymer as well as other stent-thrombosis factors, as mentioned in Fig. 6.3 [120, 141–143]. Table 6.7 lists the metallic stents with a biodegradable polymer coating or a polymer free technology [120, 121, 144–146].

Table 6.7 Metallic drug coated stents using a biodegradable polymer or polymer free coating technology together with an active pharmaceutical ingredient (API) [120, 121, 140, 145–150]

Polymer/technology to coat API	Platform alloy	Stent	API
Polylactic acid (PLA)	Nickel–titanium (Nitinol)	Axxess (Devax Inc.)	Biolimus A9
	L605 cobalt–chromium (Co-Cr)	Custom NX, Xtent (Xtent)	Biolimus A9
	316l stainless steel (316L SS)	BioMatrix (biosensors)	Biolimus A9
	316L SS	Nobori (Terumo)	Biolimus A9
	Nickel–titanium (Nitinol)	Axxess (Devax Inc.)	Biolimus A9
	L605 Co-Cr	Lumeno-Alpha (Cordis)	Biolimus A9
	L605 Co-Cr	Elixir Myolimus (Elixir Medical)	Myolimus
	316L SS with drug-polymer microdot coating	JACTAX HD (Boston Scientific) (134)	Paclitaxel
	316L SS	Excel stent (JW Medical System)	Sirolimus
	L605 Co-Cr	DESny BD (Elixir)	Novolimus
	316L SS	Champion (Boston Scientific Corp.)	Everolimus
Poly L-lactic acid (PLLA)	L605 Co-Cr	ORSIRO (Biotronik)	Sirolimus
Bioabsorbable, polylactide-co-glycolide (PLGA)	L605 Co-Cr with unique reservoir for drug-polymer	NEVO (Cordis, Johnson & Johnson)	Sirolimus
	316L SS	CORACTO (ALVIMEDICA)	Sirolimus
	Platinum chromium	SYNERGY (Boston Scientific)	Everolimus
	L-605 Co-Cr with micropore	CoStar stent (Conor MedSystems)	Paclitaxel
PLGA + PLLA	L-605 Co-Cr	BioMime (Meril Life Sciences)	Sirolimus
	Nitinol	Cardiomind (CardioMind Inc.)	Sirolimus
Bioabsorbable polymer, containing poly-L-lactide, polyvinyl pyrrolidone, polylactide-co-caprolactone and polylactide-co-glycolide	L-605 Co-Cr alloy with layered coating for controlled release	Supralimus-core (Sahajanand Medical)	Sirolimus
Poly (DL-lactide-co-caprolactone)	L-605 Co-Cr with no coating at strut curvature (hinges)	Ultimaster (Terumo)	Sirolimus
Polymer free/passive coating			
Selectively microstructured surface	L605 Co-Cr	Lumeno Free (Cordis)	Biolimus A9

(continued)

Table 6.7 (continued)

Polymer/technology to coat API	Platform alloy	Stent	API
Microstructured abluminal stent surface	316L SS	Biofreedom (Biosensors International)	Biolimus A9
Abluminal spray coated on synthetic glycocalix substrate	316L SS	Axxion (Biosensors International)	Paclitaxel
Direct drug coating	316L SS	Achieve (Cook Inc.)	Paclitaxel
	316L SS	Supra-G (Cook Inc.)	Paclitaxel
	316L SS	V-Flex Plus (Cook Inc.)	Paclitaxel
Abluminal coating with crystallized drug (microdrop spray crystallization process)	L605 Co-Cr	Amazonia PAX (Minvasys)	Paclitaxel
Microporous stent surface with top coat of shellac resin	316L SS	Yukon Choice (Translumina GmbH)	Sirolimus
Drug loading with micropores	316L SS	Yinyi (Liaoning Biomedical Materials)	Paclitaxel
Adluminal bio-inducer surface coating and drug reservoir	L605 Co-Cr	Cre8 (Alvimedica)	Amphilimus
Adluminal integral carbofilm coating and drug reservoir	316L SS	Janus (Sorin Biomedica)	Tacrolimus
Abluminal nanoporous cavities as drug reservoir	316L SS	Nano + (Lepu Medical)	Sirolimus
Diffusion from stent core	Co-Cr outer cover strut with hollow core for drug	Polymer-free drug-filled stent (Medtronic)	Sirolimus
Micropores with shellac resin	316L SS	Dual-DES	Sirolimus and antioxidant probucol
Nanothin-microporous hydroxyapatite coating	316L SS	Vestasync (MIV Therapeutics)	Sirolimus

Over the years, there have been developments such as advanced drug elution profiles, thinner and stronger strut profiles, improved biocompatible metal alloy platforms, advanced durable and biodegradable polymer coatings and advanced post-procedural medical therapies for the second generation of drug-eluting stents. These developments have resulted in a significant reduction in in-stent restenosis (ISR), primarily due to a lower incidence of neointimal hyperplasia [151, 152]. Two large-scale comprehensive clinical trials which included 12,866 and 18,334 patients utilized network meta-analysis of the data and concluded the superiority of the second-generation DES over bare metal stents, and the first-generation DES in terms of safety and efficacy. However, the very long-term clinical implications, such as very late stent thrombosis, are still a major concern for the patient population. Second-generation DES's have the side effects, such as delayed re-endothelialization,

neoatherosclerosis, medical necrosis and chronic inflammation. The use of dual antiplatelet therapy (DAPT) or anticoagulant medical therapy is prescribed to minimize these side effects which also means that there is still scope for improvement in the stent design and materials used [122, 153–159].

Although it has been proven that the second-generation drug-eluting stents have the ability to overcome the limitations of bare metal stents and first-generation DES's, in order to make further improvements, we are challenged by the performance of the second-generation DES drugs. Restenosis can be caused by an overreaction of the wound-healing response at the site of the stent injured vessel, while re-endothelialization is essential for normal wound healing. DES drugs, on the one hand, inhibit overreaction and restenosis, but on the other hand, by impairing the healing process of the injured arterial wall, these drugs result in delayed re-endothelialization and the formation of incompetent endothelium in terms of integrity and function. Such incompetent endothelium after DES therapy leads to accelerated and more frequent in-stent neoatherosclerosis [160, 161].

Current drug-eluting stents, as described above, depend on one of two mechanisms:

1. A passive coating to prevent cellular adhesion and subsequent inflammation
2. The use of a cytotoxic and antiproliferative drug

Both strategies increase the healing time due to their effect on delaying the re-endothelialization process and ultimately slowing healing. Delayed healing is the major risk associated with thrombosis and late stent restenosis [162, 163]. It has also been proven that the drugs loaded on drug-eluting stents inhibit proliferation, migration, differentiation and the endothelial nitric oxide synthase (eNOS) production in human endothelial progenitor cells [164].

Drug-Eluting Polymeric Stents

A novel development in the field of polymeric stents is the use of bioresorbable polymers instead of a permanent metal alloy. The advantage of these polymeric stents is that they absorb at the site of implantation within 6–24 months after implantation and once resorbed, it leaves no residue behind that will cause an inflammatory response. Thus, it preserves the vessel biomechanics, such as the vessel vasomotion. Due to the limited radial compression resistance and polymer-induced inflammation, these resorbable polymeric stents have a tendency to experience in-stent thrombosis. They are currently being evaluated clinically [165–167]. Table 6.8 mentions various polymers that are being used as a bioresorbable stent platform with their respective resorption time.

Table 6.8 List of commercially available and investigated bioresorbable scaffolds and specifications [165, 168–170]

Scaffold name	Strut material	Coating material	Eluted drug	Strut thickness	Radio-opacity	Resorption (months)	Crossing profile (mm)	Current status
Igaki-Tamai BRS	PLLA[a]	None	None	170	Gold	24–36	–	CE for PAD[a]
Absorb BVS[a] 1.0	PLLA	PDLLA[a]	EVL[a]	156	Pt[a]	18–24	1.4	Discontinued
Absorb BVS 1.1	PLLA	PDLLA	EVL[a]	156	Pt[a]	24–48	1.4	CE mark
Absorb new generation	PLLA	PDLLA	EVL[a]	<100	–	–	–	–
DESolve	PLLA	None	MYL[a]	150	Metallic	12–24	1.5	CE mark
DESolve 100	PLLA	PLLA	NVL[a]	100	–	24	–	CE mark
Reva scaffold	PTD-PC[a]	None	None	200	ROS[a]	24	0.1.8	Discontinued
ReZolve scaffold	PTD-PC	None	SRL[a]	115-230	ROS[a]	4–6	1.8	Clinical trial
ReZolve^2 scaffold	PTD-PC	None	SRL[a]	100	ROS[a]	48	1.5	Clinical trial
Fantom	PTD-PC	–	SRL[a]	125	–	36	–	Clinical trial
Ideal Biostent	Polymer salicylate	Salicylate	SRL[a]	175	None	>12	1.5-1.7	Clinical trial
Art18z BRS	PDLLA	None	None	170	None	3–6	6-Fr	Clinical trial
Amaranth	Semicrystalline polylactide		None	90–150	None	3–6	6-Fr	Clinical trial
Xinsorb BRS	PLLA	PDLLA	SRL[a]	160	–	24–36	–	Clinical trial
Acute BRS	PLCL,[a] PDLA, PLLA	–	SRL[a]	150	–	–	–	–
MeRes	PLLA	PDLLA	MRL[a]	100	–	24	–	Clinical trial
Fades	PLGA[a] & Mg[a]	–	–	–	–	6	–	–
Mirage bioresorbable micro-fibre scaffold	PLLA	–	SRL[a]	125–150	–	14	0.44″–0.058″	Clinical trial
AMS-1	Mg alloy	None	None	165	None	1	1.4	Discontinued
Dreams[a] 1.0	Mg with rare metal	PLGA	PXL[a]	120	None	3	1.2	Clinical trial

(continued)

Table 6.8 (continued)

Scaffold name	Strut material	Coating material	Eluted drug	Strut thickness	Radio-opacity	Resorption (months)	Crossing profile (mm)	Current status
Dreams[a] 2.0	Mg with rare metal	PLLA	SRL[a]	150	TNT[a] marker	12	1.75	Clinical trial
Unity BDS	Mg/PLLA	–	SRL[a]	–	–	12	–	Preclinical test
Dreams 3.0	Mg (WE43)	PLLA	SRL[a]	99,117,147	Yes	12	–	Preclinical test
NOR-I	Iron	NA	NA	91	–	41 mg Fe/ month	–	Preclinical test
IBS	Iron	Zinc+ PLLA	SRL[a]	70	–	13	1.04	Preclinical test

[a]*PLLA* poly-L-lactic acid, *PDLLA* poly-D,L-lactic acid, *BVS* bioresorbable vascular scaffold, *PTD-PC* poly-tyrosine-derived polycarbonate, *PLCL* poly-L-lactide-co-ε-caprolactone, *PLGA* poly-lactide-co-glycolide, *DREAMS* drug-eluting absorbable metallic stents, *EVL* everolimus, *MYL* myolimus, *NVL* novolimus, *SRL* sirolimus, *PXL* paclitaxel, *MRL* merilimus, *Mg* magnesium, *Pt* Platinum, *ROS* radio-opaque scaffold, *PAD* peripheral artery disease, *TNT* tantalum

Recent Advances in Angioplasty Devices

Recently, scientists are trying to improve DES technology by studying different approaches like innovative drug delivery or modifications to the stent platforms as listed in Tables 6.7, 6.8 and 6.9 [171, 172]. Some of the approaches have included the following:

1. Delivery of the drug on only one side or portion of that side of the stent's surface. This can be achieved by coating one side only or using microdots or reservoirs on the stent surface that leave one aspect of the stent surface (luminal or peripheral) as a bare metal surface.
2. The use of biomolecules or antibodies to mimic the natural tissue in order to diminish the inflammatory response or to encourage antibodies to capture circulating endothelial progenitor cells to promote healing.
3. Use a polymer free technology such as a hollow stent strut to be filled with the drug in order to have more controlled release of the drug without a polymer coating. Polymer-free stents having a microporous stent surface to hold the drug without the risk of a polymer-induced inflammatory reaction as mentioned in Table 6.7. But clinical trials have failed to prove any superiority over drug-polymer-eluting stents [148, 173].
4. Use of a closed cell stent design instead of an open cell to limit the size of the injury site exposed to blood and promote re-endothelialization [174–176].

Thia chapter has presented the entire timeline for the development of angioplasty technologies starting from the first balloon angioplasty in 1977 to the current technologies that are either in commercial production and clinical use or they are under investigation as mentioned in Tables 6.7, 6.8 and 6.9. There is still much room for improvement and more clinical data is requied for these current techologies and investigation approaches such as biomolecules, surface modifications, antibodies and peptide applications. There are some key factors, such as radial strength, bioresorption, stent geometry, radio-opacity, novel drug molecules and their release profile, that need to be evaluated and assessed while developing more efficient and safer angioplasty devices for the future.

Table 6.9 List of current technologies, coatings and biomolecules under study to improve stent performance [145, 147, 176–187]

Sr. no.	Technology/coating/biomolecules to improve stent efficacy	Type/category/stent platform	Mechanism/action	Effect/result
1	Heparin-functionalized coating	Sulphated glycosaminoglycan	Reaction with antithrombin III, inhibited human umbilical artery smooth muscle cell (HUASMC) adhesion and proliferation	Anticoagulant, anti-inflammatory, platelet and smooth muscle cell (SMC) inhibitor
2	Fucoidan	Sulphated polysaccharide	Recruitment of endothelial progenitor cells (EPCs), reduce SMCs proliferation	Prevents neointimal hyperplasia
3	Laminins	Glycoproteins	Mediate both cell-to-cell and cell-to-extracellular matrix adhesion, anticoagulant property	Enhance cell differentiation and proliferation of endothelial cells (ECs)
4	Chondroitin sulphate	Sulphated polysaccharide	Electrostatic repulsion towards fibrinogen	Hemocompatible, enhance the resistance of vascular cell apoptosis
5	Hyaluronic acid	Negatively charged nonsulphated polysaccharide	Cell attachment and signalling through interacting with cell surface receptors and reduce adhesion of platelets	Platelet inhibition
6	Fibronectin	Major component in ECM	Interaction with α5β1 transmembrane integrin receptor of EC cells	Promote the attachment, spreading and differentiation of ECs
7	Vascular endothelial growth factor (VEGF)	VEGF-functionalized on titanium substrate	Induce the differentiation of hMSCs into endothelial cells	Promote re-endothelialization
8	VEGF + hepatocyte growth factor (HGF) by umbilical cord blood-derived mesenchymal stem cell (UCB-MSC)-seeded stent	UCB-MSC secreted growth factors on stent seeded for 7 days	Reduced restenosis within the stent and induced natural re-endothelialization	Improved healing
9	Gallic acid	Natural plant phenol molecule	Antioxidant, anti-inflammatory property	Induce SMC death, promote EC growth
10	CD34 + antibody	API coating on stainless steel stent (Genous, OrbusNeich)	Bind to endothelial progenitor cells (EPCs)	Reduce ST and restenosis

11	Heparin/poly-l-lysine microspheres (MS) immobilized on dopamine-coated stent	MS form covalent bond with dopamine through Schiff base and/or Michael addition reaction	Improved cytocompatibility, blood compatibility	Accelerate endothelialization
12	Polydopamine (PDA) functionalized titanium dioxide nanotubes (TiO_2 NTs)	Topography modification with bio-inspired coating material	Anti-inflammatory, enhance EC adhesion	Reduce SMC adhesion and proliferation
13	Dopamine-conjugated hyaluronic acid with sirolimus	Coated with in poly(d,l-lactide) on stent	Suppressive effects on platelet adhesion and activation	Maintained the EC viability and proliferation
14	Titanium nitride oxide	Passive coating on stainless steel stent (Titan-2)	Inhibit platelet aggregation, minimize fibrin deposition, reduce inflammation	Promote healing
15	Polyzene F	NanoThin Polyzene-F polymer coating on CoCr stent (Catania)	Anti-inflammatory, bacteria resistant and pro-healing qualities	Low surface thrombogenicity
16	Paclitaxel and pimecrolimus loaded in adjacent reservoirs on stent surface micropores	SymBio stent (Conor Medsystems)	Combine effect of both drugs	Failed to show superiority over current DES
17	Sirolimus and anti-CD34 antibody on SynBiosys™ (PLA) coating	Genous L605 Co-Cr stent (Orbus Neich)	Antiproliferation by sirolimus and EPC capture effect of anti-CD34	Improved healing compared to BMS
18	Vascular smooth muscle cell (VSMC)-like biomimetic surface patterns on stents using a femtosecond laser	316L stainless steel stent nano and micropattern	Promote adhesion, proliferation and migration of VSMC	Rapid re-endothelialization
19	Nitric oxide (NO) producing coating mimicking endothelium function	NO-catalytic bioactive coating to generate NO on 316L SS stent	Suppression of collagen-induced platelet activation and aggregation	Enhanced human umbilical vein endothelial cell (HUVEC) adhesion, proliferation and migration for re-endothelialization

(continued)

Table 6.9 (continued)

Sr. no.	Technology/coating/biomolecules to improve stent efficacy	Type/category/stent platform	Mechanism/action	Effect/result
20	Use of micronet around the stent to make it closed cell design	Use of mesh covering to minimize the open struts areas thus expose to blood flow	Eliminate post-procedural debris embolization, inhibit platelet activation	Prevent cardiac microvascular dysfunction or brain stroke in case of carotid stenting
21	Mesenchymal stem cells	Cell therapy for cardiac regeneration	Inhibit the vascular smooth muscle cell proliferation, enhance neovascularization	Rapid re-endothelialization
22	Controlled delivery of sirolimus from a bioactive polymer (accelerate™ AT)	Electrospray (ES) deposition techniques onto stent surface	Support endothelial cell growth	Promotes re-endothelialization and protection against in-stent restenosis and thrombosis

API active pharmaceutical ingredient, *ST* stent thrombosis, *ECs* endothelial cells, *CoCr* cobalt-chromium, *ECM* extracellular matrix