Stents: Safety and Efficacy

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Historical Perspective

In 1964, Charles Dotter and Melvin Judkins conceptualized angioplasty laying the groundwork for Andreas Grüntzig to pioneer the first coronary angioplasty in 1977 (Fig. 10.1) [1, 2]. Hampered by high rates of restenosis and abrupt closure rates approaching more than 50 and 8 %, respectively, coronary angioplasty was performed with some trepidation [3]. Julio Palmaz devised the first balloon-expandable slotted stent for the peripheral vasculature in 1985, and Richard Schatz successfully modified it for implantation in the coronary vessels [4, 5]. Sigwart et al. were the first to implant a self-expanding covered mesh graft to treat coronary dissections and abrupt closure; however, the balloon-expandable Palmaz-Schatz stent was the first to prove superiority to balloon angioplasty and become commercially available leading to an evolution of safety in percutaneous coronary intervention [4, 6]. Although commercially successful, the initial generation of coronary stents remained limited due to device embolization, stent thrombosis, and poor deliverability. Through dual-antiplatelet therapy and recognition of stent underexpansion, cardiologists were able to mitigate thrombotic complications [7]. With the introduction of stents and optimization of anticoagulation to include glycoprotein IIb/IIIa inhibitors, successive decreases in abrupt closure and referrals for emergent CABG were seen [3]. While safety of PCI continued to improve, in-stent restenosis (ISR) remained a major liability of stents. In 2002, the first drug-eluting stent (DES), a sirolimus-eluting stenting (SES), Cypher® (Cordis Corp., Bridgewater, NJ), was released and subsequently, three major DES types are now commercially available in the United States and additional geographies: paclitaxel-eluting stents (PES), zotarolimus-eluting stents (ZES), and everolimus-eluting stents (EES). At present, these constitute the majority of intracoronary devices utilized globally. This chapter serves to delineate the key components of stent design as well as examine safety and efficacy of the current generation of stents.

Stent Design

Integral components to the current and newest generation of stents include stent platform, polymer coating, and antiproliferative drugs.

Stent Platform

Metallurgy

Stents were initially constructed of 316 L stainless steel, composed of iron, chromium, cobalt, and molybdenum, the latter three which are resistant to corrosion. The L indicates the low (<0.03 % m/m) carbon content to prevent formation of chromium carbide, a promoter of corrosion. The backbone for first-generation DES, 316 L stent platforms were not very deliverable due their inflexible nature and high crossing profiles.

Newer generation stents are composed of cobalt, nickel, chromium, and molybdenum that offer increased radial strength and radiopacity [8, 9]. This enabled construction of stents with lower crossing profiles, increasingly thinner struts, flexibility, and hence improved deliverability compared to its stainless steel counterparts. Evidence for these improvements in deliverability was in part reflected in the higher procedural success of thin cobalt chromium to 316 L stainless steel platform DES in the ENDEAVOR III trial

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C.A. Thompson (ed.), *Textbook of Cardiovascular Intervention*,
DOI 10.1007/978-1-4471-4528-8_10, © Springer-Verlag London 2014

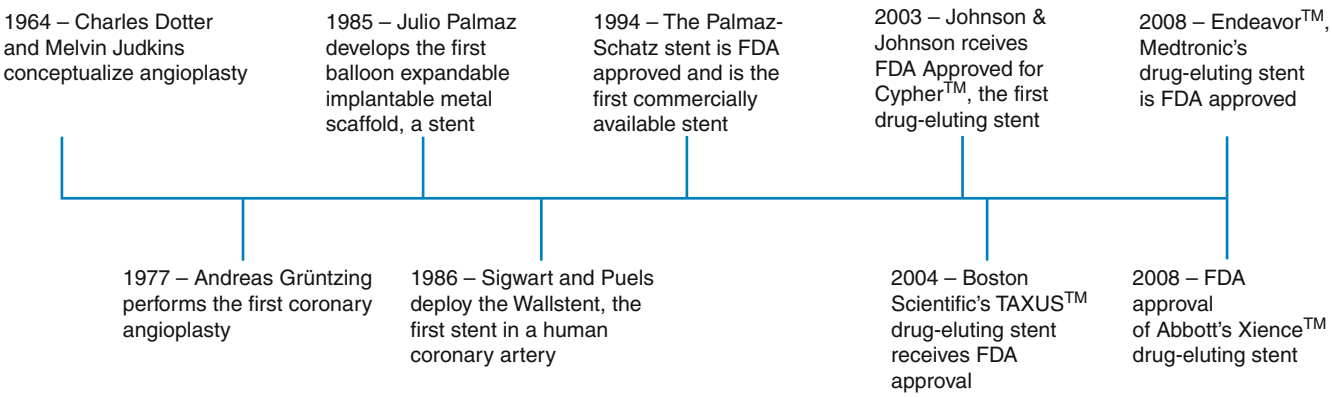

Fig. 10.1 Abbreviated timeline of percutaneous coronary intervention and stent development (Courtesy of Richard Schatz, MD)

(procedure success Endeavor 98.8 % vs. Cypher 94.7 % $p=0.02$) [10]. Aside from improved deliverability, thinner struts have reproducibly decreased restenosis rates when compared to thicker bare-metal comparators as demonstrated in the ISAR-STERO studies [11, 12].

Stent Architecture

Current stent architecture is primarily based on the initial slotted tube design by Julio Palmaz [5]. Importance of stent architecture was evident when neointimal hyperplasia and mural thrombus were significantly decreased when stent geometry was matched to the circular vessel lumen instead of distorting it into nonnative geometry [13]. A prospective study randomizing various bare-metal stents showed differences in freedom from myocardial infarction and follow-up angiographic percent diameter stenosis and late loss between different stent designs, reinforcing the concept of optimal stent architecture [14]. The current design of cellular stents is generalized as either open- or closed-cell design (Figs. 10.2 and 10.3). Computer modeling suggests that there is less tissue prolapse with open-cell design and direct comparisons of bare-metal open-cell to closed-cell stents show that the restenosis rates favor open-cell designs [14, 16]. In theory, open-cell designs should allow greater access to side branches and possibly improve patency of covered side branches. Open-cell DES may have advantages with respect to decreasing myocardial infarction (MI) and target lesion revascularization (TLR) when jailing side branches as reported in a post hoc analysis of SPIRIT III [17]. Closed-cell design may enable even distribution of drugs across the endovascular surface, although there is no prospective data indicating this significantly impacts restenosis rates.

Polymer

Most biological agents require a coating matrix for drug retention and controlling drug-release kinetics. Drugs are released either by particle dissolution or diffusion when polymer breakdown is incorporated (absorbed) into a biodegradable substance. The material should be biologically inert but be able to retain physiochemical composition after sterilization and stent expansion. First-generation DES utilized polymers, long-chained molecules in several small repeating units (Table 10.1) [18]. Although successful in retaining and delivering drug, first-generation polymers have been suspected in causing inflammation implicated in late restenosis and stent thrombosis [19]. An alternate strategy is to improve biocompatibility by using biomimetic compounds. Phosphorylcholine is a naturally occurring zwitterionic compound that emulates a phospholipid membrane that may bind drugs but has a shortened drug elution capacity [20]. Similarly, in an effort to synthetically mimic the phospholipid bilayer structure, the next generation of biocompatible copolymers is Biolinx® (Medtronic, Santa Rosa, CA), a proprietary bled of three polymers: hydrophilic c-19 copolymer, water-soluble polyvinyl pyrrolidinone, and hydrophobic c-10 copolymer [21]. Further details of polymer coatings of individual stents will be discussed further in subsequent sections ascribed to each individual stent.

Drug

Restenosis remains the chief liability of percutaneous interventions and was the impetus for the development of DES. The pathophysiology of restenosis consists of elastic recoil and negative arterial remodeling, followed by neointimal hyperplasia [22]. Inflammation from the endothelial injury and proliferation of smooth muscle cells are largely responsible for the neointimal hyperplasia; therefore, delivery of antiproliferative agents has been the dominant theme of restenosis therapy. Thus far, the armamentarium of drugs to decrease the proliferative response post-endothelial injury have been derived from chemotherapeutic agents and immunomodulators.

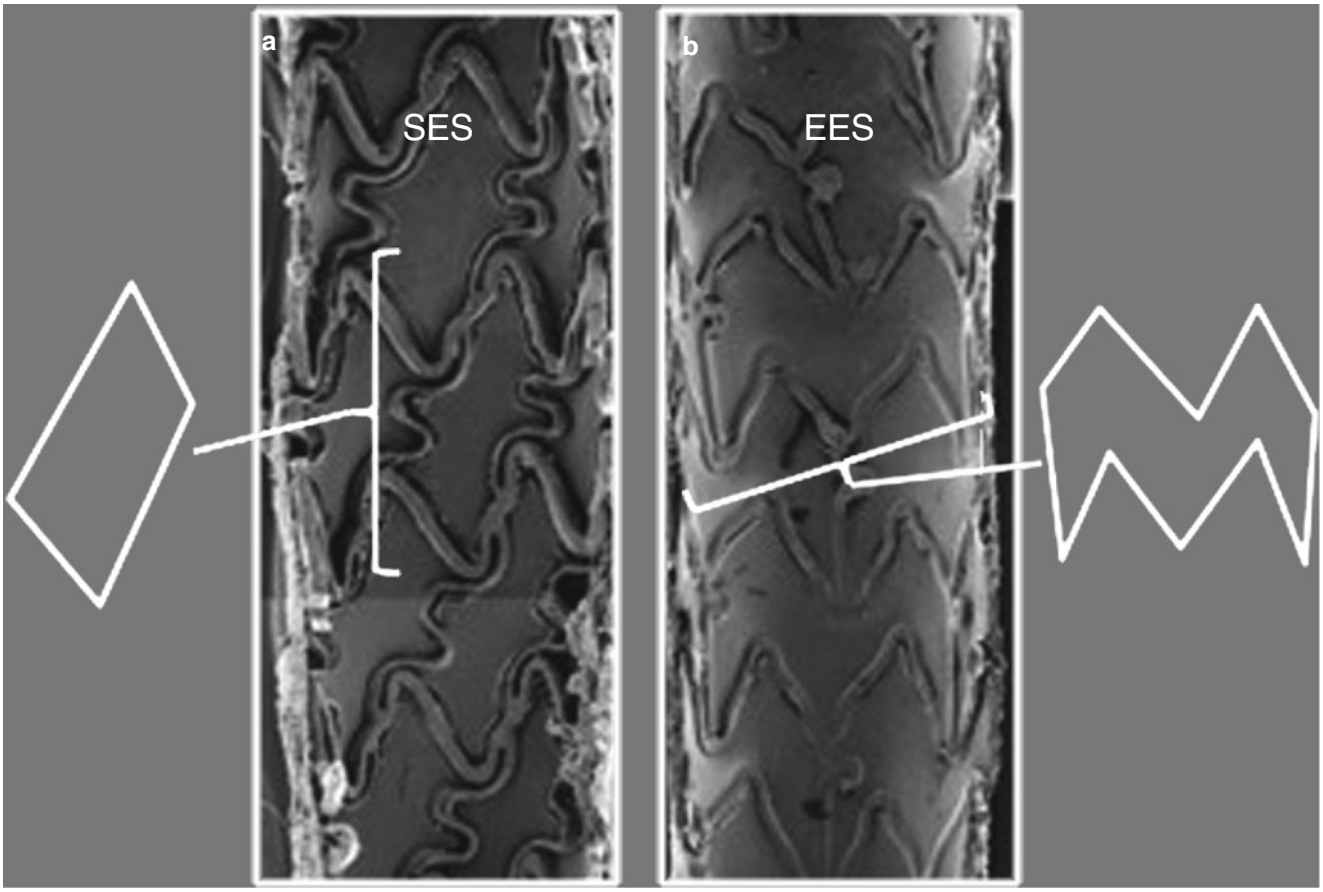

Fig. 10.2 Closed- and open-cell stent design. (**a**) Closed-cell design of the sirolimus-eluting stent (*SES*). The cell is enclosed within a simple geometric shape and retains the area regardless of how stretched the stent becomes. (**b**) Open-cell design of the everolimus-eluting stents (*EES*). The area enclosed by the cell is more complex in shape with convex and concave inflection points throughout the shape. The cell area is capable of increasing greatly with stent expansion (Adapted from Joner et al. [15], with permission)

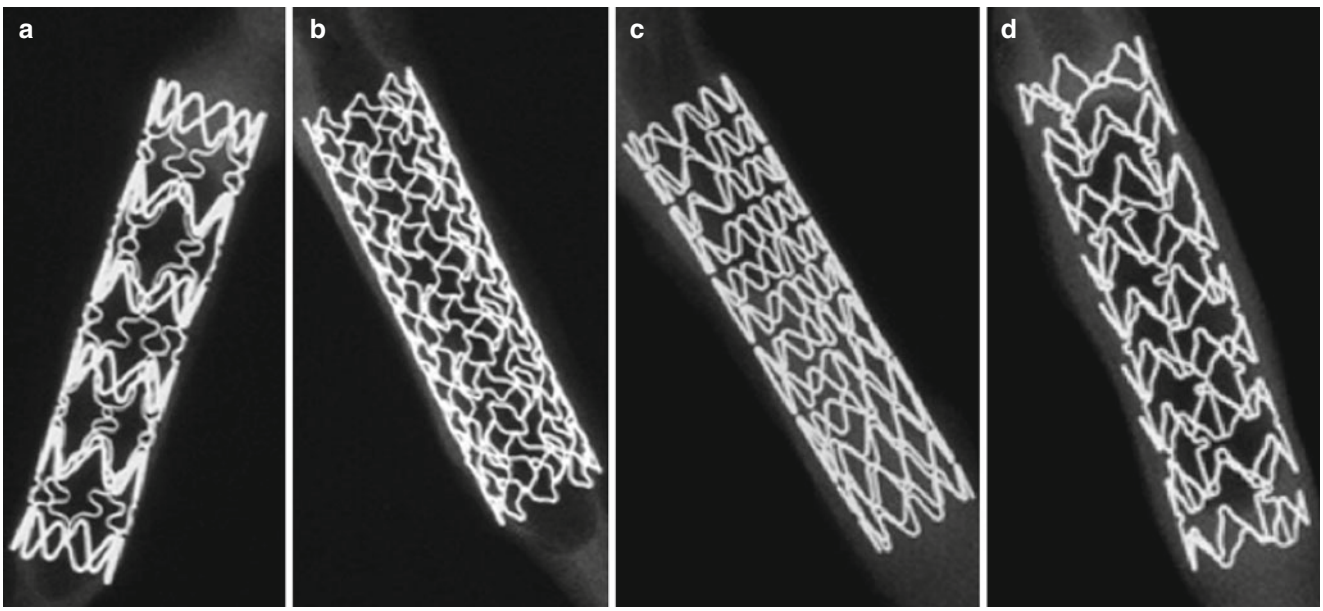

Fig. 10.3 High-resolution radiographs of each drug-eluting stent platform. (**a**) Cypher platform, BX Velocity (Cordis Corp., Johnson & Johnson, Miami, Florida). (**b**) TAXUS platform, Liberté (Boston Scientific, Natick, Massachusetts). (**c**) Endeavor platform, Driver (Medtronic Vascular, Santa Rosa, California). (**d**) XIENCE platform, Multilink Vision (Abbott Vascular, Santa Clara, California) (Adapted from Joner et al. [15], with permission)

Table 10.1 Characteristics of drug-eluting stents commercially available in the United States

	Cypher	TAXUS	Endeavor	Xience
Platform	Bx Velocity	Express/Liberte	Driver	Multilink Vision
Architecture	Closed cell	Open/open cell	Modular, open cell	Open cell
Alloy	316 L	316 L	Cobalt chromium	Cobalt chromium
Strut thickness	140 μm	132 μm/97 μm	91 μm	81 μm
Drug	Sirolimus	Paclitaxel	Zotarolimus	Everolimus
Polymer	PEVA/PMBA	SIBS (Translute®)	Phosphorylcholine	VDF-HFP
Drug elution kinetics	80 % eluted within 30 days	Slow release 10.2 % released in 10 days	98 % eluted within 14 days	80 % eluted within 30 days
Total elution time	168 days	Unknown	21–22 days	120 days

PEVA/PMBA polyethylene-co-vinyl acetate/poly-n-butyl methacrylate, *SIBS* styrene-isobutylene-styrene, *VDF-HFP* vinylidene fluoride and hexafluoropropylene

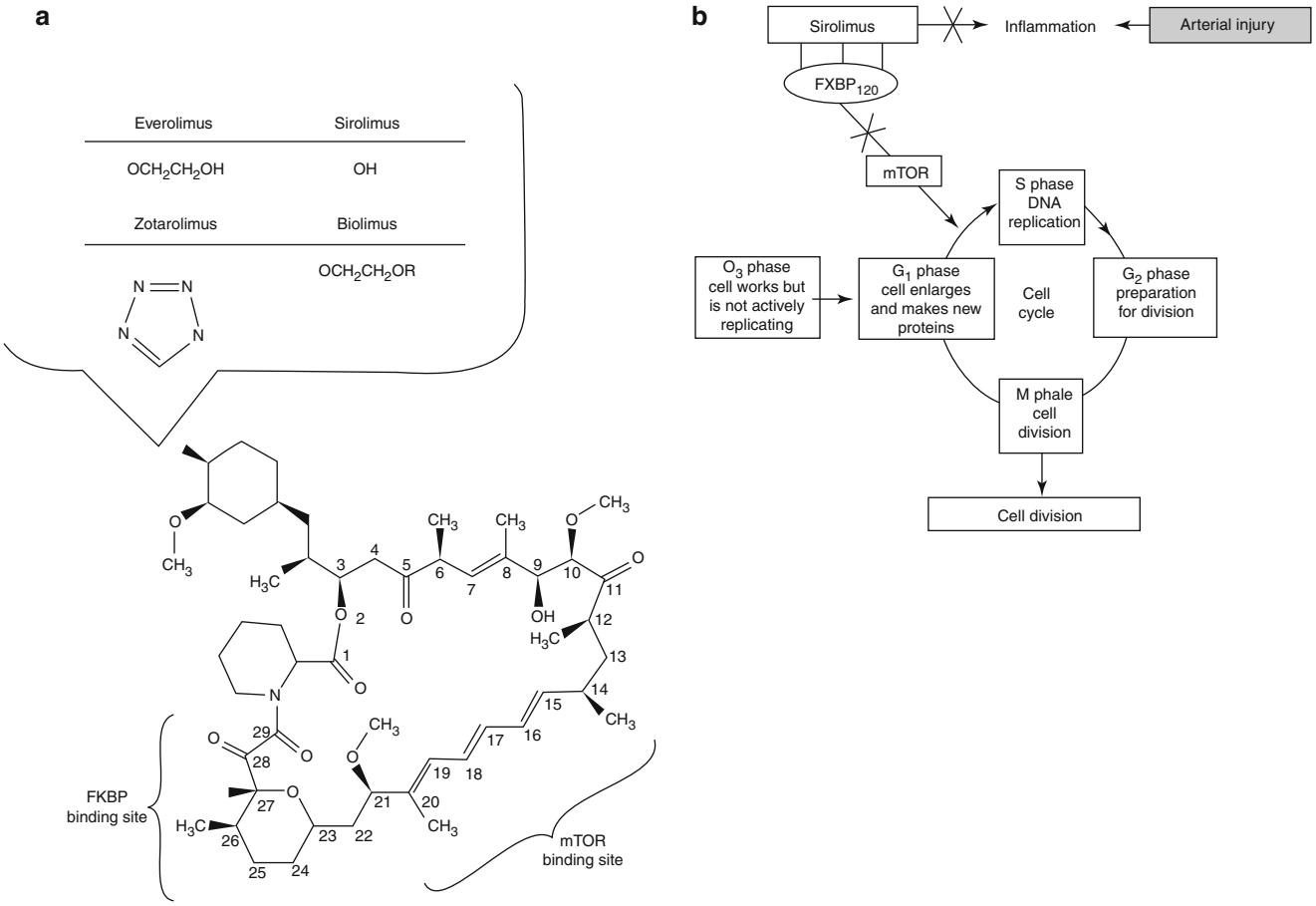

Fig. 10.4 Structure and molecular mechanism of sirolimus and its analogues. (**a**) Chemical structure of sirolimus showing the FKBP12 and mTOR binding sites. Position 42 is a hydroxyl group in sirolimus but is substituted with various side groups as shown below in other analogues. (**b**–**c**) Sirolimus binds to FK-binding protein 12 (FKBP12) and is then enabled to bind to mammalian target of rapamycin (mTOR). mTOR inhibits downregulation of $p27^{kip1}$, halting the cell cycle between the G1 and S1 phases (Adapted from Garg and Serrrys [23], with permission)

Sirolimus and Limus Analogues

Sirolimus is a macrolide antibiotic derived from cultured *Streptomyces hygroscopicus* and clinically utilized to prevent transplantation rejection. A potent antifungal, immunosuppressive, and antimitotic agent, sirolimus binds to specific cytosolic proteins instrumental to cell cycle progression (Fig. 10.4). Sirolimus binds to FK506 (FKBP12), and this complex inhibits the activation of mammalian target of rapamycin (mTOR). Binding of mTOR in turn prevents the downregulation of p27, increasing intracellular levels resulting in cyclin-dependent kinase (CDK)-clin complexes. Ultimately arrest of the G1-S phase of the cell cycle halts smooth muscle cell proliferation. Formerly used as an immunosuppressant to treat organ transplant rejection, application towards vascular restenosis was recognized and applied in the Cypher stent [18].

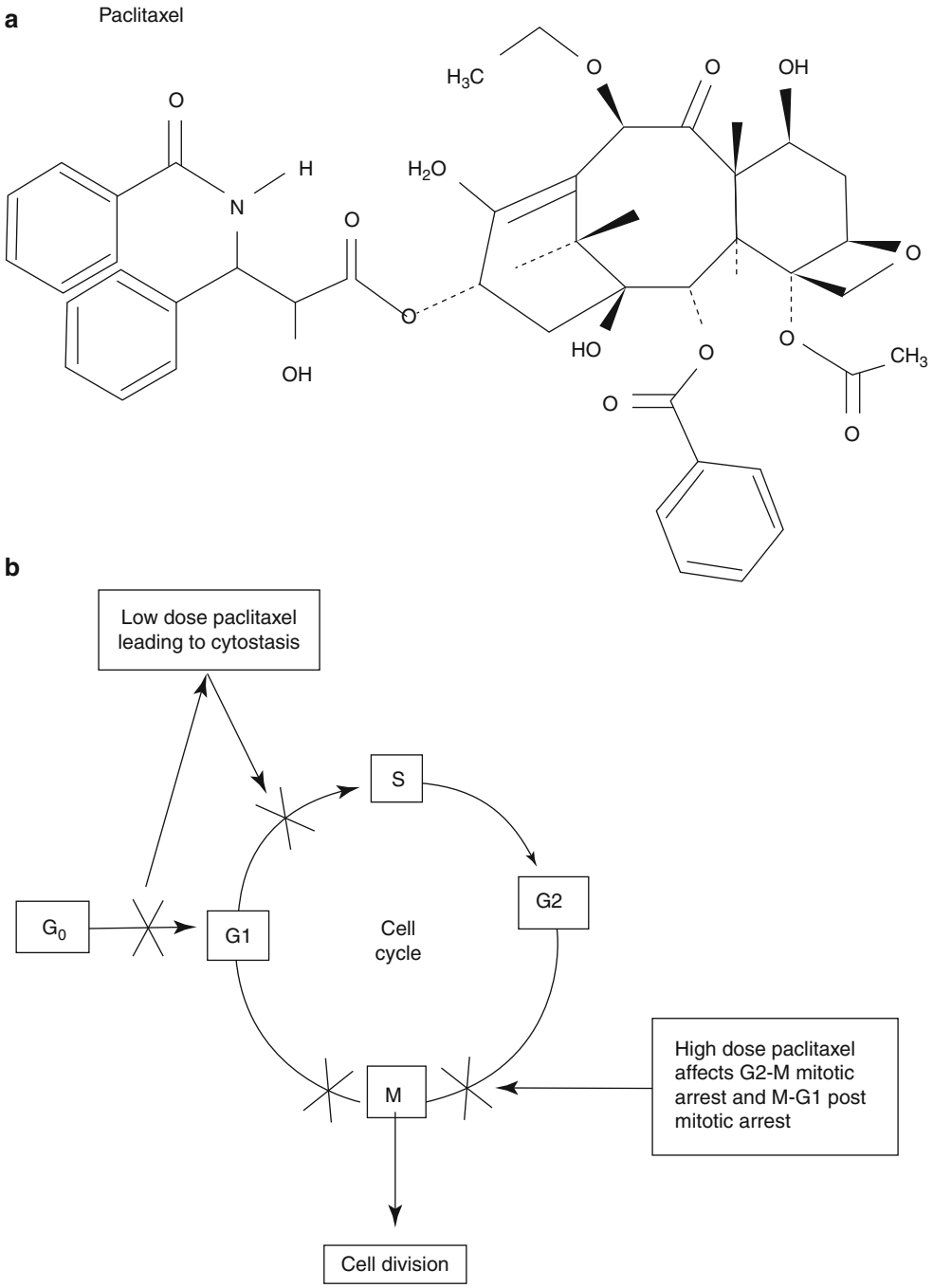

Fig. 10.5 (**a**) Chemical structure and function (**b**) of paclitaxel. Paclitaxel stabilizes microtubules resulting in arrest at the mitotic spindle checkpoint of cell division (Adapted from Garg and Serrrys [23], with permission)

Zotarolimus

Zotarolimus is a proprietary analogue created by substituting a tetrazole ring for the hydroxyl group at position 42 in sirolimus as this site was the most tolerant to modification without altering biological activity (Fig. 10.4). The most hydrophilic of DES drugs, the poor water solubility prevents rapid release into the circulation and favors crossing cell membranes to reach its molecular target [20].

Everolimus

Another analogue of sirolimus, the mechanism of action is identical but its immunosuppressive activity is two to threefold lower than sirolimus in vitro. Nevertheless, in vivo animal data has shown a potent anti-restenotic effect when delivered orally or via DES [18].

Biolimus

Another sirolimus analogue, biolimus has an alkoxy-alkyl group replacing the hydrogen at position 42-o (Fig. 10.4) [24].

Paclitaxel

Isolated from the bark of the Western yew tree, paclitaxel has a complex 8-member ring in its center that stabilizes microtubule formation (Fig. 10.5). Binding to the β-tubulin subunit of

microtubules, it antagonizes disassembly and the cell arrests in the middle of mitosis (G2/M phase). Due to its stabilization of microtubules, paclitaxel impacts cell mobility, notably inhibition of smooth muscle cell migration in vitro and in vivo [25].

Drug-Eluting Stents

Bare-metal restenosis rates of at least 20–25 % in randomized clinical trials prompted the development of strategies to improve the efficacy of stenting [26]. While the mechanical optimization of stenting approached its limits, initial attempts at localized delivery of anti-restenotic medications were unsuccessful due to washout [18]. Stents were appealing as a vehicle for local drug delivery as scaffolding evenly distributed drug to the underlying tissue and served as a reservoir for drug with the possibility of controlling the release kinetics. Harmonizing biocompatibility, drug dose, release kinetics, and drug coating elasticity to yield adequate safety and efficacy proved challenging but at last produced the first clinically efficacious drug-eluting stent, the sirolimus-eluting stent [27].

Sirolimus-Eluting Stents

The Cypher® (Cordis Corporation, Bridgewater, NJ) sirolimus-eluting stent (SES) was the first commercially available DES in the United States in 2003. A 316 L stainless steel platform, the Bx Velocity has relatively thick struts (140 μm) and is a closed-cell stent configuration (Table 10.1). A base coat of PEVA/PMBA (polyethylene-co-vinyl acetate/poly-n-butyl methacrylate) is combined with sirolimus as a base layer while a topcoat is applied to serve as a drug diffusion barrier. Approximately 80 % of sirolimus is released in the first 30 days and becomes undetectable at 168 days [28].

First-in-man experience of SES confirmed durable suppression of neointimal proliferation verified by serial angiographic and intravascular ultrasound over the duration of 12 months laying the foundation for prospective clinical evaluation of SES to treat coronary artery disease [28]. Initial randomized trials RAVEL and SIRIUS proceeded to report consistent decreases in target lesion and vessel revascularization without an increased signal of harm (RAVEL SES TLR 0.0 % vs. BMS 26.6 % $P<0.05$) (Table 10.2) [27]. Continued benefit of SES compared to BMS was reproducible across various studies (Table 10.2) in broader patient subgroups including acute myocardial infarction (MI) and more complex coronary artery disease such as long lesions, chronic total occlusions, and diabetes. Analysis of 14 SES vs. BMS trials revealed that SES decreased the risk for the combined endpoint of death, MI, and revascularization (HR 0.43 CI 0.34 to 0.54 $P<0.0001$) compared to BMS largely driven by target vessel revascularization [29]. Analysis of stent thrombosis found no significant difference between SES and BMS; however, there was very low rate but trend towards increased late stent thrombosis in patients receiving SES (SES 0.8 % vs. BMS 0.3 % $P=0.16$) [29].

Paclitaxel-Eluting Stents

The TAXUS family of DES has gone through several iterative advances involving the stent platform and polymer/drug formulation. The first-generation commercially available TAXUS Express utilized a 316 L stainless steel platform and

Table 10.2 Major clinical trial and pooled analysis results of patients receiving sirolimus-eluting stents (SES) in different clinical settings

Study	Patient population	Follow-up	N	Cardiac death	MI	TLR/TVR	MACE	ST[a]
Kastrati A et al. analysis of 14 trials[b] [29]	Pooled analysis	6–58 months	14 trials	HR 1.03	HR 0.93	HR 0.43	NA	0.8 %
Spaulding C et al. pooled analysis [30]	Pooled analysis	1,440 days	878	3.5 %	6.4 %	NA	NA	3.6 %
SIRIUS[c] [31]	Stable CAD, on-label	5 year	533	8.4 %	6.2 %	9.4 %	20.3 %	3.9 %
TYPHOON[c] [32]	Acute MI, off-label	4 year	294	2.4 %	5.2 %	7.6 %	NA	5.2 %
ARTS II [33]	Unrestricted, multivessel disease	5 year	607	5.4 %	4.4 %	14.5 %	27.2 %	9.0 %
RAVEL[c] [34]	Stable CAD, on-label	5 year	120	12.1 %	7.3 %	7.4 %	25.8 %	3.3 %
SCANDSTENT [35]	Unrestricted	3 year	163	2.5 %	3.7 %	4.9 %	12.3 %	3.1 %
J-Cypher [36]	Unrestricted, ACS	3 year	2,308	7.2 %	3.3 %	12.1 %	NA	2.2 %
RESEARCH [37]	Unrestricted	6 year	508	16.3 %	NA	13.6 %	29.7 %	3.1 %
SESAMI[c] [38]	Acute MI, off-label	3 year	157	3.2 %	2.5 %	7.0 %	12.7 %	5.1 %
ENDEAVOR III[c] [39]	Stable CAD, on-label	3 year	113	7.2 %	4.5 %	12.2 %	18.7 %	1.7 %

CAD coronary artery disease, *MI* myocardial infarction, *ACS* acute coronary syndrome
[a]All ARC defined stent thrombosis including definite, possible, and probable
[b]HR calculated against bare-metal controls in randomized trials
[c]Study protocol mandated angiographic follow-up

Table 10.3 Clinical results of patients receiving paclitaxel-eluting stents (PES) for different indications from major studies

Study	Patient population	Follow-up	*N*	Cardiac death	MI	TLR/TVR	MACE	ST[a]
TAXUS II[b] [42]	Stable CAD, on-label	5 year	131	2.4 %	4.7 %	10.3 %	20.4 %	2.7 %
TAXUS IV[b] [43]	Stable CAD, on-label	5 year	643	4.4 %	7.2 %	9.1 %	24 %	2.2 %[c]
WDHR [44]	Unrestricted, off-label	2 year	1,991	3.2 %	5.3 %	32 % RR[d]	NA	3.3 %
PASSION [45]	Acute MI, off-label	5 year	310	8.9 %	6.8 %	7.7 %	18.6 %	4.2 %
HORIZONS[b] [46]	Acute MI, off-label	3 year	2,257	3.2 %	7.0 %	9.4 %	20.0 %	4.8 %[c]
SPIRIT III[b] [47]	Stable CAD, on-label	3 year	332	1.9 %	6.6 %	12.8 %	16.4 %	1.7 %[c]
ENDEAVOR IV[b] [48]	Stable CAD, on-label	3 year	775	2.4 %	4.9 %	6.1 %	13.6 %	3.0 %
T-SEARCH [37]	Unrestricted, off-label	6 year	576	16.0 %[e]	NA	12.5 %	29.9 %	2.8 %

[a]All ARC defined stent thrombosis including definite, possible, and probable
[b]Study protocol mandated angiographic follow-up
[c]Reported only definite and probable stent thrombosis
[d]Relative reduction of TLR compared to bare-metal stents
[e]All-cause mortality

was coated with a hydrophobic, elastomeric triblock copolymer (styrene-isobutylene-styrene) commercially known as Translute™ (Boston Scientific, Natick, MA) [40]. Three formulations were developed with increasing drug to polymer ratio from 8.8 to 35 % weight in weight (w/w) at a constant dose density to yield a slow-, moderate-, and fast-release stent coating. The slow-release (TAXUS-SR) drug-polymer combination is commercially available on both the TAXUS Express and TAXUS Liberté stents, while the moderate-release (TAXUS-MR) version of TAXUS was clinically tested in prospective trials, but not made commercially available [41].

TAXUS clinical trial development mirrored that of the Cypher stent. Initial studies determined efficacy of PES in patients with CAD and simple complexity lesions (Table 10.3). TAXUS I showed that PES was indeed superior to BMS with respect to repeat revascularization [49]. TAXUS II compared efficacy of slow-release to moderate-release PES, and while moderate-release PES was found to have lower rates of TLR, it was not commercially developed (5-year TLR TAXUS-SR 10.3 % vs. TAXUS-MR 64.5 %) [42]. The pivotal trial for FDA approval of PES was TAXUS IV, a prospective randomized study comparing TAXUS Express to its identical bare-metal counterpart in treating simple coronary lesions. In short-term and 5-year follow-up, durable efficacy relative to bare-metal stents with respect to TLR was maintained with comparable rates of stent thrombosis between each group (5-year ST BMS 2.1 % vs. TAXUS-SR 2.2 % P=NS) [43].

In order to enhance procedural performance, paclitaxel and Translute were affixed to a different stainless steel platform, the Liberté™ (Natick, MA, Boston Scientific) stent. The Liberté is a 316 L stainless steel platform with significantly thinner struts (Express 132 μm vs. Liberté 97 μm) and a more uniform strut pattern to improve distribution of drug. Subsequently, TAXUS Liberté was clinically tested in the TAXUS ATLAS prospective trial, comparing patients receiving TAXUS Liberté to historical controls pooled from TAXUS IV and V trials [50]. Overall, the TAXUS Liberté platform met its endpoints for non-inferiority compared to the TAXUS Express stent at 9-month follow-up; however, in a prespecified subgroup analysis, TAXUS Liberté treatment of small vessels was superior to TAXUS EXPRESS in reducing 9-month TLR in small vessels (16.9 % vs. 6.1 % $P<0.05$) [51].

Expansion of PES utilization in the setting of acute MI showed consistent results in decreased TLR rates compared to bare-metal counterparts (PES 4.5 % vs. BMS 7.5 % $P=0.002$) in HORIZONS-AMI, a multicenter trial with a 2×2 factorial design randomizing against bivalirudin and heparin/glycoprotein IIb/IIIa inhibitors and PES vs. BMS [52, 53]. Notably, stent thrombosis for both BMS and PES remained relatively high for each cohort (ST PES 3.2 % vs. BMS 3.4 % $P=0.77$) at 1 year [54].

Sirolimus-Eluting Stents vs. Paclitaxel-Eluting Stents

After the release of both first-generation DES, head to head comparisons were drawn as both stents had contrasting drug mechanisms, elution kinetics, and polymers. Direct comparisons in patients with stable CAD in real-world context were performed in the SIRTAX trial comparing SES and PES [55]. Angiographic follow-up showed increased late lumen loss and binary restenosis translating into increased TLR for the PES group (Table 10.4). Increased late loss and binary restenosis were again observed in a trial with simpler lesion subsets, the REALITY trial, signaling that PES intrinsically may carry greater risks of in-stent restenosis [61]. Despite higher rates of binary restenosis, no significant clinical impact was observed as similar rates of TLR occurred in both SES and PES cohorts (TLR SES 6.0 % vs. PES 6.1 % $P>0.99$) [61]. Based on the less favorable angiographic restenosis seen in studies with angiographic follow-up, expectation for greater separation in TLR events between SES and PES would have

Table 10.4 Results of major studies comparing the performance of sirolimus-eluting stents (SES) and paclitaxel-eluting stents (PES) against the background of different clinical indications

				MACE		MI		TLR/TVR		Death		ST	
Study	Stent	Follow-up	*N*	%	*P*	%	P	%	*P*	%	*P*	%	*P*
SORT OUT II [56]	SES	546 d	1,065	10	0.21	4.2	0.32	4.5	0.14	1.7	0.8	2.6	0.7
	PES		1,033	11.6		5.1		5.9		1.5		2.8	
SIRTAX [55]	SES	9 mo	503	6.2	0.009	2.8	0.49	4.8	0.03	0.6	0.15	2.0	0.62
	PES		509	10.8		3.5		8.3		1.6		1.6	
Diabetes [57]	SES	2 year	200	3.5	0.001	0.5	0.999	3.5	0.004	0	0.248	1.0	0.499
	PES		200	12.5		1.0		11.0		1.5		0	
ISAR DIABETES [58]	SES	9 mo	125	NA	NA	4.0	0.72	6.4	0.13	3.2	0.52	NA	NA
	PES		125	NA		2.4		12.0		4.8		NA	
ISAR DESIRE [59]	SES	1 year	100	NA	NA	1.0	NS	8.0	0.02	2.0	NS	NA	NA
	PES		100	NA		2.0		19.0		1.0		NA	
ISAR DESIRE 2 [60]	SES	1 year	225	20.4	0.71	2.7	0.53	16.6	0.52	3.4	0.60	0.4	0.67
	PES		225	19.6		1.8		14.6		4.5		0.4	
RESEARCH [37]	SES	6 year	508	29.7	HR 1.01	NA	NA	13.6	HR 1.06	16.3	HR 1.0	3.1	0.9
	PES		576	29.9	(0.9–1.14)	NA		12.5	(0.89–1.26)	16.0	(0.86–1.17)	2.8	
REALITY [61]	SES	1 year	684	10.7	0.73	5.1	0.55	6.0	0.99	1.5	0.63	NA	NA
	PES		669	11.4		6.0		6.1		1.0			
Meta-analysis [62]	SES						HR 0.84		HR 0.74		HR 0.92		HR 0.66
	PES						(0.69–1.03)		(0.63–0.87)		(0.74–1.13)		(0.46–0.94)

D days, *HR* hazard ratio, *mo* months, *NA* not applicable

been expected in diabetic populations. While PES was found to have more in-stent restenosis (ISR) in the DIABETES trial (TLR SES 2.0 % vs. PES 7.5 % $P=0.017$) [63], equivalent performance with respect to major adverse cardiac events (MACE) and target lesion revascularization/target vessel revascularization (TLR/TVR) was seen in subsequent head to head SES/PES trials for different lesion subsets including randomized comparison for treating bare-metal or SES restenosis (Table 10.4) [59, 64]. A nonrandomized comparison of SES and PES in a real-world context was published from the Rotterdam DES registries also showing no significant difference in terms of MACE [37]. However, when the data is pooled in meta-analysis, PES was found to have an increased hazard towards myocardial infarction, TLR/TVR, and stent thrombosis compared to SES utilization (Table 10.4) [62].

On-Label vs. Off-Label Use of DES

The approval of both first-generation drug-eluting stents was based on clinical trials enrolling symptomatic patients treating vessel diameters between 2.5 and 3.5 mm and discrete lesions less than 30 mm in length. These patients did not represent high-risk clinical indications (e.g., acute coronary syndromes) or complex lesion morphologies and therefore constitute the most stable segment of the patient spectrum undergoing PCI yet only make up an estimated 51 % of patients of the NHLBI registry referred for stent implantation [65]. Off-label indications include higher-risk patient and lesion subsets such as acute myocardial infarction, chronic total occlusions, saphenous vein graft lesions, bifurcations, and long stenoses (Table 10.5). The remaining 49 % of patients in the NHLBI Dynamic Registry treated for off-label indications and predictably TVR, MI, stent thrombosis, and death are consistently

Table 10.5 Definitions of on-label and off-label use of drug-eluting stents

On-label indications for DES
Patients with symptomatic CAD of inducible ischemia
Discrete de novo coronary lesions
Vessel diameter ≥2.5 mm to ≤3.5 mm
Lesion length ≤30 mm
Off-label indications for DES
ST-elevation myocardial infarction
Chronic total occlusions
Saphenous vein grafts
Bifurcation lesions
Ostial lesions
Left main stenosis
In-stent restenosis
Long lesions
Small vessels
Large vessels
Multi-lesion percutaneous coronary intervention

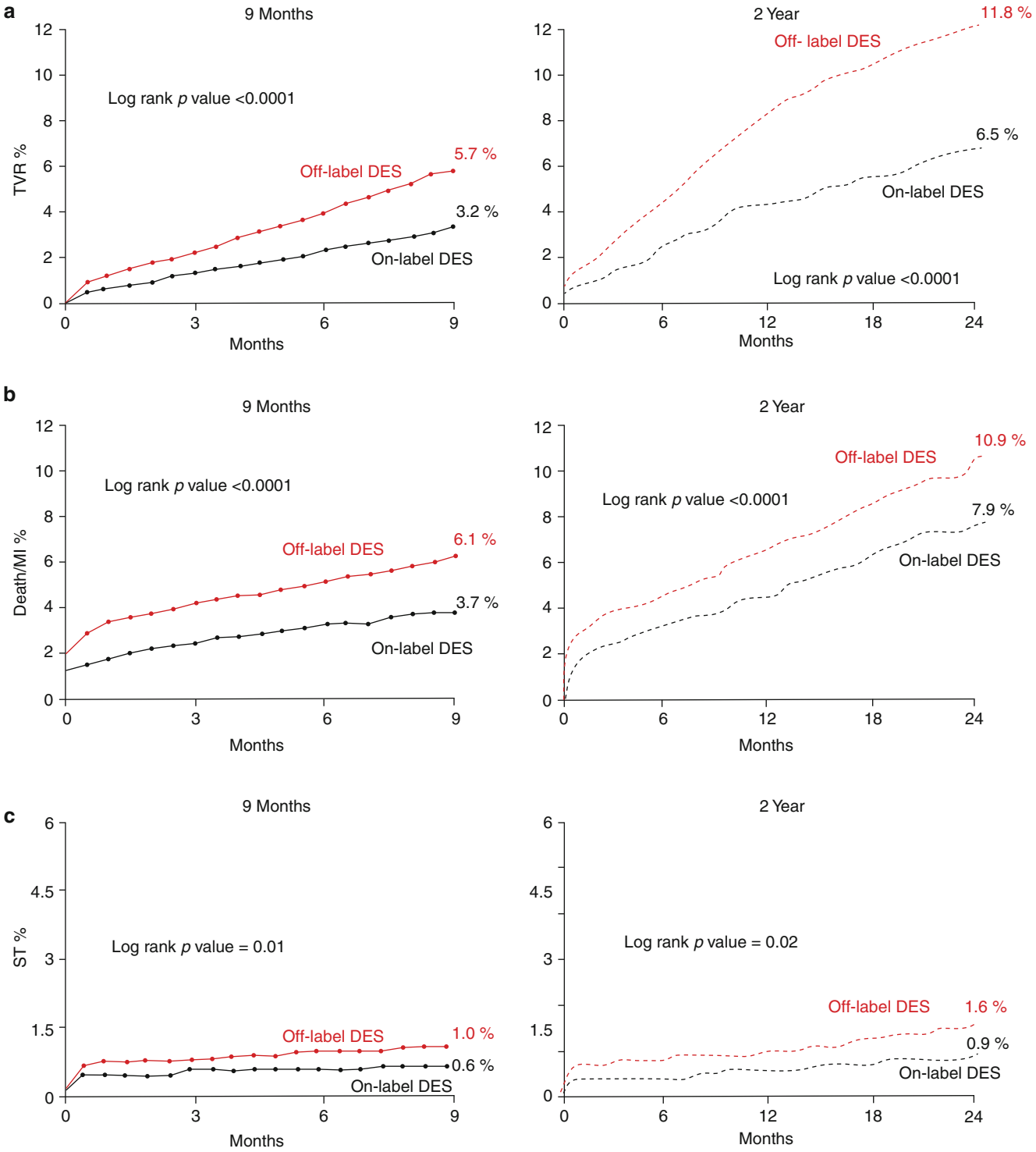

Fig. 10.6 Comparison of event rates between off-label and standard use of drug-eluting stents (*DES*). Kaplan-Meier estimates comparing event rates at 9 months and 2 years between off-label and on-label use of *DES* in the *STENT* (Strategic Transcatheter Evaluation of New Therapies) group, a US multicenter prospective registry. (**a**) Target vessel revascularization (*TVR*), (**b**) death or myocardial infarction (death/MI), and (**c**) stent thrombosis (From Brodie et al. [66], with permission)

worse in the off-label cohort (Fig. 10.6) [66]. The efficacy of DES compared to BMS in off-label use mirrors on-label DES use with improvements in repeat revascularization, but the analysis showed decreased rates for death and MI for DES use (Table 10.6) [65]. High atherosclerotic burden, selection bias towards higher-risk patients (acute myocardial infarction), and more complex anatomy (chronic total occlusions) temper the effectiveness of DES. For instance, in the E-Five Registry,

Table 10.6 Cumulative 1-year rates of safety and efficacy of bare-metal and drug-eluting stents in the NHLBI Dynamic Registry [65]

	Standard			Off-label		
	Bare-metal stent	Drug-eluting stent		Bare-metal stent	Drug-eluting stent	
	N = 1,748	*N* = 1,381		*N* = 2,110	*N* = 1,312	
	%		*p*-Value	%		*p*-Value
Safety						
Death	2.7	2.8	0.88	6.4	3.7	<0.001
Myocardial infarction	4.1	3.3	0.24	5.9	4.4	0.06
Death or myocardial infarction	6.4	5.8	0.42	11.6	7.5	<0.001
Efficacy						
Repeat percutaneous coronary intervention	10.5	6.5	<0.001	13.6	11.4	0.07
Coronary artery bypass grafting	4.3	1.4	<0.001	5.1	1.5	<0.001
Repeat revascularization	13.4	7.7	<0.001	17.5	12.7	<0.001

DES assessment of safety and efficacy was derived from the 2004–2006 recruitment waves while bare-metal endpoints were abstracted from recruitment waves from 1997 to 2002. Patients receiving only bare-metal stents 2004–2006 were excluded due to significant selection bias (i.e., more cardiogenic shock), and this is essentially a comparison of outcomes between the bare-metal and DES era

Table 10.7 Compiled results of patients receiving zotarolimus-eluting stents (ZES) in major clinical trials and registries

Study	Patient population	Follow-up	N	Cardiac death	MI	TLR/TVR	MACE	ST[a]
ENDEAVOR I [67]	Stable CAD, on-label	12 month	100	0.0 %	1.0 %	1.0 %	2.0 %	1.0 %
ENDEAVOR II[b] [68]	Stable CAD, on-label	270 day	592	1.2 %	2.7 %	4.6 %	7.3 %	0.5 %
ENDEAVOR III[b] [10]	Stable CAD, on-label	3 year	323	3.3 %	0.6 %	17.9 %	18.6 %	0.9 %
ENDEAVOR IV [48]	Stable CAD, on-label	3 year	773	1.7 %	2.1 %	6.5 %	11.3 %	2.2 %
E-Five Registry [69]	Standard use, on-label	12 month	2,125	0.9 %	0.7 %	2.8 %	4.3 %	0.8 %
E-Five Registry [69]	Unrestricted, off-label	12 month	6,189	2.0 %	1.9 %	5.0 %	8.6 %	2.2 %
SORT OUT III [70]	Unrestricted, off-label	18 month	1,162	2.0 %	2.0 %	6.0 %	10.0 %	1.0 %

[a]All ARC defined stent thrombosis including definite, possible, and probable
[b]Study protocol mandated angiographic follow-up

comparison of the on- and off-label use showed increases in stent thrombosis (all ARC ST on-label 0.8 % vs. off-label 2.2 % $P<0.001$), myocardial infarction (MI on-label 0.7 % vs. off-label 1.9 % $p<0.001$), and cardiac death (cardiac death 0.9 % vs. 2.2 % $p<0.001$) (Table 10.7) [69].

Zotarolimus-Eluting Stents

Zotarolimus-eluting stents (ZES) (Endeavor®, Medtronic Vascular, Santa Rosa, California) are composed of a cobalt chromium (Driver®, Medtronic) platform. The stent is coated with phosphorylcholine, a blended composite polymer primarily comprised of hydrophilic monomers engineered to mimic the chemical structure of phospholipid head groups. A basecoat of phosphorylcholine is applied to the stent followed by a layer of zotarolimus, which then overlaid with a final coat of phosphorylcholine. A unique feature of ZES stents is rapid eluting of zotarolimus as 90 % is dispersed within 14 days and should remain within the vessel for 28 days. Zotarolimus (ABT-578, Abbott Pharmaceuticals, Abbott Park, Il) is a tetrazole-containing macrocyclic immunosuppressant that shares structural similarity and biological activity with sirolimus (Fig. 10.4).

Clinical testing of ZES first began in 2003 with ENDEAVOR I trial, a single-arm prospective observational study conducted in patients with stable CAD evaluating the medium- and long-term safety and efficacy in this first-in-man trial. With a low MACE rate of 2 % and 1 year TLR rate of 1 %, this paved the way for subsequent trials (Table 10.7) [67].

Zotarolimus-Eluting Stents vs. Bare-Metal Stents

A prospective multicenter trial outside the United States, the ENDEAVOR II randomized 1,197 patients to ZES or its corresponding Driver bare-metal stent platform (Table 10.7). This study confirmed that ZES successfully decreases rates of TLR and TVR compared to its bare-metal platform without any increase in death, MI, or stent thrombosis [68]. Angiographic and IVUS 8-month follow-up showed that late loss and binary restenosis consistently favored ZES compared to BMS. With regard to the overall safety and efficacy compared to bare-metal stents, a pooled analysis of six studies with a mean follow-up of 4.1 years comparing ZES and BMS in 2,132 and 596 patients, respectively, demonstrated

Table 10.8 Academic Research Consortium (ARC) definitions for stent thrombosis

Academic Research Consortium definitions of stent thrombosis
Definite
Angiographic evidence of thrombosis
Pathological confirmation of stent thrombosis
Probable
Any unexplained death within first 30 days
Irrespective of time after the index procedure, any MI that is related to the documented acute ischemia in the territory of the implanted stent without angiographic confirmation of stent thrombosis
Possible stent thrombosis
Clinical definition of possible stent thrombosis is considered to have occurred with any unexplained death from 30 days after intracoronary stenting until the end of follow-up
Acute stent thrombosis
0 to 24 h after stent implantation
Subacute stent thrombosis
>24 h to 30 days after stent implantation
Late stent thrombosis
>30 days to 1 year after stent implantation
Very late stent thrombosis
>1 year after stent implantation

From Cutlip et al. [72], with permission

equivalence in outcomes with respect to hard endpoints and a 58 % reduction in TLR in patients implanted with ZES compared BMS. A small nonsignificant increase in Academic Research Consortium (ARC)-defined definite/probable stent thrombosis favoring ZES (ZES 0.8 %; BMS 1.7 % P=NS) was observed, signaling that the lower stent thrombosis risk in ZES may confer an advantage to first-generation DES counterparts [71] (Table 10.8).

Zotarolimus-Eluting Stents Compared to Other Drug-Eluting Stents

Clinical development of ZES continued with a non-inferiority comparison of ZES to SES in ENDEAVOR III. Evaluating a primary endpoint of angiographic in-segment late lumen loss at 8 months, the study did not achieve non-inferiority, demonstrating significantly higher late lumen loss and restenosis with the Endeavor stent despite no significant differences in repeat revascularization (SES 0.13±0.32 mm vs. ZES 0.34±0.44 mm P<0.001) [10]. Differences in rate of non-Q-wave MI favoring ZES (ZES 0.6 % vs. SES 3.5 % P=0.04) were observed largely driven by post-procedure myonecrosis. In spite of initially higher angiographic late lumen loss, rates of clinical restenosis beyond the period of protocol-specified angiographic follow-up remained stable with ZES compared with SES, resulting in similar late-term efficacy [73]. Over 5 years, significant differences in death, MI, and composite endpoints favored treatment with ZES, contesting the notion that less favorable early angiographic surrogates of efficacy accurately predict important clinical events.

ENDEAVOR IV compared ZES to PES in standard de novo coronary stenosis (Table 10.6). ZES compared favorably with PES, with regard to MACE at 1 year, but after extending the follow-up to 3 years, a significant difference in rates of myocardial infarction was observed (ZES 2.1 % vs. PES 4.9 % p=0.005) [39]. This was attributed to increased rates in very late stent thrombosis (VLST) observed in the PES cohort (definite/probable ST ZES 0.1 % vs. PES 1.6 % p=0.004) with a minimal increase of VLST in ZES during the 2nd and 3rd year of follow-up. Again primary angiographic endpoint at 8 months in the trial showed greater late lumen loss and binary restenosis for ZES; however, this did not confer higher rates of TLR at the 3-year assessment [48, 74].

Zotarolimus-Eluting Stents in Routine Clinical Practice

Results of ZES in routine clinical practice outside stringent clinical trial restrictions on lesion type or patient clinical risk had yet to be tested (e.g., STEMI); therefore, greater than 8,000 patients in post-marketing surveillance were followed for safety and efficacy across a broad spectrum of lesions and patient groups. The 12-month clinical outcomes for ZES implantation showed that implantation in an off-label fashion yielded favorable but less comparable results to on-label utilization of ZES. For instance, higher rates of stent thrombosis (definite/probable ST off-label 1.4 % vs. on-label 0.4 %) and TLR (off-label 5 % vs. on-label 2.8 %) were observed, suggesting that low thrombosis rates previously observed in simple and moderately complexity disease in the ENDEAVOR III/IV trials could not be assumed when treating unselected patients with complex coronary disease [69].

Effectiveness of ZES and SES were directly compared in routine clinical practice in the randomized SORT OUT III trial. A total of 2,332 patients were randomized to receive ZES or SES and followed clinically for 18 months. At 18 months, patients receiving ZES experienced higher rates of TLR (ZES 6 % vs. SES 2 % P<0.0001). A slightly higher rate of myocardial infarction was observed in the ZES group (ZES 2 % vs. SES 1 % P=0.029), although rates of stent thrombosis were similar between groups at 18 months [70].

New-Generation Zotarolimus-Eluting Stents

The latest generation of zotarolimus-eluting stents is the RESOLUTE® DES (Medtronic Vascular, Santa Rosa, California) which utilizes the identical Driver® platform and

Table 10.9 Clinical results of zotarolimus-eluting Resolute® (Medtronic Cardiovascular, Santa Rosa, California) stents

Study	Patient population	Follow-up	*N*	Cardiac death	MI	TLR/TVR	MACE	ST[a]
RESOLUTE FIM [75]	Stable CAD, on-label	12 month	138	0.7 %	5.8 %	0.7 %	8.7 %	0.7 %
RESOLUTE ALL COMERS [76]	Unrestricted, off-label	12 month	1,119	1.3 %	4.2 %[b]	3.9 %	8.7 %	2.3 %
RESOLUTE ALL COMERS [77]	Unrestricted, off-label	2 year	1,119	2.6 %	5.5 %[b]	8.0 %	12.5 %	1.9 %
RESOLUTE US [78]	Stable CAD, on-label	12 month	1,376	1.3 %	1.4 %	2.8 %	NA	0.1 %

FIM first in man
*Study protocol mandated angiographic follow-up
[a]Definite and probable stent thrombosis
[b]Target vessel myocardial infarction

Table 10.10 Late loss and binary restenosis rates for each drug-eluting stent in pivotal clinical trials

Study	Stent type	Angiographic follow-up	In-stent late loss	Binary restenosis
SIRIUS [79]	SES	240 days	0.17 ± 0.45 mm	3.2 %
TAXUS VI [80]	PES	9 months	0.39 ± 0.57 mm	9.1 %
ENDEAVOR III [10]	ZES	8 months	0.60 ± 0.48 mm	9.2 %
SPIRIT III [81]	EES	8 months	0.16 ± 0.41 mm	2.3 %

SES sirolimus-eluting stent, *PES* paclitaxel-eluting stent, *ZES* zotarolimus-eluting stent, *EES* everolimus-eluting stent

zotarolimus drug but has a different polymer. The Biolinx® (Medtronic Vascular, Santa Rosa, California) polymer is a blend of three polymers: hydrophilic c-19 copolymer, water-soluble polyvinyl pyrrolidinone, and hydrophobic c-10 copolymer [21]. This new polymer extends drug elution to 180 days total in attempts to decrease restenosis rates. RESOLUTE stents showed equivocal outcomes compared to EES with respect to death, ischemia-driven TLR, myocardial infarction, and overall MACE through the 2 years of follow-up (Tables 10.9 and 10.10) in the RESOLUTE ALL COMERS trial. The first year reported rates of definite stent thrombosis favored EES (definite ST RESOLUTE 1.2 % vs. EES 0.3 % $p = 0.01$) as did combined definite/probable stent thrombosis rates (definite/probable ST RESOLUTE 1.6 % vs. EES 0.7 % $P = 0.05$) [76]. This combined rate of definite/probable stent thrombosis remained numerically higher for the RESOLUTE stent cohort at 2 years but was no longer significantly different (definite/probable ST RESOLUTE 1.9 % vs. EES 1.0 % $P = 0.077$) [77]. The RESOLUTE-US study was prospective observational trial enrolling 1,402 patients with stable CAD and demonstrated lower of stent thrombosis relative to RESOLUTE ALL COMERS study (definite/probable ST 0.1 %), likely related to high proportion of patients with myocardial infarction (33–34 %) enrolled in the ALL COMERS study, while the US study excluded acute coronary syndromes [78].

Everolimus-Eluting Stents

The Xience V (Abbott Vascular, Santa Clara, CA) is a next-generation DES consisting of an everolimus-coated Vision (Abbott Vascular, Santa Clara, CA) bare-metal platform. Everolimus is a semisynthetic macrolide analogue of sirolimus substitution at 2-hydroxyethyl group at position 42 (Fig. 10.4). The Vision stent platform is a thin-strutted cobalt chromium open-cell stent coated with a primer layer followed by a drug matrix layer. The primer is an acrylic polymer while the drug matrix layer is a durable copolymer, vinylidene fluoride and hexafluoropropylene (VDF-HFP), blended with everolimus.

Clinical development of the everolimus-eluting stent (EES) began with SPIRIT FIRST, a randomized superiority first-in-man trial enrolling 60 patients. The trial was single-blind 1:1 randomization to Vision bare-metal platform with the primary endpoint of angiographic in-stent late loss at 6 months. EES in-stent late loss of 0.10 mm represented an 88 % reduction compared with bare-metal late loss (0.87 mm), and there was significantly less restenosis in the EES cohort (Table 10.11) [82].

Subsequently the SPIRIT II compared EES to PES with the primary endpoint of angiographic late loss (Table 10.11) [90]. In this study, 6-month angiographic follow-up confirmed superiority to PES with respect to in-stent late loss prompting the larger SPIRIT III trial of EES compared to PES powered for non-inferiority with respect to both angiographic and clinical endpoints. After randomizing 1,002 patients to 2:1 ratio of EES to PES in the SPIRIT III trial, 9-month angiographic follow-up confirmed superiority of EES compared to PES in terms of angiographic late loss (EES 0.14 ± 0.41 vs. PES 0.28 ± 0.48 $P = 0.004$) with no difference in target vessel failure at 1 year [91]. At 3-year follow-up, increased late loss translated into higher rates of PES TLR (EES 7.2 % vs. PES 12.8 %, $P = 0.008$) with a trend towards higher MI in the PES cohort (EES 3.8 % vs. PES 6.6 % $P = 0.07$) [47].

Table 10.11 Published results of patient receiving everolimus-eluting stents in major clinical studies

Study	Patient population	Follow-up	*N*	Cardiac death	MI	TLR/TVR	MACE	ST[a]
SPIRIT I[b] [82]	Stable CAD, on-label	180 day	26	0	3.8 %	3.8 %	7.7 %	0.0 %
SPIRIT II[b] [83]	Stable CAD, on-label	3 year	223	0.5 %	3.6 %	3.1 %	7.2 %	1.0 %
SPIRIT III[b] [81]	Stable CAD, on-label	3 year	669	1.6 %	3.8 %	7.2 %	9.7 %	1.3 %[c]
SPIRIT IV [84]	Stable CAD, on-label	1 year	2,458	0.4 %	1.9 %	2.5 %	4.2 %	0.3 %
SPIRIT IV [85]	Stable CAD, on-label	2 year	2,458	0.9 %	2.5 %	4.5 %	7.1 %	0.42 %
SPIRIT V [86]	Unrestricted, off-label	1 year	2,600	1.1 %	3.5 %	1.8 %	5.1 %	0.66 %
COMPARE [87]	Unrestricted, off-label	1 year	897	1.0 %	3.0 %	2.0 %	6.0 %	0.7 %[c]
COMPARE [88]	Unrestricted, off-label	2 year	897	2.2 %	3.9 %	2.9 %	9.0 %	0.9 %[c]
RESOLUTE[b] [77]	Unrestricted, off-label	2 year	1,126	2.2 %	5.0 %	7.3 %	12.9 %	1.0 %
X-SEARCH [89]	Unrestricted, off-label	6 month	649	5.9 %[d]	NA	3.1 %	9.2 %	0.6 %

[a]All ARC defined stent thrombosis including definite, possible, and probable
[b]Study protocol mandated angiographic follow-up
[c]Definite/probable stent thrombosis
[d]All-cause mortality

SPIRIT IV prospectively randomized EES to PES with more complex lesions with the primary endpoint of ischemia-driven target lesion failure (TLF) at 1 year without angiographic follow-up. Powered for non-inferiority with respect to TLF, 3,690 patients were followed for 1 year and found that PES had an early hazard towards TLF (EES 4.2 %, PES 6.8 % $P=0.001$). In addition rates of MI (MI EES 1.9 % vs. PES 3.1 % $P=0.02$) and stent thrombosis (ST EES 0.3 % vs. PES 1.1 % $p=0.004$) were noted to favor EES significantly. Although TLR rates in this trial were remarkably low, in part due to the absence of protocol-specified angiographic surveillance, a 45 % relative reduction in ischemia-driven TLR was nevertheless demonstrated in the EES (EES 2.5 % vs. PES 4.6 %, $p=0.001$) [84]. The benefits of lower TLR, myocardial infarction, and stent thrombosis of EES implantation compared to PES were durable over a 2-year follow-up [92].

Randomization of EES to PES in unrestricted real-world use recapitulated results from SPIRIT IV with statistically significantly greater myocardial infarctions, ischemia-driven TLR, and stent thrombosis in the PES arm at 1 year and extended into 2-year follow-up in the COMPARE trial (Table 10.11) [86, 88]. Irrespective of treating complex or simple coronary lesions, EES use results in less TLR and stent thrombosis relative to PES. Compiled 3-year data for patients enrolled in SPIRIT II and III showed persistent reductions in ischemia-driven TLR (EES 5.4 % vs. PES 9.1 % $p=0.02$) for EES, but no differences in definite/probable stent thrombosis were observed after 3 years (EES 1.2 % vs. PES 1.9 % $P=0.43$) [93].

DES Safety

Stent Thrombosis

Early clinical experience with bare-metal stents was complicated by a stent thrombosis at a rate of 3–4 % in prospective studies and rates more than doubled (8–16 %) if performed as a rescue from abrupt closure [4, 94–96]. Against the background of aggressive oral vitamin K antagonist (warfarin) use, stent thrombosis rates remained high at 3.4 % while simultaneously incurring excessive vascular complications [97]. Aggressive balloon dilation and use of dual-antiplatelet therapy (DAPT) by adding ticlopidine to aspirin reduced stent thrombosis rates to 0.8 % [7]. Pooled data from prospective stent trials indicate that the 30-day thrombosis rates approximate to 0.9 % that further decline to 0.76 % after 30 days [98, 99]. Preapproval trials of first-generation DES demonstrated acceptably low rates of stent thrombosis rate of 0.4 % for SES and 0.6 % for PES resulting in the initial product labeling recommendation of 3 and 6 months of dual-antiplatelet therapy for SES and PES, respectively [79, 100]. However, implementation of DES in a broader patient population as seen in the BASKET-LATE study using DES in an open-label fashion observed a rate of 1.3 and 2.6 % thrombosis-related clinical events in the BMS and DES cohorts, respectively [101]. Given the dire consequences of stent thrombosis with 25–45 % mortality rate, intensive investigation of late DES safety was launched [102, 103]. This culminated in an FDA advisory panel meeting in December 2006 with patient-level meta-analysis from several sources identifying a numerical excess of late stent thrombosis in both SES and PES but no significant difference with bare-metal controls [104]. Pooled analysis of multiple SES trials showed increased yet low incidence of stent thrombosis beyond 1 year compared to BMS counterparts [29]. Follow-up from unrestricted use of SES and PES in a two-institutional cohort study showed that the late stent thrombosis rate was 1.1 % and a steady late-thrombosis rate of 0.6 % per year with a maximum follow-up of 3 years (Fig. 10.7) [106]. Retrospective analysis of 6,033 patients in the SCAAR Swedish national registry reported a 30 % increase in death after 6 months in the DES population

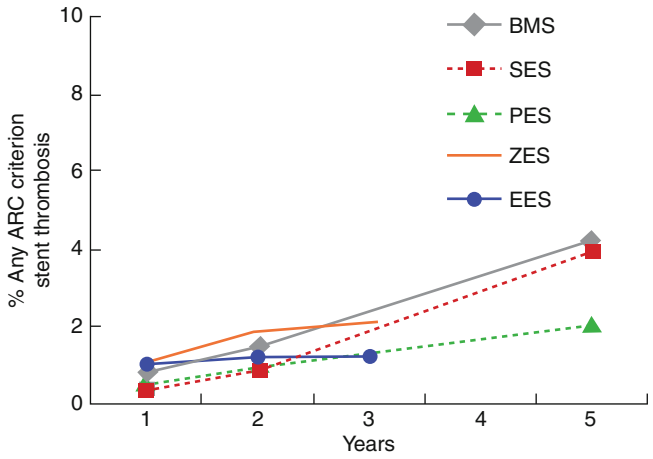

Fig. 10.7 Longitudinal rates of cumulative stent thrombosis for each stent type through long-term follow-up. Event rates included definite, probable, and possible stent thrombosis. Rates for each stent type were derived from the following published trials: (*1*) bare-metal stent (BMS), SIRIUS trial [31, 79, 105]; (*2*) sirolimus-eluting stent (SES), SIRIUS trial [31, 79, 105]; (*3*) paclitaxel-eluting stent (PES), TAXUS IV trial [43, 100]; (*4*) zotarolimus-eluting stent (ZES), ENDEAVOR IV trial [48, 74]; and (*5*) everolimus-eluting stent (EES), SPIRIT III trial [47, 81, 91]

Table 10.12 Factors influencing stent thrombosis

Contributors to stent thrombosis
Patient
Premature antiplatelet therapy discontinuation
Diabetes
Renal failure (acute or chronic)
Left ventricular systolic dysfunction
Malignancy
Acute coronary syndrome
Mechanical
Stent underexpansion or undersizing
Stent malapposition
Incomplete neointimitalization
Bifurcation stenting (especially crush technique)
Stent fracture
Aneurysm formation
Biological
Hypersensitivity
Stenting of highly necrotic plaques

compared to patients receiving BMS with a concurrent increase in myocardial infarction, although such differences were not observed with longer-term and more comprehensive follow-up [107]. In addressing these concerns, multidisciplinary societal guidelines based largely on consensus opinion were released recommending at least 12-month duration of a thienopyridine therapy with indefinite treatment with aspirin despite a paucity of data to assess the efficacy and risks of long-term DAPT [108].

Procedural and biological variables influencing stent thrombosis include inadequate stent expansion, incomplete neointimalization, hypersensitivity, aneurysm formation, stent fracture, and late stent malapposition (Table 10.12). Inadequate stent expansion or stent undersizing has been known to cause for stent thrombosis leading to the practice of high-pressure balloon dilation for optimal procedural results [7, 109–111]. Residual dissections and treatment of bifurcation lesions contribute to the risk of stent thrombosis. Particular stenting techniques, especially the crush technique or leaving stent struts unopposed, predispose to thrombotic complications [112]. The same anti-restenotic agents used to prevent neointimal proliferation likely delay endothelialization, possibly leading to increased fibrin deposition [113, 114]. Stent- or polymer-specific causes of thrombotic events are being identified; pathological analysis of patients with late stent thrombosis demonstrates that those with SES late thrombosis have more inflammation while those with PES have greater amounts of fibrin deposition [115]. Hypersensitivity and aneurysm formation have been implicated in select cases suggesting that allergy to either the drug or polymer may play a role in stent thrombosis [116, 117]. The presence of highly necrotic plaque cores with plaque prolapse is associated with greater rates of stent thrombosis and may also explain relatively high rates of recurrent thrombotic events in patients with acute coronary syndromes [118]. Additionally exposure of stent surface due to loss of stent apposition secondary to positive remodeling or resolution of thrombus has also been implicated in late stent thrombosis [119, 120]. Stent fractures, particularly severe fractures, have also been attributed to stent thrombosis [121, 122]. New pathological studies now reveal formation of atherosclerotic plaques in areas of neointimal hyperplasia, yet it is unclear whether such findings may be associated with late thrombotic events [123].

Patient factors that are independently associated with increased stent thrombosis include early discontinuation of DAPT, diabetes, renal failure, left ventricular systolic dysfunction, malignancy, and acute coronary syndromes (Table 10.12) [102, 124–126]. Patient compliance bears a tremendous impact on the probability of stent thrombosis as early (i.e., <6 months) cessation of DAPT is the most predictive variable in several post hoc analyses and patients stopping clopidogrel early have nearly a ten-fold increase in mortality [126–129]. DES implantation in the setting of acute coronary syndromes, particularly acute myocardial infarction (AMI), increases the incidence of stent thrombosis of 3.4 % range within 1 year, and 1.4 % patients in NSTEMI present with early stent thrombosis as demonstrated in the ACUITY trial [130, 131].

Since stent thrombosis is multifactorial, mitigating its occurrence requires a combination of procedural improvements and recognition of patient variables. First and foremost, the key is appropriate selection of patients with the means to acquire and maintain compliance with antiplatelet

medications. Careful ascertainment of patient histories is essential to clarify if susceptibility to bleeding events and possible need for future surgery may lead to premature thienopyridine discontinuation. From a procedural standpoint, appropriate stent sizing and apposition should optimized using high-pressure inflations, and if necessary, the use of intravascular ultrasound. Dissections require early recognition and treatment, usually an additional stent. Although most patient factors are not modifiable (e.g., diabetes, acute coronary syndromes), intensifying antiplatelet therapy to match stent thrombosis risk with agents such as prasugrel may be a strategy helpful in not only decreasing stent thrombosis but also future thrombotic events [132].

Coronary Artery Aneurysm

Coronary aneurysms are defined as a luminal dilation 50 % larger than the adjacent reference vessel diameter, and its appearance post-DES or BMS implantation has an incidence of 0.2–2.3 % in contemporary trials [133, 134]. Dissections or deep arterial wall injury caused by aggressive balloon dilation, oversized stents, or atherectomy has previously been implicated in aneurysm formation [135–137]. Additional mechanisms unique to DES include inflammatory reactions as patients may react to the polymer coating, antiproliferative drug, and alloy of the stent platform. Histological analysis shows extensive inflammation consisting of eosinophils and lymphocytes encompassing stent struts following DES implantation [113, 116]. Incomplete endothelialization has been observed in serial invasive evaluation, and delayed healing may contribute to aneurysm formation [114]. Incomplete stent apposition has been observed in serial follow-up and may be a precursor for aneurysmal dilation; however, these two events have not yet been directly associated with each other. Furthermore, in serial evaluation, some incomplete stent apposition does resolve [138].

Clinical Implications

In the largest reported series of post-DES coronary artery aneurysms, the authors detected 15 (1.25 %) aneurysms in 1,197 consecutive patients undergoing surveillance angiography at 9 months [139]. The investigators reported a 51 % rate of death, MI, and TVR and 33 % rate of death and MI among these 15 patients, in whom 2 events were associated with stent thrombosis.

Management

While there are no guideline recommendations for when to treat aneurysmal dilation of coronary vessels, some investigators advocate individualizing treatment according to rate of expansion, severity of dilation, anatomic location, and symptoms [134]. There are no prospective data to guide practitioners with selection of modalities best at treating aneurysm with respect to observation, balloon overdilation, coils, stent graft implantation, or open surgical procedures. The propensity for adverse outcomes is proportional to aneurysm size, and luminal dimensions may provide the threshold for treatment. Mycotic coronary aneurysms are exceedingly rare but do require immediate surgical intervention as they have typically manifested in critically ill patients [134]. Given the multiple reports of stent thrombosis in association with aneurysms, antiplatelet therapy should likely be extended indefinitely if possible as death and stent thrombosis were consistently associated with platelet discontinuation in the largest reported series [139].

Stent Fracture

Bare-metal stent restenosis was noted in saphenous vein grafts of coronary arteries, and in the intense search to identify safety parameters of drug-eluting stents, stent fracture was found to be a possible contributor to in-stent restenosis and thrombosis. The incidence of stent fracture has been reported to vary between 0.8 and 7.7 % in clinical studies [140]. However, pathological analysis of patients with first-generation drug-eluting stents noted an incidence of 27.5 %, far exceeding those quoted in clinical reports, likely due to improved ability to detect fractures using high-contrast radiography that provides superior resolution compared to fluoroscopy or intravascular ultrasound [121]. The majority of data regarding the incidence of stent fracture originates from single-center studies and published studies from Asian countries and may reflect practice patterns from those regions that incorporate routine angiographic surveillance as part of clinical practice.

Contributors to stent fracture are extreme vessel tortuosity, angulation, calcification, and length of time in the vessel [140]. Given excessive tortuosity and angulation of the right coronary artery, it is not surprising that stents implanted here have the highest fracture rate [141]. Cardiac motion in combination with tortuosity and angulation is certain to cause metal fatigue leading to fracture. Hinge points caused by stent overlap may also contribute, as these segments have the greatest rigidity thus leading to fracture [142].

Stent design is felt to be a factor as most DES stent fractures have been observed in SES [140]. Relatively thick struts combined with a closed-cell design yield a relatively nonconformable, inflexible stent. However, SES are also more radiopaque and constitute the majority of our experience with DES, and these factors may increase the bias towards detecting stent fracture in SES compared to other stent types. Pathological analysis identified stent length, SES use, and duration of implantation as independent predictors of stent fracture [121].

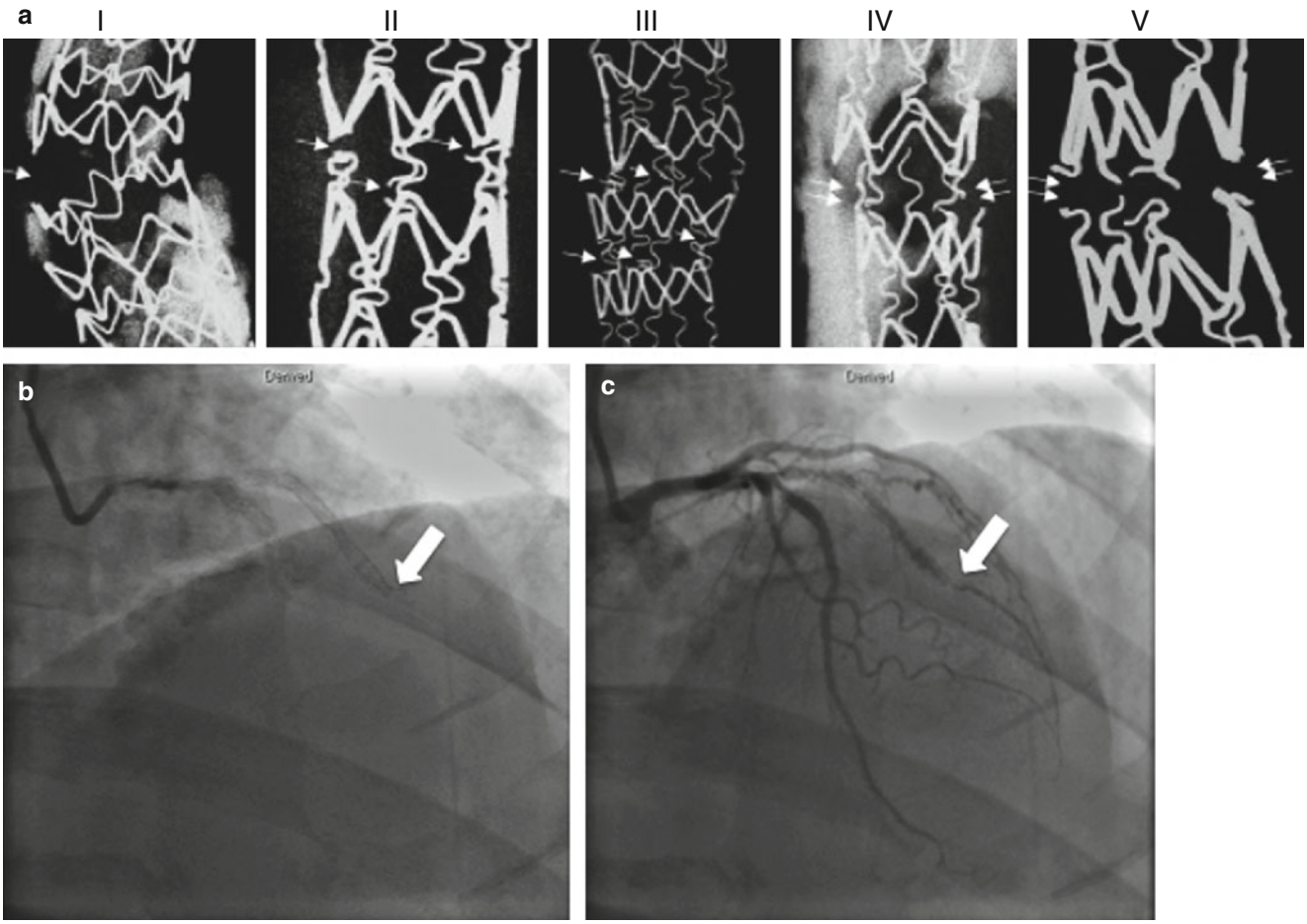

Fig. 10.8 (**a**) Grade I fracture of TAXUS stent (single-strut fracture), grade II fracture of Cypher stent (multiple breaks but alignment is preserved), grade III fracture of Cypher stent (multiple breaks with deformation), grade IV fracture of Cypher stent (multiple breaks with transection of but without gap), and grade V fracture of Cypher stent (total separation) (From Nakazawa et al. [121], with permission). (**b**) High-resolution x-ray of fractured Cypher stent in distal diagonal branch. (**c**) Angiogram of same fractured stent demonstrating severe in-stent restenosis within the fractured segment (*arrows* denote fracture points)

Clinical implications of stent fracture include increased rates of restenosis and stent thrombosis. In the ACROSS Cypher trial evaluating SES treatment in chronic total occlusions, stent fracture was identified in 32/200 patients undergoing 6-month angiographic follow-up [143]. Although stent fracture was associated with a higher likelihood of angiographic restenosis and TLR, when restenosis was identified, its occurrence was seldom at the site of stent fracture, thus raising question as to whether higher TLR are related specifically to fracture or instead greater lesion complexity. In other studies, the rates of restenosis with fracture ranged from 15 to 60 % in published clinical studies. It should be noted that most of these studies included surveillance angiography in the protocol and not necessarily ischemia-driven revascularizations. Pathological analysis reveals that clinical important pathological findings were mostly associated with grade V stent fractures, which defined as complete transection and separation of a stent segment (Fig. 10.8). Associated with greatest amount of inflammation, the investigators documented 6 episodes of stent thrombosis among 51 grade V fractures [121].

Management

Management of stent fracture remains a clinical dilemma with little guidance from any prospective data. Patients presenting with target vessel failure obviously require revascularization, and generally repeat stenting is performed out of practicality and ease. However, operators should consider whether implanting another stent in the milieu responsible for prior stent fracture is wise and bypass surgery should be considered in select cases. In cases of asymptomatic stent fracture, extension of dual-antiplatelet therapy beyond the consensus recommended duration of 1 year should be considered, particularly if associated with disruption of vessel integrity.

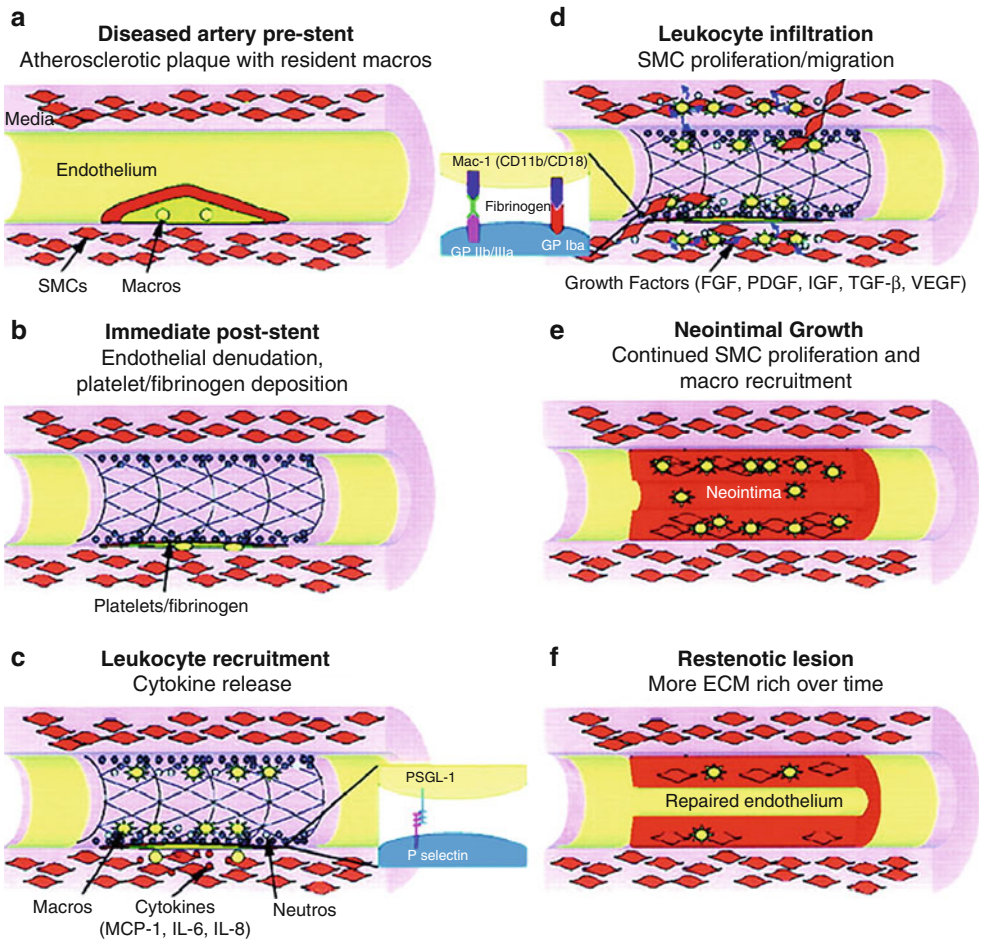

Fig. 10.9 (**a**) Atherosclerotic plaque prior to stent implantation. (**b**) Endothelial denudation and platelet/fibrinogen deposition occur immediately after stenting. (**c**) and (**d**) Days after injury, leukocyte recruitment, infiltration, and smooth muscle cell (*SMC*) proliferation and migration occur within the stented segment. (**e**) Weeks after injury, there is continued SMC proliferation and monocyte recruitment causing neointimal thickening. (**f**) Weeks to months post-stent implantation, the neointima changes from a predominantly cellular to less cellular ECM-rich plaque (From Welt and Rogers [22], with permission)

Restenosis

Comparative trials of PCI and coronary bypass surgery have largely shown that repeat revascularization due to lesion restenosis—rather than death or MI—is responsible for this difference in outcomes between the two revascularization strategies [144]. Restenosis remains the Achilles' heel of percutaneous revascularization, and both balloon angioplasty and stent implantation have distinct mechanisms of restenosis. Vessel recoil and negative remodeling are responsible for restenosis in balloon angioplasty [22]. In contradistinction, stenting mitigates negative remodeling due to greater acute gain, scaffolding, and prevention of vessel recoil; however, late loss due to neointimal hyperplasia causes late ISR. The first model of restenosis was proposed by Forrester consisting of a modified model for wound healing in the endovascular space [145]. The major events in restenosis formation were described as platelet aggregation, inflammatory cell infiltration, release of growth factors, medial smooth muscle cell (SMC) modulation and proliferation, proteoglycan deposition, and extracellular matrix remodeling (Fig. 10.9) [22]. Observations of inflammatory cell deposition and smooth muscle proliferation led to the advances of adding antiproliferative medications to mitigate neointimal hyperplasia. Although ISR in seminal DES trials was minimal (0–4.1 %), subsequent long-term follow-up in unselected patients with more complex pathology has shown restenosis rates greater than 10 % over 5 years [27, 37, 79].

Mechanisms of Restenosis

Biological, mechanical, and technical factors are implicated in restenosis (Table 10.13). Sirolimus and its analogues (zotarolimus, everolimus, biolimus A9) bind to the FK506 binding protein halting the cell cycle. Paclitaxel is a hydrophobic molecule that halts microtubule disassembly and interrupts the cell cycle at G2/mitosis. Several mutations have been identified to binding sites of sirolimus and paclitaxel or to segments of the cell proliferation cascade that render antiproliferative drugs ineffective [147, 148]. Hypersensitivity remains an issue and further inflammation beyond the normal healing response may certainly worsen restenosis. Reactions to nickel and molybdenum in 316 L stainless steel are potential triggering mechanisms for ISR [116]. In the RADAR (Research on Adverse Drug/Device Events and Reports) project, 261 hypersensitivity reactions of 5,783 adverse events were

Table 10.13 Biological, mechanical, and technical variables associated with restenosis

Mechanisms of restenosis
Biological
Drug resistance
Hypersensitivity
Mechanical
Stent underexpansion
Nonuniform drug elution/deposition
Polymer peeling
Stent fracture
Technical factors
Barotrauma outside stented segment
Stent gap
Residual uncovered plaque

Adapted from Dangas et al. [146], with permission

noted, perhaps contributing to ISR formation as well as stent thrombosis [117].

Mechanical factors in ISR formation include stent underexpansion, nonuniform drug distribution, and stent fracture. Suboptimal expansion would simply leave a smaller cross-sectional area and has been implicated in ischemia-driven TLR [110]. Stenting in tortuous segments or arteries with significant mismatch or noncompliant vessels may lead to stent underexpansion and poor drug delivery, especially for longer stents [149]. As mentioned previously, stent fracture, particularly when there is a complete transection and separation of the stent components, is associated with TLR and stent thrombosis [121]. Local blood flow characteristics, stent overlap, and stripping of polymer during stent deliver may also play a role in restenosis formation [150].

Technique-dependent factors include geographic miss, stent gap, and balloon injury outside of stent region. Stent edge restenosis was the major contributor to in-segment binary restenosis early in the DES era [79]. Stent gaps will not receive any drug and furthermore balloon injury may occur in those segments during post-dilation. Finally, geographic miss during the procedure is associated with increased risk of TVR and MI at 1 year as described in the STLLR (Stent Deployment Techniques on Clinical Outcomes of Patients Treated With the Cypher Stent) evaluating the outcomes of suboptimal PCI [151].

Post hoc analyses of real-world, drug eluting stent registries have revealed that many of the predictors of ISR are similar to those in bare-metal stents: diabetes mellitus, complex lesions, small vessels, long lesions, stent underexpansion, and calcified vessels (Table 10.14) [152, 153]. PES was identified to more likely be associated with TVR compared to SES. Certainly, final diameter stenosis and achieving excellent angiographic results are important. Retrospective analysis of IVUS-guided PCI in an unselected patient population showed that a minimal cross-sectional area of 5.5 mm^2 and stented length less than 40 mm were predictive of decreased future ISR events in SES implantation while a cross-sectional area 5.7 mm^2 was predictive of 9-month patency of PES [154, 155].

Table 10.14 Independent predictors of in-stent restenosis (ISR) formation conceptualized as patient, lesion, and procedural attributes

Independent predictors of DES in-stent restenosis
Patient attributes
Age
Female sex
Diabetes mellitus
Multivessel coronary artery disease
Lesion attributes
In-stent restenosis lesion
Bypass graft
Chronic total occlusion
Small vessel diameter
Calcified lesion
Ostial lesion
Lesion length
Procedural attributes
Stent underexpansion
Type of DES
Final diameter stenosis
Bifurcation 2 stent technique

Adapted from Dangas et al. [146]

Table 10.15 Angiographic classification of restenosis based on morphology proposed by Mehran et al.

Angiographic restenosis and classification
Type I focal: ≤10 mm in length
IA articulation or gap
IB margin
IC focal body
ID multifocal
Type 2 diffuse: >10 mm intrastent
Type 3 proliferative : >10 mm extending beyond the stent margins
Type 4 total occlusion: restenotic lesions with TIMI 0 flow

Adapted from Mehran et al. [156], with permission

In-Stent Restenosis Outcomes

Morphology of ISR varies according to DES vs. bare metal with more diffuse patterns observed in bare-metal restenosis, while DES restenosis tends be more focal (Table 10.15) [149, 157, 158]. Observational studies and randomized trials show that a greater proportion of SES have focal restenosis compared to PES and the restenosis patterns. Morphological differences are predictive of repeat revascularization, analysis of 288 episodes of bare-metal stenting showed that focal restenosis portends better outcomes, and propensity for repeat revascularization increased with diffuse restenosis [156]. These observations were consistent in the DES era as diffuse restenosis and total occlusion of DES resulted in greater rates of repeat revascularization [159].

Table 10.16 Metallic Stents with a biodegradable polymer that are either currently available outside the United States or undergoing clinical evaluation

Stent (manufacturer)	Drug (dosage)	Drug release (%), time (Days)	Stent platform	Strut/max coating thickness, μm	Polymer type (duration of biodegradation, months)
Supralimus (Sahajanand Medical)	Sirolimus (125 μg/19 mm)	50 %, 9–11	316 L SS	80/4–5	PLLA PLGA, PLC, PVP (7)
Excel stent (JW Medical System)	Sirolimus (195–376 μg)	NA	316 L SS	119/15	PLA (6–9)
NEVO (Cordis)	Sirolimus (166 μg/17 mm)	80 %, 30	CoCr	99	Reservoirs of PLGA (3)
BioMatrix (Biosensors)	Biolimus A9 (15.6 μg/mm)	45 %, 30	316 L SS	112/10	Abluminal PLA (6–9)
NOBORI (Terumo)	Biolimus A9 (15.6 μg/mm)	45 %, 30	316 L SS	112/10	Abluminal PLA (6–9)
Axxess (Devax Inc.)	Biolimus A9 (22 μg/mm)	45 %, 30	Nitinol	152/15	Abluminal PLA (6–9)
XTENT (XTENT)	Biolimus A9 (15.6 μg/mm)	45 %, 30	CoCr	NA	Abluminal PLA (6–9)
SYNERGY (Boston Scientific)	Everolimus (LD 56 μg/20 mm) (SD 113 μg/20 mm)	50 %, 60	PtCr	71/3 (LD) 4 (SD)	PLGA Rollcoat Abluminal (3)
Combo (OrbusNeich)	EPC + sirolimus (5 μg/mm)	NA	316 L SS	NA	Abluminal
Elixir Myolimus (Elixir Medical)	Myolimus (3 μg/mm)	90 %, 90	CoCr	80/<3	Abluminal PLA (6–9)
Infinnium (Sahajanand)	Paclitaxel (122 μg/19 mm)	50 %, 9–11	316 L SS	80/4–5	PLL PLGA, PLC PVP (7)
JACTAX Liberte (Boston Scientific)	Paclitaxel (9.2 μg/16 mm)	100 %, 60	316 L SS	97/<1	JAC polymer Abluminal (4)

Adapted from Garg and Serruys [163]
BES biolimus-eluting stent, *BMS* bare-metal stents, *CoCr* cobalt chromium, *EPC* endothelial progenitor capture, *JAC* juxtaposed abluminal coating, *LD* low dose, *NA* not available, *PLC* 75/25 poly-L-lactide-co-caprolactone, *PLGA* 50:50 poly-D,L-lactide-co-glycolide, *PLLA* poly-L-lactic acid, *PtCr* platinum chromium, *PVP* polyvinyl pyrrolidone, *SD* standard dose, *SS* stainless steel

Treatment of In-Stent Restenosis

Therapeutic options for ISR include repeat balloon dilation, vascular brachytherapy, repeat stenting, and coronary artery bypass surgery. Initial treatment of ISR for bare-metal stent restenosis consisted of repeat balloon angioplasty dilation alone; however, up to 44–54 % of patients receiving balloon angioplasty dilation will have restenosis on repeat angiography, and approximately 33 % of patients will require target vessel revascularization at 1 year [59, 160]. Repeat stent implantation is the most common therapy for drug-eluting stent restenosis. Once DES were commercially available, the natural expansion of its use spread to treatment of bare-metal ISR. At the time of their introduction, vascular brachytherapy was the standard of care for treatment of restenosis. Compared to vascular brachytherapy (VBT), SES was found to decrease TVR 50 % (VBT 21.6 % vs. SES 10.8 % $P=0.008$), despite the lack of differences in late loss or binary restenosis at 9 months between SES and VBT [161]. Similarly, PES was shown to decrease rates of TVR (VBT 17.5 % vs. PES 10.5 % $p=0.046$) and binary restenosis (VBT 31.2 % vs. PES 14.5 % $P<0.001$) relative to brachytherapy [162]. ISAR-DESIRE randomized 300 patients to either receive balloon angioplasty, SES, or PES for bare-metal restenosis with repeat angiography at 9 months. SES proved to reduce late loss more effectively than PES, translating into a lower TLR rate of 8 % vs. 19 % ($P<0.001$) at 1-year follow-up. ISAR-DESIRE 2 randomized 483 patients with SES ISR to either repeat PCI with SES or PES. At 9 months, binary restenosis rates were nearly identical (SES 19.0 % vs. PES 20.6 %), and repeat revascularization events were similar at 1 year (SES 16.6 % vs. PES 14.6 %, $P=$NS) [60]. Thus far, the optimal method for treatment of DES ISR has not yet been determined, yet it does not appear that alternating the type of antiproliferative agent (paclitaxel vs. sirolimus) impacts restenosis giving credence to the notion that ISR is a multifactorial process and extends beyond drug sensitivity and resistance.

Future Directions

Developing advances in DES include improvements in platform design and bioresorbable polymers. Prior observations in clinical studies have suggested that polymers while important for regulating drug-release kinetics may play a role in late inflammatory responses and contribute to target lesion failure in the form of stent thrombosis or restenosis. To address this issue, stents with either biodegradable polymers or polymer-free DES systems have emerged as a developing alternative to the current stent design. While several of each type are undergoing concurrent design (Tables 10.16 and 10.17), a discussion limited to one biodegradable polymer and polymer-free stent will serve as an example for each category.

The BioTronix stent is a flexible stainless steel stent that delivers biolimus using a biodegradable polymer [164].

Table 10.17 Polymer-free metallic stents that are either currently available outside the United States or undergoing clinical development

Stent (manufacturer)	Drug (dosage)	Drug release (%), time	Stent platform	Strut/coating thickness, μm	Surface modification
Amazonia Pax (Minvasys)	Paclitaxel (2.5 μg/mm^2)	98 %, 30 days	CoCr	73/5[a]	Abluminal microdrop spray crystallization process
BioFREEDOM (Biosensors)	Biolimus A9 (SD) SD† 15.6 μg/mm LD‡ 7.8 μg/mm	90 % 50 h	316 L SS	112	Microporous surface
VESTAsync (MIV Therapeutics)	Sirolimus (total = 55 μg)	100 %, 3 months	316 L SS	65/0.6	Nanoporous hydroxyapatite
Yukon (Transluminal)	Sirolimus (11.7–21.9 μg)	67 %, 7 days	316 L SS	Microporous surface	

Adapted from Garg and Serruys [163]
h hours, *SD* standard dose, *LD* low dose, *SS* stainless steel
[a]Abluminal

Biolimus is a highly lipophilic sirolimus analogue with an alkoxy-alkyl group replacing hydrogen at position 42-O. After submerging the drug in polylactic acid, the combination is applied to the abluminal surface of the stent. In vivo data indicates that polymer absorption should be complete by 6 months [164]. To test the safety and efficacy of the biolimus-eluting stent (BES), 1,757 patients were enrolled in the multicenter European LEADERS study and randomized against SES. A broad patient population was enrolled reflecting "real-world" practice, and at 9 months, outcomes with respect to death (BES 2.6 % vs. SES 2.8 % p = NS), myocardial infarction (BES 5.7 % vs. SES 4.6 % p = NS), and TLR (BES 5.7 % vs. SES 4.6 % p = NS) were similar. Stent thrombosis rates were similar (definite/probable ST BES 2.6 % vs. SES 2.2 % p = NS), although the study follow-up did not extend long enough to detect differences in late stent thrombosis [164].

Another iterative advance in DES technology is to deliver drug without any polymer. While many of these stents are still in preliminary development, a stent-eluting dual DES through micropores has recently undergone clinical testing. YUKON Choice DES contain micropores capable of adsorption of drugs, and once released, the microporous surface favors adhesion of endothelial cells [165]. Several drug combinations may be used, but recently a sirolimus/probucol dual DES stent was randomized against SES and ZES in 1,007 patients in the ISAR-TEST 2 trial. After 2 years of follow-up, all three stent cohorts showed similar rates of MACE endpoints outside of restenosis [166]. However, clinical restenosis in the ZES groups was significantly greater at 1 and 2 years, while the SES and dual DES arms remained similar at 1 year (TLR 2-year SES 10.7 % vs. dual DES 7.7 % vs. ZES 14.3 % P = 0.009). Notably, the dual DES cohort showed less late catch-up restenosis than the SES group at 2 years [166] (Fig. 10.10).

Bioresorbable stents (BRS) are constructed of polymers that are sensitive to enzymatic breakdown such as magnesium, tyrosine polycarbonate, poly-L-lactic acid (PLLA), and poly-D,L-lactic acid (PDLLA) (Table 10.18). While the entire development of BRS extends beyond the scope of this chapter, we will briefly discuss the current prototype for this class of stent, the everolimus-eluting BRS. The stent itself is composed of semicrystalline polymer PLLA backbone and coated with a poly-D,lactide acid (PDLLA), a random copolymer of and D- and L-lactic acid. PDLLA prevents crystallization and forms a completely amorphous phase as it solidifies. This coating contains and regulates the release of everolimus. PDLLA and PLLA are both bioresorbable and progressively shortened as ester bonds between repeat units of lactide are hydrolyzed and particles are phagocytized by macrophages. Eventually PDLLA and PLLA are degraded into lactic acid and metabolized by the Krebs cycle.

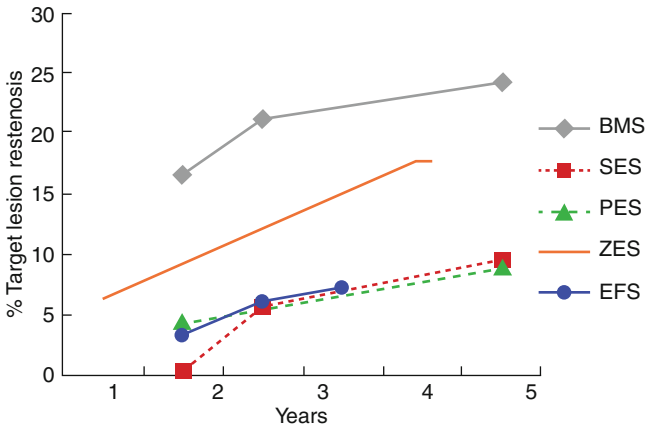

Fig. 10.10 Longitudinal rates of target lesion revascularization (*TLR*) for each stent type through long-term clinical evaluation. Rates of TLR were derived from the following clinical trial data: (*1*) bare-metal stent (*BMS*), SIRIUS trial [31, 79, 105]; (*2*) sirolimus-eluting stent (*SES*), SIRIUS trial [31, 79, 105]; (*3*) paclitaxel-eluting stent (*PES*), TAXUS IV trial [43, 100]; (*4*) zotarolimus-eluting stent (*ZES*), ENDEAVOR III trial [10, 39]; and (*5*) everolimus-eluting stent (*EES*), SPIRIT III trial [47, 81, 91]

The macrostructure of the first-generation BRS (Bioresorbable Vascular Scaffold 1.0) is circumferential

Table 10.18 Currently available bioresorbable stents tested in clinical trials

Scaffolds	Strut material	Coating material	Design	Absorption products	Drug elution	Stent radiopacity	Deployment	Total strut thickness (stent + coating) μm	Crossing profile, mm	Stent-to-artery coverage, %	Duration radial support	Absorption time
Igaki-Tamai	PLLA	None	Zigzag helical coils	Lactic acid, CO_2, H_2O	None	Gold markers	Self-expanding with heated balloon	170	?	24	6 mo	2 y
AMS-1	Metal-Mg alloy	None	Sinusoidal in-phase hoops linked by straight bridges	Not applicable	None	None	Balloon	165	1.2	10	Days or weeks	<4 mo
AMS-2	Metal-Mg alloy	None		Not applicable	None	None	Balloon	125	__	__	Weeks	>4 mo
AMS-3	Metal-Mg alloy	None		Not applicable	None	Yes	Balloon	125	__	__	Weeks	>4 mo
REVA	Poly-tyrosine-derived polycarbonate polymer	None	Side and lock	Amino acid, ethanol, CO_2	None	Iodine impregnated	Balloon	200	1.7	55	3–6 mo	6 mo
BTI	Polymer salicylate + linker	Salicylate + different linker	Tube with laser-cut voids	Salicylate, CO_2, H_2O	Sirolimus salicylate	None	Balloon	200	2	65	3 mo	6 mo
BVS 1.0	Poly-L-lactide	Poly-D,L-lactide	Out-of-phase sinusoidal hoops with straight and direct links	Lactic acid, CO_2, H_2O	Everolimus	Platinum markers	Balloon	156	1.4	25	Weeks	2 y
BVS 1.1	Poly-L-lactide	Poly-D,L-lactide	In-phase hoops with straight links	Lactic acid, CO_2, H_2O	Everolimus	Platinum markers	Balloon	156	1.4	25	3 mo	2 y

Adapted from Garg and Serruys [163], with permission
AMS absorbable metallic stent, *BTI* Bioabsorbable Therapeutics Inc., *BVS* bioabsorbable vascular solutions, *D* day, *mo* month, *y* year

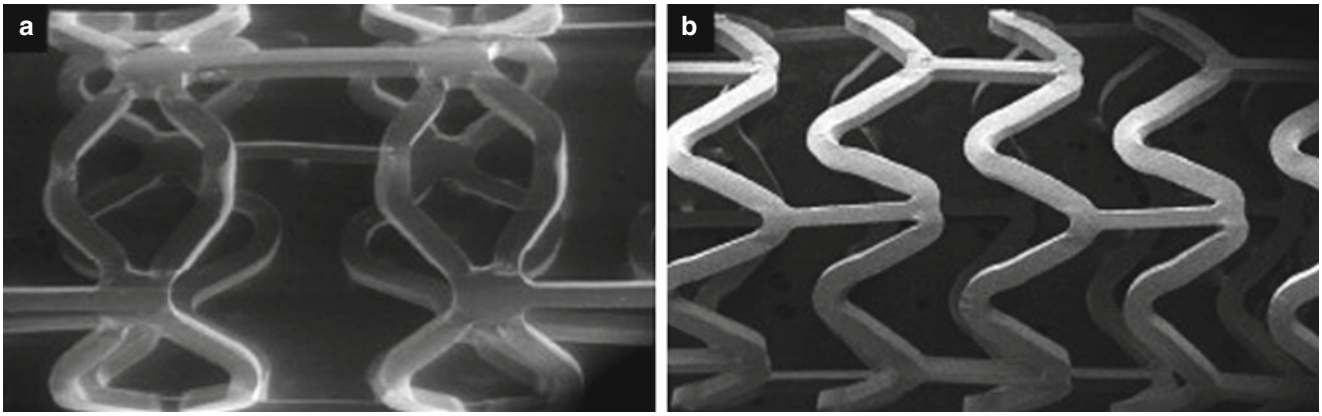

Fig. 10.11 Stent architecture of BioVascular Scaffold (*BVS*) 1.0 and 1.1. (**a**) BVS 1.0 has circumferential out-of-phase zigzag hoops linked together by 3 longitudinal struts between each group. (**b**) BVS 1.1 has in-phase zigzag hoops linked by bridges. Maximum circular unsupported cross-sectional areas are larger in BVS 1.0 than BVS 1.1 (From Garg and Serruys [163], with permission)

hoops of PLLA with struts 150 μm thick either joined or linked by straight bridges (Fig. 10.11). The stent has a crossing profile of 1.4 mm, both ends of the stent of 2 adjacent radiopaque platinum markers, and the stent has comparable radial strength to the Vision bare-metal stent [167]. Everolimus is eluted from the polymer coating, and 80 % of the drug is eluted within 28 days. Arterial tissue concentration is maintained at 0.9–2 ng/mg for 28 days, comparable to the XIENCE V EES.

First-in-human implantation of everolimus-eluting BRS has primarily taken place in the ABSORB A and B cohorts testing the first-generation Bioresorbable Vascular Scaffold (BVS 1.0) and second-generation BVS 1.1, respectively. In ABSORB cohort A, 30 patients were enrolled and followed clinically for 2 years. Serial invasive assessment occurred at 6 months and 2 years, and noninvasive imaging with multislice computed tomography (MSCT) was performed at 18 months. Serial imaging in ABSORB cohort A observed a 11.8 % reduction in stent area and a 24.3 % reduction in minimal luminal area (MLA) at 6 months signaling that there is late recoil of the stent suggesting that the radial strength was lacking [167]. Although in vivo porcine data indicate that the stent is resorbed at 24 months, 2-year optical coherence tomography (OCT) demonstrates a 34.5 % reduction in struts with resolution of any malapposition. Clinically, there was 1 non-Q wave myocardial infarction related to a non-stented lesion [168].

The second iteration BVS 1.1 improved on the original design by adding in-phase zigzag hoops linked by bridges to allow uniform stent distribution as well as a modification in the manufacturing process to slow the in vivo hydrolysis rate (Fig. 10.11) [24]. These revisions that increase the intermediate-term structural integrity to counter the late recoil observed in the ABSORB cohort A were tested in 45 patients to be followed for 2 years. The 6-month results demonstrated a mean scaffold area and MLA loss of 2.0±4.8 % and 5.4±8.7 %, respectively, showing a significant improvement. There were two episodes of TLR (1 related to edge restenosis) and no deaths. One- and 2-year data will elucidate the effects of polymeric stent struts and their rate of degradation.

BRS are in the beginning of clinical development and some unresolved issues will require resolution. Outside of late recoil, another caveat to BVS is the inability to overdilate these stents, as doing so may cause fractures or fissuring of the stent [169]. Therefore, using BVS will be heavily reliant on intravascular imaging for accurate sizing and likely aggressive predilation to ensure good expansion, especially in extremely fibro-calcific lesions. Since the lesion characteristics in the ABSORB trials were carefully selected and fairly simple, it remains uncertain how BRS will perform in "off-label" patients with complex anatomy and more complex pathology.

Conclusion

Drug-eluting stents revolutionized the safety and efficacy of percutaneous coronary intervention and remain the backbone of percutaneous revascularization. Through iterative advances and persistent innovation stent design, vascular biology, and pharmacology, the continued expectation is that advances in design and composition will provide long-term durability and safety for the millions of patients with coronary disease globally.

References

1. Dotter CT, Judklns MP. Transluminal treatment of arteriosclerotic obstruction. Circulation. 1964;30:654–70.
2. Grüntzig A. Transluminal dilation of coronary-artery stenosis. Lancet. 1978;311:263.
3. Venkitachalam L, Kip KE, Selzer F, et al. Twenty-year evolution of percutaneous coronary intervention and its impact on clinical

outcomes: a report from the National Heart, Lung, and Blood Institute-sponsored, multicenter 1985–1986 PTCA and 1997-2006 Dynamic Registries. Circ Cardiovasc Interv. 2009;2:6–13.
4. Schatz R, Baim D, Leon M, et al. Clinical experience with the Palmaz-Schatz coronary stent. Initial results of a multicenter study. Circulation. 1991;83:148–61.
5. Palmaz JC, Richter GM, Noeldge G, et al. Intraluminal stents in atherosclerotic iliac artery stenosis: preliminary report of a multicenter study. Radiology. 1988;168:727–31.
6. Sigwart U, Puel J, Mirkovitch V, Joffre F, Kappenberger L. Intravascular stents to prevent occlusion and restenosis after transluminal angioplasty. N Engl J Med. 1987;316:701–6.
7. Colombo A, Hall P, Nakamura S, et al. Intracoronary stenting without anticoagulation accomplished with intravascular ultrasound guidance. Circulation. 1995;91:1676–88.
8. Kereiakes DJ, Cox D, Hermiller J, et al. Usefulness of a cobalt chromium coronary stent alloy. Am J Cardiol. 2003;92:463–6.
9. Sketch MH, Ball M, Rutherford BD, Popma JJ, Russell C, Kereiakes DJ. Evaluation of the Medtronic (Driver) cobalt-chromium alloy coronary stent system. Am J Cardiol. 2005;95:8–12.
10. Kandzari DE, Leon M, Popma JJ, et al. Comparison of zotarolimus-eluting and sirolimus-eluting stents in patients with native coronary artery disease. J Am Coll Cardiol. 2006;48:2440–7.
11. Kastrati A, Mehilli J, Dirschinger J, et al. Intracoronary stenting and angiographic results: strut thickness effect on restenosis outcome (ISAR-STERO) trial. Circulation. 2001;103(23):2816–21.
12. Pache J, Kastrati A, Mehilli J, et al. Intracoronary stenting and angiographic results: strut thickness effect on restenosis outcome (ISAR-STERO-2) trial. J Am Coll Cardiol. 2003;41:1283–8.
13. Garasic JM, Edelman ER, Squire JC, Seifer P, Williams MS, Rogers C. Stent and artery geometry determine intimal thickening independent of arterial injury. Circulation. 2000;101:812–8.
14. Kastrati A, Dirschinger J, Boekstegers P, et al. Influence of stent design on 1-year outcome after coronary stent placement: a randomized comparison of five stent types in 1,147 unselected patients. Catheter Cardiovasc Interv. 2000;50:290–7.
15. Joner M, et al. Endothelial cell recovery between comparator polymer-based drug-eluting stents. J Am Coll Cardiol. 2008;53:333–42.
16. Capelli C, Gervaso F, Petrini L, Dubini G, Migliavacca F. Assessment of tissue prolapse after balloon-expandable stenting: influence of stent cell geometry. Med Eng Phys. 2009;31:441–7.
17. Applegate RJ, Hermiller J, Williams J, et al. Evaluation of the effects of everolimus-eluting and paclitaxel-eluting stents on target lesions with jailed side branches: 2-year results from the SPIRIT III randomized trial. Catheter Cardiovasc Interv. 2010;76:644–51.
18. Sousa E, Serruys PW, Costa MA. New frontiers in cardiology: drug-eluting stents: Part I. Circulation. 2003;107:2274–9.
19. Virmani R, Liistro F, Stankovic G, et al. Mechanism of late in-stent restenosis after implantation of a paclitaxel derivate-eluting polymer stent system in humans. Circulation. 2002;106:2649–51.
20. Burke SE, Kuntz RE, Schwartz LB. Zotarolimus (ABT-578) eluting stents. Adv Drug Deliv Rev. 2006;58:437–46.
21. Udipi K, Melder RJ, Chen M, et al. The next generation Endeavor Resolute Stent: role of the BioLinx™ Polymer System. EuroIntervention. 2007;3:137–9.
22. Welt FGP, Rogers C. Inflammation and restenosis in the stent era. Arterioscler Thromb Vasc Biol. 2002;22:1769–76.
23. Garg S, Serrrys PW. Coronary stents: current status. J Am Coll Cardiol. 2010;56:S1–42.
24. Serruys PW, Onuma Y, Ormiston J, et al. Evaluation of the second generation of a bioresorbable everolimus drug-eluting vascular scaffold for treatment of de nevo coronary artery stenosis: six-month clinical and imaging outcomes. Circulation. 2010;122:2301–13.
25. Sousa E, Serruys PW, Costa MA. New frontiers in cardiology: drug-eluting stents: Part II. Circulation. 2003;107:2383–9.
26. Al Suwaidi J, Berger PB, Holmes Jr DR. Coronary artery stents. JAMA. 2000;284:1828–36.
27. Morice M-C, Serruys PW, Sousa E, et al. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. N Engl J Med. 2002;346:1773–80.
28. Sousa JE, Costa MA, Abizaid A, et al. Sustained suppression of neointimal proliferation by sirolimus-eluting stents: one-year angiographic and intravascular ultrasound follow-up. Circulation. 2001;104:2007–11.
29. Kastrati A, Mehilli J, Pache J, et al. Analysis of 14 trials comparing sirolimus-eluting stents with bare-metal stents. N Engl J Med. 2007;356:1030–9.
30. Spaulding C, Daemen J, Boersma E, Cutlip DE, Serruys PW. Pooled analysis of data comparing sirolimus-eluting stents with bare-metal stents. N Engl J Med. 2007;356:989–97.
31. Weisz G, Leon M, Holmes Jr DR, et al. Five-year follow-up after sirolimus-eluting stent implantation. J Am Coll Cardiol. 2009;53:1488–97.
32. Spaulding C, Teiger E, Commeau P, et al. Four-year follow-up of TYPHOON (trial to assess the use of the CYPHer sirolimus-eluting coronary stent in acute myocardial infarction treated with BallOON angioplasty). J Am Coll Cardiol Intv. 2011;4:14–23.
33. Serruys PW, Onuma Y, Garg S, et al. 5-year clinical outcomes of the ARTS II (Arterial Revascularization Therapies Study II) of the sirolimus-eluting stent in the treatment of patients with multivessel de novo coronary artery lesions. J Am Coll Cardiol. 2010;11:1093–101.
34. Morice M-C, Serruys PW, Barragan P, et al. Long-term clinical outcomes with sirolimus-eluting coronary stents. J Am Coll Cardiol. 2007;50:1299–304.
35. Kelbaek H, Kløvgaard L, Helqvist S, et al. Long-term outcome in patients treated with sirolimus-eluting stents in complex coronary artery lesions. J Am Coll Cardiol. 2008;51:2011–6.
36. Kawaguchi R, Kimura T, Morimoto T, et al. Safety and efficacy of sirolimus-eluting stent implantation in patients with acute coronary syndrome in the real world. Am J Cardiol. 2010;106:1550–60.
37. Simsek C, Magro M, Boersma E, et al. The unrestricted use of sirolimus- paclitaxel-eluting stents results in the better clinical outcomes during 6-year follow-up than bare-metal stents: an analysis of the RESEARCH (Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital) and T-SEARCH (Taxus Stent Evaluated At Rotterdam Cardiology Hospital) registries. J Am Coll Cardiol Intv. 2010;3:1051–8.
38. Violini R, Musto C, De Felice F, et al. Maintenance of long-term clinical benefit with sirolimus-eluting stents in patients with ST-segment elevation myocardial infarction. J Am Coll Cardiol. 2010;55:810–4.
39. Eisenstein EL, Leon M, Kandzari DE, et al. Long-term clinical and economic analysis of the endeavor zotarolimus-eluting stent versus the cypher sirolimus-eluting stent: 3-year results from the ENDEAVOR III Trial (Randomized Controlled Trial of the Medtronic Endeavor Drug [ABT-578] Eluting Coronary Stent System Versus the Cypher Sirolimus-Eluting Coronary Stent System in De Novo Native Coronary Artery Lesion). J Am Coll Cardiol Intv. 2009;2:1199–207.
40. Kamath KR, Barry JJ, Miller KM. The TAXUS drug-eluting stent: a new paradigm in controlled drug delivery. Adv Drug Deliv Rev. 2006;58:412–36.
41. Colombo A, Drzewiecki J, Banning AP, et al. Randomized study to assess the effectiveness of slow-and moderate-release polymer-based paclitaxel-eluting stents for coronary artery lesions. Circulation. 2003;108:788–94.

42. Silber S, Colombo A, Banning AP, et al. Final 5-year results of the TAXUS II trial: a randomized study to assess the effectiveness of slow- and moderate-release polymer-based paclitaxel-eluting stents for de novo coronary artery lesions. Circulation. 2009;120: 1498–504.
43. Ellis SG, Stone GW, Cox D, et al. Long-term safety and efficacy with paclitaxel-eluting stents: 5-year final results of the TAXUS IV clinical trial (TAXUS IV-SR: treatment of de novo coronary disease using a single paclitaxel-eluting stent). J Am Coll Cardiol Intv. 2009;2:1248–59.
44. Kaltoft A, Jensen LO, Maeng M, et al. 2-year clinical outcomes after implantation of sirolimus-eluting, paclitaxel-eluting, and bare-metal coronary stents. J Am Coll Cardiol. 2009;53: 658–64.
45. Vink MA, Dirksen MT, Suttorp MJ, et al. 5-year follow-up after primary percutaneous coronary intervention with a paclitaxel-eluting stent versus a bare-metal stent in acute ST-segment elevation myocardial infarction: a follow-up study of the PASSION (Paclitaxel-Eluting Versus Conventional Stent in Myocardial Infarction With ST-Segment Elevation) trial. J Am Coll Cardiol Intv. 2011;4:24–9.
46. Stone GW, Witzenbichler B, Guagliumi G, et al. Heparin plus a glycoprotein IIb/IIIa inhibitor versus bivalirudin monotherapy and paclitaxel-eluting stents versus bare-metal stents in acute myocardial infarction (HORIZONS-AMI): final 3-year results from a multicentre, randomised controlled trial. Lancet. 2011;377(9784): 2193–204.
47. Applegate RJ, Yaqub M, Hermiller J, et al. Long-term (three-year) safety and efficacy of *everolimus*-eluting stents compared to *paclitaxel-eluting* stents (from the SPIRIT III Trial). Am J Cardiol. 2011;107:833–40.
48. Leon M, Nikolsky E, Cutlip DE, et al. Improved late clinical safety with zotarolimus-eluting stents compared with paclitaxel-eluting stents in patients with de novo coronary lesions: 3-year follow-up from the ENDEAVOR IV (Randomized Comparison of Zotarolimus- and Paclitaxel-Eluting Stents in Patients With Coronary Artery Disease) trial. J Am Coll Cardiol Intv. 2010;3: 1043–50.
49. Grube E, Silber S, Hauptmann K, et al. TAXUS I: six- and twelve-month results from a randomized, double-blind trial on a slow-release paclitaxel-eluting stent for de novo coronary lesions. Circulation. 2003;107:38–42.
50. Turco M, Ormiston J, Popma JJ, et al. Polymer-based, paclitaxel-eluting TAXUS Liberté stent in de novo lesions. J Am Coll Cardiol. 2007;49:1676–83.
51. Turco M, Ormiston J, Popma JJ, et al. Reduced risk of restenosis in small vessels and reduced risk of myocardial infarction in long lesions with the new thin-strut TAXUS Liberté stent: 1-year results from the TAXUS ATLAS program. J Am Coll Cardiol Intv. 2008;1:699–709.
52. Stone GW, Lansky AJ, Pocock SJ, et al. Paclitaxel-eluting stents versus bare-metal stents in acute myocardial infarction. N Engl J Med. 2009;360:1946–59.
53. Laarman GJ, Suttorp MJ, Dirksen MT, et al. Paclitaxel-eluting versus uncoated stents in primary percutaneous coronary intervention. N Engl J Med. 2006;355:1105–13.
54. Guo N, Maehara A, Mintz G, et al. Incidence, mechanisms, predictors, and clinical impact of acute and late stent malapposition after primary intervention in patients with acute myocardial infarction: an intravascular ultrasound substudy of the Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial. Circulation. 2010;122:1077–84.
55. Windecker S, Remondino A, Eberli FR, et al. Sirolimus-eluting and paclitaxel-eluting stents for coronary revascularization. N Engl J Med. 2005;353:653–62.
56. Galloe A, Thuesen L, Kelbaek H, et al. Comparison of paclitaxel- and sirolimus- eluting stents in everyday clinical practice. JAMA. 2008;299:409–16.
57. Lee CW, Hong M-K, Rhee K-S, et al. A randomized comparison of sirolimus- versus paclitaxel-eluting stent implantation in patients with diabetes mellitus. J Am Coll Cardiol. 2009;53: 812–3.
58. Dibra A, Kastrati A, Mehilli J, et al. Paclitaxel-eluting or sirolimus-eluting stents to prevent restenosis in diabetic patients. N Engl J Med. 2005;353:663–70.
59. Kastrati A, Mehilli J, von Beckerath N, et al. Sirolimus-eluting stent of paclitaxel-eluting stent vs balloon angioplasty for prevention of recurrences in patients with coronary in-stent restenosis. JAMA. 2005;293:165–71.
60. Mehilli J, Byrne RA, Tiroch K, et al. Randomized trial of paclitaxel- versus sirolimus-eluting stents for treatment of coronary restenosis in sirolimus-eluting stents. J Am Coll Cardiol. 2010; 55(24):2710–6.
61. Morice M-C, Colombo A, Meier B, et al. Sirolimus- vs. paclitaxel-eluting stents in de novo coronary artery lesions. JAMA. 2006;295:895–904.
62. Schomig A, Dibra A, Windecker S, et al. A meta-analysis of 16 randomized trials of sirolimus-eluting stents versus paclitaxel-eluting stents in patients with coronary artery disease. J Am Coll Cardiol. 2007;50:1373–80.
63. Lee S-W, Park S-W, Kim Y-H, et al. A randomized comparison of sirolimus- versus paclitaxel-eluting stent implantation in patients with diabetes mellitus. J Am Coll Cardiol. 2008;52:727–33.
64. Mehilli J, Byrne RA, Tiroch K, et al. Sirolimus-eluting stents for treatment of coronary restenosis in sirolimus-eluting stents. J Am Coll Cardiol. 2010;55:2710–6.
65. Marroquin OC, Selzer F, Mulukutla SR, et al. A comparison of bare-metal and drug-eluting stents for off-label indications. N Engl J Med. 2008;358:342–52.
66. Brodie BR, Stuckey T, Downey WE, et al. Outcomes and complications with off-label use of drug-eluting stents: results from the STENT (Strategic Transcatheter Evaluation of New Therapies) group. JACC Cardiovasc Interv. 2008;1:405–14.
67. Meredith I, Ormiston J, Whitbourn R, et al. First-in-human study of the Endeavor ABT-578-eluting phosphorylcholine-encapsulated stent system in *de novo* native coronary artery lesions: Endeavor I trial. EuroIntervention. 2005;1:157–64.
68. Fajadet J, Wijns W, Laarman GJ, et al. Randomized, double-blind, multicenter study of the Endeavor zotarolimus-eluting phosphorylcholine-encapsulated stent for treatment of native coronary artery lesions: clinical and angiographic results of the ENDEAVOR II trial. Circulation. 2006;114:798–806.
69. Lotan C, Meredith I, Mauri L, Liu M, Rothman MT. Safety and effectiveness of the Endeavor zotarolimus-eluting stent in real-world clinical practice: 12-month data from the E-Five registry. J Am Coll Cardiol Intv. 2009;2:1227–35.
70. Rasmussen K, Maeng M, Kaltoft A, et al. Efficacy and safety of zotarolimus-eluting and sirolimus-eluting coronary stents in routine clinical care (SORT OUT III): a randomised controlled superiority trial. Lancet. 2010;375:1090–9.
71. Mauri L, Massaro J, Jiang S, et al. Long-term clinical outcomes with zotarolimus-eluting versus bare-metal coronary stents. J Am Coll Cardiol Intv. 2010;3:1240–9.
72. Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation. 2007;111(17):2344–51.
73. Kandzari DE, Mauri L, Popma JJ, et al. Late-term clinical outcomes with zotarolimus- and sirolimus-eluting stents: 5-year follow-up of the ENDEAVOR III (A Randomized Controlled Trial of the Medtronic Endeavor Drug (ABT-578) Eluting Coronary Stent System Versus the Cypher Sirolimus-Eluting

Coronary Stent System in De novo Native Coronary Artery Lesions). J Am Coll Cardiol Intv. 2011;4:543–50.
74. Leon MB, Mauri L, Popma JJ, et al. A randomized comparison of the ENDEAVOR zotarolimus-eluting stent versus the TAXUS paclitaxel-eluting stent in de novo native coronary lesions: 12-month outcomes from the ENDEAVOR IV trial. J Am Coll Cardiol. 2010;55:543–54.
75. Meredith I, Worthley S, Whitbourn R, et al. Clinical and angiographic results with the next-generation resolute stent system: a prospective, multicenter, first-in-human trial. J Am Coll Cardiol Intv. 2009;2:977–85.
76. Serruys PW, Silber S, Garg S, et al. Comparison of zotarolimus-eluting and everolimus-eluting coronary stents. N Engl J Med. 2010;363:136–46.
77. Silber S, Windecker S, Vranckx P, Serruys PW. Unrestricted randomised use of two new generation drug-eluting coronary stents: 2-year patient-related versus stent-related outcomes from the RESOLUTE All Comer trial. Lancet. 2011;377:1241–7.
78. Yeung AC, Leon M, Jain A, et al. Clinical evaluation of the resolute zotarolimus-eluting coronary stent system in the treatment of de novo lesions in native coronary arteries. J Am Coll Cardiol. 2011;57:1778–83.
79. Moses JW, Leon MB, Popma JJ, et al. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. N Engl J Med. 2003;349:1315–23.
80. Dawkins KD, Grube E, Guagliumi G, et al. Clinical efficacy of polymer-based paclitaxel-eluting stents in the treatment of complex, long coronary artery lesions from a multicenter, randomized trial: support for the use of drug-eluting stents in contemporary clinical practice. Circulation. 2005;112:3306–13.
81. Stone GW, Midei MG, Newman W, et al. Comparison of an everolimus-eluting stent and a paclitaxel-eluting stent in patients with coronary artery disease. JAMA. 2008;299:1903–13.
82. Serruys PW, Ong ATL, Piek JJ, et al. A randomized comparison of a durable polymer Everolimus-eluting stent with a bare metal coronary stent: the SPIRIT first trial. EuroIntervention. 2005;1:58–65.
83. Garg S, Serruys PW, Onuma Y, et al. 3-year clinical follow-up of the XIENCE V everolimus-eluting coronary stent system in the treatment of patients with de novo coronary artery lesions: the SPIRIT II trial (Clinical Evaluation of the XIENCE V Everolimus Eluting Coronary Stent System in the Treatment of Patients with de novo Native Coronary Artery Lesions). J Am Coll Cardiol Intv. 2009;2:1190–8.
84. Stone GW, Rizvi A, Newman W, et al. Everolimus-eluting versus paclitaxel-eluting stents in coronary artery disease. N Engl J Med. 2010;362:1663–74.
85. Stone GW, Rizvi A, Sudhir K, et al. Randomized comparison of everolimus- and paclitaxel-eluting stents. J Am Coll Cardiol. 2011;58:1–7.
86. Grube E, Chevalier B, Smits P, et al. The Spirit V study: a clinical evaluation of the XIENCE V everolimus-eluting coronary stent system in the treatment of patients with de novo coronary artery lesions. J Am Coll Cardiol Intv. 2011;4:168–75.
87. Kedhi E, Joesef S, McFadden E, et al. Second-generation everolimus-eluting and paclitaxel-eluting stents in real-life practice (COMPARE): a randomised trial. Lancet. 2010;375:201–9.
88. Smits P, Kedhi E, Royaards K-J, et al. 2-year follow-up of a randomized controlled trial of everolimus- and paclitaxel-eluting stents for coronary revascularization in daily practice. J Am Coll Cardiol. 2011;58:2011.
89. Onuma Y, Kukreja N, Piazza N, et al. The everolimus-eluting stent in real-world patients. J Am Coll Cardiol. 2009;54:269–76.
90. Serruys PW, Ruygrok P, Neuzner J, et al. A randomised comparison of an everolimus-eluting coronary stent with a paclitaxel-eluting coronary stent: the SPIRIT II trial. EuroIntervention. 2006;2:286–94.
91. Stone GW, Midei MG, Newman W, et al. Randomized comparison of everolimus-eluting and paclitaxel-eluting stents: two-year clinical follow-up from the Clinical Evaluation of the Xience V Everolimus Eluting Coronary Stent System in the Treatment of Patients with de novo Native Coronary Artery Lesions (SPIRIT) III trial. Circulation. 2009;119:680–6.
92. Ambrosio G, Steinhubl SR, Gresele P, et al. Impact of prior chronic antiplatelet therapy on short- and long-term adverse events in patients presenting with an acute coronary syndrome: insights from the acuity trial. J Am Coll Cardiol. 2010;55:A113. E1059–A113.E.
93. Caixeta A, Lansky AJ, Serruys PW, et al. Clinical follow-up 3 years after everolimus- and paclitaxel-eluting stents: a pooled analysis from the SPIRIT II (A Clinical Evaluation of the XIENCE V Everolimus Eluting Coronary Stents System in the Treatment of Patients With De Novo Native Coronary Artery Stent System in the Treatment of Patients With De Novo Native Coronary Artery Lesions) and SPIRIT III (A Clinical Evaluation of the Investigational Device Xience V Everolimus Eluting Coronary Stent System [EECSS] in the Treatment of Subjects With De Novo Native Coronary Artery Lesions) randomized trials. J Am Coll Cardiol Intv. 2010;3:1220–8.
94. George BS, Voorhees WD, Roubin GS, et al. Multicenter investigation of coronary stenting to treat acute or threatened closure complicating percutaneous transluminal coronary angioplasty. J Am Coll Cardiol. 1993;22:135–43.
95. Roubin GS, Cannon AD, Agrawal SK, et al. Intracoronary stenting for acute and threatened closure complicating percutaneous transluminal coronary angioplasty. Circulation. 1992;85:916–27.
96. Herrman NC, Buchbinder M, Clemen MW, et al. Emergent use of balloon expandable coronary artery stenting for failed percutaneous transluminal coronary angioplasty. Circulation. 1992;86: 812–9.
97. Fischman DL, Leon MB, Baim DS, et al. A randomized comparison of coronary-stent placement and balloon angioplasty in the treatment of coronary artery disease. N Engl J Med. 1994;331: 496–501.
98. Cutlip DE, Baim DS, Ho KKL, et al. Stent thrombosis in the modern era: a pooled analysis of multicenter coronary stent clinical trials. Circulation. 2001;103:1967–71.
99. Wang F, Stouffer GA, Waxman S, Uretsky BF. Late coronary stent thrombosis: early vs. late stent thrombosis in the stent era. Catheter Cardiovasc Interv. 2002;55:142–7.
100. Stone GW, Ellis SG, Cox D, et al. One-year clinical results with the slow-release, polymer-based paclitaxel-eluting TAXUS stent: the TAXUS-IV trial. Circulation. 2004;109:1942–7.
101. Pfisterer M, Brunner-La Rocca HP, Buser PT, et al. Late clinical events after clopidogrel discontinuation may limit the benefit of drug-eluting stents. J Am Coll Cardiol. 2006;48:2584–91.
102. Iakovou I, Schmidt T, Bonizzoni E, et al. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. JAMA. 2005;293:2126–30.
103. Ong ATL, Hoye A, Aoki J, et al. Thirty-day incidence and six-month clinical outcome of thrombotic stent occlusion after bare-metal, sirolimus, or paclitaxel stent implantation. J Am Coll Cardiol. 2005;45:947–53.
104. Laskey WK, Yancy CW, Maisel WH. Thrombosis in coronary drug-eluting stents: report from the meeting of the Circulatory System Medical Devices Advisory Panel of the Food and Drug Administration Center for Devices and Radiologic Health, December 7–8, 2006. Circulation. 2007;115:2352–7.
105. Weisz G, Leon M, Holmes Jr DR, et al. Two-year outcomes after sirolimus-eluting stent implantation. J Am Coll Cardiol. 2006;47: 1350–5.
106. Daemen J, Tsuchida K, Stefanini GG, et al. Two-year clinical follow-up of the unrestricted use of the paclitaxel-eluting stent

compared to the sirolimus-eluting stent as part of the Taxus-Stent Evaluated at Rotterdam Cardiology Hospital (T-SEARCH) registry. EuroIntervention. 2006;2:330–7.
107. James S, Stenestrand U, Lindbäck J, et al. Long-term safety and efficacy of drug-eluting versus bare-metal stents in Sweden. N Engl J Med. 2009;360:1933–45.
108. Grines CL, Bonow RO, Casey Jr DE, et al. Prevention of premature discontinuation of dual antiplatelet therapy in patients with coronary artery stents. J Am Coll Cardiol. 2007;49:734–9.
109. Cheneau E, Leborgne L, Mintz G, et al. Predictors of subacute stent thrombosis: results of a systematic intravascular ultrasound study. Circulation. 2003;108:43–7.
110. Fujii K, Carlier SG, Mintz G, et al. Stent underexpansion and residual reference segment stenosis are related to stent thrombosis after sirolimus-eluting stent implantation. J Am Coll Cardiol. 2005;45:996–8.
111. Alfonso F, Suárez A, Pérez-Vizcayno M-J, et al. Intravascular ultrasound findings during episodes of drug-eluting stent thrombosis. J Am Coll Cardiol. 2007;50(21):2095–7.
112. Hoye A, Iakovou I, Ge L, et al. Long-term outcomes after stenting bifurcation lesions with the "crush" technique. J Am Coll Cardiol. 2006;47:1949–58.
113. Joner M, Finn AV, Mont EK, et al. Pathology of drug-eluting stents in humans. J Am Coll Cardiol. 2006;48:193–202.
114. Awata M, Kotani J-i, Uematsu M, et al. Serial angioscopic evidence of incomplete neointimal coverage after sirolimus-eluting stent implantation: comparison with bare-metal stents. Circulation. 2007;116:910–6.
115. Nakazawa G, Finn AV, Vorpahl M, Ladich E, Kolodgie FD, Virmani R. Coronary responses and differential mechanisms of late stent thrombosis attributed to first-generation sirolimus- and paclitaxel-eluting stents. J Am Coll Cardiol. 2011;57:390–8.
116. Virmani R, Guagliumi G, Farb A, et al. Localized hypersensitivity and late coronary thrombosis secondary to a sirolimus-eluting stent: should we be cautious? Circulation. 2004;109:701–5.
117. Nebeker JR, Virmani R, Bennett CI, et al. Hypersensitivity cases associated with drug-eluting coronary stents. J Am Coll Cardiol. 2006;47:175–81.
118. Farb A, Burke AP, Kolodgie FD, Virmani R. Pathological mechanisms of fatal late coronary stent thrombosis in humans. Circulation. 2003;108:1701–6.
119. Cook S, Wenaweser P, Togni M, et al. Incomplete stent apposition and very late stent thrombosis after drug-eluting stent implantation. Circulation. 2007;115:2426–34.
120. Siqueira DA, Abizaid A, de Ribamar CJ, et al. Late incomplete apposition after drug-eluting stent implantation: incidence and potential for adverse outcomes. Eur Heart J. 2007;28:1304–9.
121. Nakazawa G, Finn AV, Vorpahl M, et al. Incidence and predictors of drug-eluting stent fracture in human coronary artery. J Am Coll Cardiol. 2009;54:1924–31.
122. Umeda H, Gochi T, Iwase M, et al. Frequency, predictors and outcome of stent fracture after sirolimus-eluting stent implantation. Int J Cardiol. 2009;133:321–6.
123. Nakazawa G, Otsuka F, Nakano M, et al. The pathology of neoatherosclerosis in human coronary implants: bare-metal and drug-eluting stents. J Am Coll Cardiol. 2011;57:1–9.
124. Lasala JM, Cox D, Dobies D, et al. Drug-eluting stent thrombosis in routine clinical practice: two-year outcomes and predictors from the TAXUS ARRIVE registries. Circ Cardiovasc Interv. 2009;2:285–93.
125. Kuchulakanti PK, Chu WW, Torguson R, et al. Correlates and long-term outcomes of angiographically proven stent thrombosis with sirolimus- and paclitaxel-eluting stents. Circulation. 2006;113:1108–13.
126. van Werkum JW, Heestermans AA, Zomer C, et al. Predictors of coronary stent thrombosis. J Am Coll Cardiol. 2009;53:1399–409.
127. Park D-W, Park S-W, Park K-H, et al. Frequency of and risk factors for stent thrombosis after drug-eluting stent implantation during long-term follow-up. Am J Cardiol. 2006;98(3):352–6.
128. Roy P, Bonello L, Torguson R, et al. Temporal relation between *Clopidogrel* cessation and stent thrombosis after drug-eluting stent implantation. Am J Cardiol. 2009;103:801–5.
129. Spertus J, Kettelkamp R, Vance C, et al. Prevalence, predictors, and outcomes of premature discontinuation of thienopyridine therapy after drug-eluting stent placement: results from the PREMIER registry. Circulation. 2006;113:2803–9.
130. Spaulding C, Henry P, Teiger E, et al. Sirolimus-eluting versus uncoated stents in acute myocardial infarction. N Engl J Med. 2006;355:1093–104.
131. Aoki J, Lansky AJ, Mehran R, et al. Early stent thrombosis in patients with acute coronary syndromes treated with drug-eluting and bare metal stents: the Acute Catheterization and Urgent Intervention Triage Strategy trial. Circulation. 2009;119:687–98.
132. Montalescot G, Wiviott SD, Braunwald E, et al. Prasugrel compared with clopidogrel in patients undergoing percutaneous coronary intervention for ST-elevation myocardial infarction (TRITON-TIMI 38): double-blind, randomised controlled trial. Lancet. 2009;373:723–31.
133. Demopoulos VP, Olympios CD, Fakiolas CN, et al. The natural history of aneurysmal coronary artery disease. Heart. 1997;78:136–41.
134. Aoki J, Kirtane AJ, Leon MB, Dangas G. Coronary artery aneurysms after drug-eluting stent implantation. J Am Coll Cardiol. 2008;1:14–21.
135. Bell MR, Garratt KN, Bresnahan J, Edwards W, Holmes Jr DR. Relation of deep arterial resection and coronary artery aneurysms after directional coronary atherectomy. J Am Coll Cardiol. 1992;20:1474–81.
136. Baumbach A, Bittl JA, Fleck E, et al. Acute complications of excimer laser coronary angioplasty: a detailed analysis of multicenter results. Coinvestigators of the U.S. and European Percutaneous Excimer Laser Coronary Angioplasty (PELCA) Registries. J Am Coll Cardiol. 1994;23:1305–13.
137. Slota P, Fischman DL, Savage MDMP, Rake BSR, Goldberg MDS. Frequency and outcome of development of coronary artery aneurysm after intra-coronary stent placement and angioplasty. STRESS Trial Investigators. Am J Cardiol. 1997;79:1104–6.
138. Kimura M, Mintz G, Carlier SG, et al. Outcome after acute incomplete sirolimus-eluting stent apposition as assessed by serial intravascular ultrasound. Am J Cardiol. 2006;98:436–42.
139. Alfonso F, Pérez-Vizcayno M-J, Ruiz M, et al. Coronary aneurysms after drug-eluting stent implantation. J Am Coll Cardiol. 2009;53:2053–60.
140. Canan T, Lee MS. Drug-eluting stent fracture: incidence, contributing factors, and clinical implications. Catheter Cardiovasc Interv. 2010;75:237–45.
141. Aoki J, Nakazawa G, Tanabe K, et al. Incidence and clinical impact of coronary stent fracture after sirolimus-eluting stent implantation. Catheter Cardiovasc Interv. 2007;69:380–6.
142. Kereiakes DJ, Wang H, Popma JJ, et al. Periprocedural and late consequences of overlapping Cypher sirolimus-eluting stents. J Am Coll Cardiol. 2006;48:21–31.
143. Kandzari DE, Rao SV, Moses JW, et al. Clinical and angiographic outcomes with sirolimus-eluting stents in total coronary occlusions: ACROSS/TOSCA-4 trial. J Am Coll Cardiol Intv. 2009;2:97–106.
144. Daemen J, Boersma E, Flather M, et al. Long-term safety and efficacy of percutaneous coronary intervention with stenting and coronary artery bypass surgery for multivessel coronary artery disease: a meta-analysis with 5-year patient-level data from the ARTS, ERACI-II, MASS-II, and SoS trials. Circulation. 2008;118:1146–54.

145. Forrester J, Fishbein M, Helfant R, Fagin J. A paradigm for restenosis based on cell biology: clues for the development of new preventive therapies. J Am Coll Cardiol. 1991;17:758–69.
146. Dangas G, et al. In-stent restenosis in the drug-eluting stent era. J Am Coll Cardiol. 2010;56:1897–907.
147. Yusuf RZ, Duan Z, Lamendola DE, Penson RT, Seiden MV. Paclitaxel resistance: molecular mechanisms and pharmacologic manipulation. Curr Cancer Drug Targets. 2003;3:1–19.
148. Huang S, Houghton PJ. Mechanisms of resistance to rapamycins. Drug Resist Updat. 2001;4:378–91.
149. Kang S-J, Mintz G, Park D-W, et al. Mechanisms of in-stent restenosis after drug-eluting stent implantation: intravascular ultrasound analysis. Circ Cardiovasc Interv. 2011;4:9–14.
150. Balakrishnan B, Tzafriri AR, Seifert P, Groothuis A, Rogers C, Edelman ER. Strut position, blood flow, and drug deposition: implications for single and overlapping drug-eluting stents. Circulation. 2005;111:2958–65.
151. Costa MA, Angiolillo DJ, Tannenbaum M, et al. Impact of stent deployment procedural factors on long-term effectiveness and safety of sirolimus-eluting stents (final results of the multicenter prospective STLLR trial). Am J Cardiol. 2008;101:1704–11.
152. Kastrati A, Dibra A, Mehilli J, et al. Predictive factors of restenosis after coronary implantation of sirolimus- or paclitaxel-eluting stents. Circulation. 2006;113:2293–300.
153. Lemos PA, Hoye A, Goedhart D, et al. Clinical, angiographic, and procedural predictors of angiographic restenosis after sirolimus-eluting stent implantation in complex patients: an evaluation from the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) study. Circulation. 2004;109:1366–70.
154. Hong M-K, Mintz G, Lee CW, et al. Intravascular ultrasound predictors of angiographic restenosis after sirolimus-eluting stent implantation. Eur Heart J. 2006;27:1305–10.
155. Doi H, Maehara A, Mintz G, et al. Impact of post-intervention minimal stent area on 9-month follow-up patency of paclitaxel-eluting stents: an integrated intravascular ultrasound analysis from the TAXUS IV, V and IV and TAXUS ATLAS Workhorse, Long Lesion, and Direct Stent Trials. JACC Cardiovasc Interv. 2009;2:1269–75.
156. Mehran R, Dangas G, Abizaid AS, et al. Angiographic patterns of in-stent restenosis: classification and implications for long-term outcome. Circulation. 1999;100:1872–8.
157. Lemos PA, Saia F, Ligthart JMR, et al. Coronary restenosis after sirolimus-eluting stent implantation: morphological description and mechanistic analysis from a consecutive series of cases. Circulation. 2003;108:257–60.
158. Iakovou I, Dangas G, Mehran R, et al. Intravascular ultrasound predictors of late recurrence after stent implantation in small coronary arteries. J Am Coll Cardiol. 2003;41:35.
159. Latib A, Mussardo M, Ielasi A, et al. Long-term outcomes after the percutaneous treatment of drug-eluting stent restenosis. J Am Coll Cardiol Intv. 2011;4:155–64.
160. Teirstein PS, Massullo V, Jani S, et al. Catheter-based radiotherapy to inhibit restenosis after coronary stenting. N Engl J Med. 1997;336:1697–703.
161. Holmes Jr DR, Teirstein PS, Satler LF, et al. Sirolimus-eluting stents vs vascular brachytherapy for in-stent restenosis within bare-metal stents. JAMA. 2006;295:1264–73.
162. Stone GW, Ellis SG, O'Shaughnessy CD, et al. Paclitaxel-eluting stents vs vascular brachytherapy for in-stent restenosis within bare-metal stents. JAMA. 2006;295:1253–63.
163. Garg S, Serruys PW. Coronary stents: looking forward. J Am Coll Cardiol. 2010;56:S43–78.
164. Windecker S, Serruys PW, Wandel S, et al. Biolimus-eluting stent with biodegradable polymer versus sirolimus-eluting stent with durable polymer for coronary revascularisation (LEADERS): a randomised non-inferiority trial. Lancet. 2008;372:1163–73.
165. Abizaid A, Costa Jr JR. New drug-eluting stents: an overview on biodegradable and polymer-free next-generation stent systems. Circ Cardiovasc Interv. 2010;3:384–93.
166. Byrne RA, Kastrati A, Tiroch K, et al. 2-year clinical and angiographic outcomes from a randomized trial of polymer-free dual drug-eluting stents versus polymer-based Cypher and Endeavor, drug-eluting stents. J Am Coll Cardiol. 2010;55:2536–43.
167. Ormiston J, Serruys PW, Regar E, et al. A bioabsorbable everolimus-eluting coronary stent system for patients with single de-novo coronary artery lesions (ABSORB): a prospective open-label trial. Lancet. 2008;371:899–907.
168. Serruys PW, Ormiston J, Onuma Y, et al. A bioabsorbable everolimus-eluting coronary stent system (ABSORB): 2-year outcomes and results from multiple imaging methods. Lancet. 2009;373:897–910.
169. Onuma Y, Serruys PW. Bioresorbable scaffold: the advent of a new era in percutaneous coronary and peripheral revascularization? Circulation. 2011;123:779–97.