Review Article

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Coronary Stent Thrombosis: Current Insights into New Drug-Eluting Stent Designs

Hyun Kuk Kim[1,2] and Myung Ho Jeong[1,2]*

[1]The Heart Research Center Nominated by Korea Ministry of Health and Welfare, Chonnam National University Hospital, [2]Korea Cardiovascular Stent Research Institute, Chonnam National University, Gwangju, Korea

The advances of interventional cardiology have been achieved by new device development, finding appropriate drug regimes, and understanding of pathomechanism. Drug-eluting stents (DES) implantation with dual anti-platelet therapy reduced revascularization without increasing mortality or myocardial infarction compared with bare-metal stenting. However, late-term stent thrombosis (ST) and restenosis limited its value and raised the safety concern. Main mechanisms of this phenomenon are impaired endothelialization and hypersensitivity reaction with polymer. The second generation DES further improved safety and/or efficacy by using thinner stent strut and biocompatible polymer. Recently, new concept DES with biodegradable polymer, polymer-free and bioabsorbable scaffold are under investigation in the quest to minimize the risk of ST.

Key Words: *Drug-eluting stents; Coronary thrombosis; Blood platelets*

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Corresponding Author:
Myung Ho Jeong
The Heart Research Center Nominated by Korea Ministry of Health and Welfare, Chonnam National University Hospital, Korea Cardiovascular Stent Research Institute, Chonnam National University, 42 Jaebong-ro, Dong-gu, Gwangju 501-757, Korea
TEL: +82-62-220-6243
FAX: +82-62-228-7174
E-mail: myungho@chollian.net

INTRODUCTION

Bare metal stents (BMS) prevent acute recoil and negative remodeling by maintaining radial force with enlarging luminal dimensions as a result of the ability to act as a scaffold,[1] thereby reducing the incidence of angiographic restenosis, repeated revascularization, ischemic re-occlusion, and emergency coronary artery bypass grafting (CABG).[2-5]

Vascular injury after stent implantation leads to the proliferation and migration of vascular smooth muscle cells through the cell cycle pathway, which results in the development of neointimal hyperplasia and in-stent restenosis.[6] Drug-eluting stents (DES) consist of a standard metallic stent and a polymer coating with anti-proliferative drugs such as sirolimus or paclitaxel mixture. These drugs are released over a period of time with the aid of a polymer. This local delivery system allows for drug application at the precise site and time of vessel injury with a decreased risk of toxicity due to systemic release.[7] By preventing the proliferation of smooth muscle and other cell types associated with the formation of neointimal hyperplasia, DES were expected to decrease late luminal loss and restenosis.

THE FIRST-GENERATION DES

1. Benefits of DES

The Randomized Study with the Sirolimus-eluting Bx Velocity Balloon Expandable Stent (RAVEL) study was the first randomized trial to compare BMS and DES.[8] A total of 238 patients at 19 medical centers were randomly assigned to sirolimus-eluting stents (SES) or BMS. At 6 months, the degree of neointimal proliferation (late luminal loss) was significantly lower in the SES (-0.01 ± -0.33 mm) than in the BMS (0.80 ± -0.53 mm, $p<0.001$) group. During a follow-up period of up to 1 year, the overall rate of major cardiac events was 5.8% in the SES group and 28.8% in the BMS group ($p<0.001$). This difference was entirely due to a higher rate of revascularization of the target vessel in the BMS group.

The Sirolimus-Eluting Stent in De-Novo Native Coronary Lesions (SIRIUS) trial included more study populations (1058 patients), the frequent presence of diabetes (in 26% of patients), and a high percentage of patients with longer lesions (mean, 14.4 mm) and small vessels (mean, 2.80 mm) compared with the RAVEL study.[9] In that study, SES also demonstrated a significant benefit with respect to target lesion revascularization (TLR) and less neointima hyper-

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plasia, which was assessed by using angiography and intravascular ultrasonography. Paclitaxel-eluting stents (PES) showed similar angiographic and clinical outcomes with SES in the TAXUS II and IV trials.[10,11] Both DES were approved by the US Food and Drug Administration (FDA) for patients with a newly diagnosed single lesion less than ≤30 mm in length and 2.5 to 3.5 mm in diameter for SES and ≤28 mm in length and 2.5 to 3.75 mm in diameter for PES in clinically stable patients without additional serious medical conditions after these trials. Use of DES in patients with these characteristics is called "on-label." The findings of the 5-year follow-up data from these trials are as follows: 1) efficacy to clinical restenosis maintained and 2) safety profiles such as stent thrombosis, myocardial infarction (MI), and death occurred similarly in the BMS and DES groups.[12-15]

DES reduced restenosis without long-term safety concerns in complex lesions such as left main lesions, long lesions, small vessels, and chronic total occlusion.[16-21] Recent studies have shown similar clinical outcomes during long-term follow-up in high-risk patients who had acute MI or diabetes mellitus.[22-29]

2. Safety concerns

Intracoronary stent thrombosis (ST) is an infrequent but devastating complication after percutaneous coronary intervention (PCI). Because intracoronary stents are generally implanted in proximal segments of major coronary arteries, acute thrombotic occlusion of stents is usually associated with severe ischemia or MI (-50 to 70-80%) that often leads to death (-20 to 40%).[30,31] Early (<30 days) or late ST (30 days to 1 year) occurred similarly between BMS and DES; however, significantly higher rates of very late ST (>1 year) were seen with DES in a large collaborative meta-analysis.[31,32] Registries of all comers treated with DES showed that very late ST developed at an annual rate about 0.3-0.6%/year after DES implantation.[32,33]

The main mechanisms of this phenomenon are impaired endothelialization and hypersensitivity reaction with the polymer. The anti-proliferative agents impair endothelialization and the blood is then exposed to the stent struts more, potentially precipitating ST. Postmortem pathological specimens and angioscopy of DES reveal a significant number of uncovered struts with an inflammatory reaction.[34-37] Polymers facilitate drug release in DES, but remain long after completion of drug elution. That could cause localized vascular inflammation, eosinophilia, apoptosis of smooth muscle cells, and thrombosis.[38-40]

THE SECOND-GENERATION DES

The new DES designs should be safer by decreasing ST, which is more effective for reducing restenosis, especially for high-risk PCI, with more durable results for decreasing rates of late restenosis or thrombosis compared with the first-generation DES.[41] The four key components of DES are drug, polymer, stent platform, and stent delivery system. The second-generation DES are designed to provide better stent deployment, safety, and efficacy by improving the key components. In 2008, the zotarolimus-eluting stents (ZES) and the everolimus-eluting stents (EES) were approved by the US FDA for use and are referred to as "second-generation" DES. Their anti-proliferative drug is released from a thin coating of a biocompatible polymer on a flexible stent frame with thin struts.[42]

1. Advances in design

The prominent differences between the first- and the second-generation DES designs are the stent strut and the polymer. The stent scaffold design has a role in determining performance, including deliverability, side branch access, and the surface area for drug delivery. The initial stent scaffold was 316L stainless steel because this material is radio-opaque and provides enough radial strength to prevent acute recoil. Several studies have shown that thinner struts may reduce restenosis, facilitate endothelialization, and decrease thrombogenicity.[43-45] Therefore, stent platform materials have moved from stainless steel to cobalt chromium (CoCr) and platinum chromium (PtCr), which allow for thinner struts while preserving radial strength and recoil.

Phosphorylcholine is used as a polymer of ZES. Its molecular design improves surface biocompatibility and lowers the risk of causing inflammation or thrombosis.[46] Another contemporary biocompatible polymer is the fluoropolymer that is used in EES. The fluoropolymer surface elicits a biological response known as fluoropassivation that minimizes the fibrin deposition and thrombogenicity, thereby reducing the inflammatory reaction and enhancing endothelial healing.[47,48]

The second-generation DES were associated with more strut coverage, re-endothelialization, and less endothelial dysfunction in several pathologic and coronary imaging studies.[49-53]

2. Clinical studies of ZES

ZES are inferior to SES and PES with respect to the angiographic finding of in-stent late loss. In terms of clinical outcomes, ZES have similar or better outcomes compared with PES.[54,55] The data on ZES compared with SES are less definitive but there appears to be similar safety but higher rates of target vessel revascularization (TVR) with ZES.[55-57] The rapid elution of zotarolimus from a polymer may be related to the high rate of late loss compared with other DES. After 1 year, however, ZES showed superior safety outcomes (death/MI, ST) compared with both SES and ZES,[58,59] and the TLR rate of ZES was closer to that of SES, possibly because of the late catch phenomenon.[59]

The Resolute ZES use dual polymer technology that extends the release of zotarolimus and drug exposure to the vessel to 4 months for decreasing in-stent late loss. Patients with ZES experienced more TVR rates than did patients with EES in real-world practice.[60] In contrast, the Resolute ZES had similar revascularization rates and safety profiles

compared with EES even in patients with complex PCI during 1 to 2 years of follow-up.[61-63] According to a recent optical coherence tomography (OCT) study, the Resolute ZES had better suppression of neointimal growth but a higher proportion of uncovered and malapposed struts compared with ZES.[64] Longer follow-up data are needed for the new generation of ZES.

3. The current workhorse: EES

EES were superior to PES in preventing both restenosis (TVR) and thrombosis (MI, ST) in two large randomized controlled studies.[65,66] At least, EES were not inferior to SES. Three randomized trials and one observational study demonstrated similar angiographic late loss and ST rates between EES and SES.[67-70] One randomized trial and one observational study reported less ST with EES.[71,72] In a large cohort study and a meta-analysis, the second-generation DES, especially EES, had superior efficacy and safety compared with the first-generation DES (SES and PES).[73,74]

There are many published studies demonstrating the efficacy and safety of EES in high-risk patients. Table 1 briefly summarizes these studies. EES had comparable results in this high-risk group.[75-82] During long-term follow-up (4-5 years), EES showed durable efficacy without the late catch phenomenon and safety compared with BMS and PES.[83,84]

PROMISING NEW DES DESIGNS WITH EVIDENCE

1. DES with a small amount of a biodegradable polymer

Stent polymers have potential effects on hypersensitivity and inflammation, which could be translated into ST. DES with biodegradable polymers can offer the anti-restenotic effects of a DES initially and the safety benefits of a BMS after degradation of the polymer.[85] There are several representative published studies about biodegradable polymers.

In the Limus Eluted from A Durable vs. ERodable Stent Coating (LEADERS) trial, 1707 patients with both stable and unstable coronary artery disease were randomly assigned to either a biolimus- (a sirolimus analog) eluting stent (BES) with a biodegradable polymer applied only to the abluminal (outer) surface or to an SES. The BES was noninferior to the SES for the primary composite endpoint of cardiac death, MI, or clinically indicated TVR at 9 months. The rate of definite ST was also similar (2.5% vs. 2.2%).[86] According to the Optical Coherence Tomography (OCT) substudy of the LEADERS trial, biodegradable stents showed more complete strut coverage at an average follow-up of 9 months compared with SES.[87] By reducing the risk of cardiac events associated with very late ST, BES with a biodegradable polymer improved long-term clinical outcomes for up to 4 years of follow-up of the LEADERS trial.[88]

Other trials such as the Intracoronary Stenting and Angiographic Restenosis-Test Equivalence Between 2 Drug-Eluting Stents (ISAR-TEST) 3 and 4 reported comparable results with SES in terms of both efficacy and safety.[69,89,90] A meta-analysis using the results of the ISAR-TEST 3, ISAR-TEST 4, and LEADERS studies showed that biodegradable polymer DES reduced definite ST and TLR at 3 years compared with SES.[91]

TABLE 1. Studies of EES in high-risk groups

Study	Number of patients	Clinical setting	Follow-up (months)	Major results
PRECOMBAT-2[75]	EES (n=334) vs. SES (n=327) vs. CABG (n=272)	Unprotected left main	18	Death/MI/TVR: similar More TVR in PCI than CABG
Pan et al.[76]	EES (n=148) vs. SES (n=145)	Bifurcation	12	Death/TLR: similar
Claessen et al.[77]	EES (n=3944) vs. PES (n=2239)	Small, long	24	Short and large: similar Long and/or short: EES better
Song et al.[78]	EES (n=34) vs. SES (n=32)	Diffuse ISR	9	In segment restenosis: similar Death/MI/TLR: similar
XAMI[79]	EES (n=404) vs. SES (n=221)	AMI	12	Death/MI/TVR: EES better
Kalesan et al.[80]	EES (n=903) vs. SES (n=843)	ACS	36	Death/MI/TVR: EES better TVR, ST: EES better
ESSENCE-DIABETES trial[81]	EES (n=149) vs. SES (n=151)	DM	9 12	In segment restenosis: similar Death, MI, TLR: similar
The SPIRIT V diabetic study[82]	EES (n=218) vs. PES (n=106)	DM	9 12	In segment restenosis: EES better Death/MI/TVR: similar

EES: everolimus-eluting stent, PRECOMBAT: premier of randomized comparison of bypass surgery versus angioplasty using sirolimus-eluting stent in patients with left main coronary artery disease, SES: sirolimus-eluting stent, MI: myocardial infarction, TVR: target vessel revascularization, PCI: percutaneous coronary intervention, CABG: coronary artery bypass grafting, TLR: target lesion revascularization, PES: paclitaxel-eluting stent, ISR: in-stent restenosis, XAMI: xiencev stent vs. cypher stent in primary PCI for acute myocardial infarction, AMI: acute myocardial infarction, ACS: acute coronary syndrome, ESSENCE-DIABETES: everolimus-eluting stent versus sirolimus-eluting stent implantation for de novo coronary artery disease in patients with diabetes mellitus, DM: diabetes mellitus, SPIRIT: clinical evaluation of the xience V everolimus eluting coronary stent system.

TABLE 2. Published advantages over the first-generation DES

Stent name	Safety			Efficacy		
	Stent thrombosis	Long-term FU (4-5 year)		On-label	Off-label	
		With BMS	With DES		Complex lesion	High-risk patients
ZES	O	O	O	X	X	X
Resolute ZES	O	X	X	O	O	O
EES	O	O	O	O	O	O
Biodegradable polymer	O	X	O	O	X	X
PF DES	O	X	X	X	X	X
Dual PF DES	O	X	X	O	X	X

DES: drug-eluting stent, BMS: bare metal stent, ACS: acute coronary syndrome, DM: diabetes mellitus, ZES: zotarolimus-eluting stent, EES: everolimus-eluting stent, PF: polymer-free.

2. Polymer-free DES

The polymer-free stent may be associated with less chronic inflammation and improved vascular healing. The difficulty in designing a polymer-free stent is achieving adequate levels of the antiproliferative drug over time to effectively inhibit neointimal hyperplasia and restenosis. Like ZES, polymer-free DES suffer high late loss during short-term follow-up, but are less susceptible to late restenosis.[89,92]

Dual polymer-free DES use two anti-proliferative agents (sirolimus and probucol) that target a different part of the cell cycle for improving the anti-restenosis effect.[85] This concept was evaluated in the ISAR-TEST 2 and 5. The ISAR-TEST 2 study randomly assigned 1007 patients to SES (n=335), ZES (n=339), or a dual polymer-free DES (n=333). Safety profiles were similar among the 3 groups. TLR rates were significantly lower with dual polymer-free DES than with ZES and were comparable between dual polymer-free DES and SES at 2 years of follow-up. However, the increase in TLR and binary restenosis between the 1- and 2-year follow-up was significantly higher with SES.[93,94] The ISAR-TEST 5 study showed that dual polymer-free DES were noninferior to ZES in terms of the rate of primary endpoints (cardiac death, target-vessel related MI, target lesion revascularization) out to 12 months.[95] Table 2 briefly summarizes the advantages of the new DES designs over the first-generation DES.

3. Bioresorbable scaffold

Complete bioabsorbable stent platforms are currently undergoing clinical trials. Potential advantages over current DES are as follows: 1) the removal of the scaffold facilitates the return of vessel vasomotion, adaptive shear stress, late luminal enlargement, and the reduction of scaffold thrombosis; 2) a reduction in the requirements for long-term dual anti-platelet therapy, thereby reducing the bleeding complications; 3) allowance for future revascularization and the use of noninvasive imaging techniques such as computed tomography or magnetic resonance imaging for follow-up.[96] The A Bioabsorbable Everolimus-Eluting Coronary Stent System for Patients With Single De-Novo Coronary Artery Lesions (ABSORB) study showed complete stent resorption, arterial healing, and restoration of normal vascular function.[97] The second generation of bioabsorbable stents has overcome the shortcomings of the first generation (early bioresorption and device shrinkage).[98] Several randomized studies have recently commenced to demonstrate the efficacy and safety of bioabsorbable stents. However, many obstacles, such as higher cost, a thicker device, and long-term safety, should be overcome to use this stent.

In conclusion, the first-generation DES were limited in value because of late-term ST and restenosis. The second-generation DES, the current workhorse, further improved safety and efficacy by the use of thinner stent struts and biocompatible polymers. Recently, DES with new concept designs such as biodegradable polymers, polymer-free stents, and bioabsorbable scaffolds have shown promising results. However, more well-organized studies with large-scale and long-term follow-up are needed before these new DES become the next workhorse.

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REFERENCES

1. 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.
2. Kimmel SE, Localio AR, Krone RJ, Laskey WK. The effects of contemporary use of coronary stents on in-hospital mortality. Registry Committee of the Society for Cardiac Angiography and Interventions. J Am Coll Cardiol 2001;37:499-504.
3. Roubin GS, Cannon AD, Agrawal SK, Macander PJ, Dean LS, Baxley WA, et al. Intracoronary stenting for acute and threatened closure complicating percutaneous transluminal coronary angioplasty. Circulation 1992;85:916-27.
4. Serruys PW, de Jaegere P, Kiemeneij F, Macaya C, Rutsch W,

Heyndrickx G, et al. A comparison of balloon-expandable-stent implantation with balloon angioplasty in patients with coronary artery disease. Benestent Study Group. N Engl J Med 1994;331: 489-95.
5. Fischman DL, Leon MB, Baim DS, Schatz RA, Savage MP, Penn I, et al. A randomized comparison of coronary-stent placement and balloon angioplasty in the treatment of coronary artery disease. Stent Restenosis Study Investigators. N Engl J Med 1994;331:496-501.
6. Costa MA, Simon DI. Molecular basis of restenosis and drug-eluting stents. Circulation 2005;111:2257-73.
7. Regar E, Sianos G, Serruys PW. Stent development and local drug delivery. Br Med Bull 2001;59:227-48.
8. Morice MC, Serruys PW, Sousa JE, Fajadet J, Ban Hayashi E, Perin M, et al; RAVEL Study Group. Randomized Study with the Sirolimus-Coated Bx Velocity Balloon-Expandable Stent in the Treatment of Patients with de Novo Native Coronary Artery Lesions. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. N Engl J Med 2002;346:1773-80.
9. Moses JW, Leon MB, Popma JJ, Fitzgerald PJ, Holmes DR, O'Shaughnessy C, et al; SIRIUS Investigators. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. N Engl J Med 2003;349:1315-23.
10. Colombo A, Drzewiecki J, Banning A, Grube E, Hauptmann K, Silber S, et al; TAXUS II Study Group. 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.
11. Stone GW, Ellis SG, Cox DA, Hermiller J, O'Shaughnessy C, Mann JT, et al; TAXUS-IV Investigators. A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. N Engl J Med 2004;350:221- 31.
12. Morice MC, Serruys PW, Barragan P, Bode C, Van Es GA, Stoll HP, et al. Long-term clinical outcomes with sirolimus-eluting coronary stents: five-year results of the RAVEL trial. J Am Coll Cardiol 2007;50:1299-304.
13. Weisz G, Leon MB, Holmes DR Jr, Kereiakes DJ, Popma JJ, Teirstein PS, et al. Five-year follow-up after sirolimus-eluting stent implantation results of the SIRIUS (Sirolimus-Eluting Stent in De-Novo Native Coronary Lesions) Trial. J Am Coll Cardiol 2009;53:1488-97.
14. Silber S, Colombo A, Banning AP, Hauptmann K, Drzewiecki J, Grube E, 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.
15. Ellis SG, Stone GW, Cox DA, Hermiller J, O'Shaughnessy C, Mann T, et al; TAXUS IV Investigators. 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). JACC Cardiovasc Interv 2009;2:1248-59.
16. Kim YH, Park DW, Lee SW, Yun SC, Lee CW, Hong MK, et al; Revascularization for Unprotected Left Main Coronary Artery Stenosis: Comparison of Percutaneous Coronary Angioplasty Versus Surgical Revascularization Investigators. Long-term safety and effectiveness of unprotected left main coronary stenting with drug-eluting stents compared with bare-metal stents. Circulation 2009;120:400-7.
17. Grube E, Dawkins K, Guagliumi G, Banning A, Zmudka K, Colombo A, et al. TAXUS VI final 5-year results: a multicentre, randomised trial comparing polymer-based moderate-release paclitaxel-eluting stent with a bare metal stent for treatment of long, complex coronary artery lesions. EuroIntervention 2009;4:572-7.
18. Menozzi A, Solinas E, Ortolani P, Repetto A, Saia F, Piovaccari G, et al; SES-SMART Investigators. Twenty-four months clinical outcomes of sirolimus-eluting stents for the treatment of small coronary arteries: the long-term SES-SMART clinical study. Eur Heart J 2009;30:2095-101.
19. Kelbaek H, Kløvgaard L, Helqvist S, Lassen JF, Krusell LR, Engstrøm T, et al. Long-term outcome in patients treated with sirolimus-eluting stents in complex coronary artery lesions: 3-year results of the SCANDSTENT (Stenting Coronary Arteries in Non-Stress/Benestent Disease) trial. J Am Coll Cardiol 2008;51:2011-6.
20. Van den Branden BJ, Rahel BM, Laarman GJ, Slagboom T, Kelder JC, et al. Five-year clinical outcome after primary stenting of totally occluded native coronary arteries: a randomised comparison of bare metal stent implantation with sirolimus-eluting stent implantation for the treatment of total coronary occlusions (PRISON II study). EuroIntervention 2012;7:1189-96.
21. Rubartelli P, Petronio AS, Guiducci V, Sganzerla P, Bolognese L, Galli M, et al; Gruppo Italiano di Studio sullo Stent nelle Occlusioni Coronariche II GISE Investigators. Comparison of sirolimus-eluting and bare metal stent for treatment of patients with total coronary occlusions: results of the GISSOC II-GISE multicentre randomized trial. Eur Heart J 2010;31:2014-20.
22. Brar SS, Leon MB, Stone GW, Mehran R, Moses JW, Brar SK, et al. Use of drug-eluting stents in acute myocardial infarction: a systematic review and meta-analysis. J Am Coll Cardiol 2009;53: 1677-89.
23. Violini R, Musto C, De Felice F, Nazzaro MS, Cifarelli A, Petitti T, et al. Maintenance of long-term clinical benefit with sirolimus-eluting stents in patients with ST-segment elevation myocardial infarction 3-year results of the SESAMI (sirolimus-eluting stent versus bare-metal stent in acute myocardial infarction) trial. J Am Coll Cardiol 2010;55:810-4.
24. Stone GW, Lansky AJ, Pocock SJ, Gersh BJ, Dangas G, Wong SC, et al; HORIZONS-AMI Trial Investigators. Paclitaxel-eluting stents versus bare- metal stents in acute myocardial infarction. N Engl J Med 2009;360:1946-59.
25. Stone GW, Witzenbichler B, Guagliumi G, Peruga JZ, Brodie BR, Dudek D, et al; HORIZONS-AMI Trial Investigators. 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;377:2193-204.
26. Kirtane AJ, Ellis SG, Dawkins KD, Colombo A, Grube E, Popma JJ, et al. Paclitaxel-eluting coronary stents in patients with diabetes mellitus: pooled analysis from 5 randomized trials. J Am Coll Cardiol 2008;51:708-15.
27. Garg P, Normand SL, Silbaugh TS, Wolf RE, Zelevinsky K, Lovett

A, et al. Drug-eluting or bare-metal stenting in patients with diabetes mellitus: results from the Massachusetts Data Analysis Center Registry. Circulation 2008;118:2277-85.
28. Daemen J, Garcia-Garcia HM, Kukreja N, Imani F, de Jaegere PP, Sianos G, et al. The long-term value of sirolimus- and paclitaxel-eluting stents over bare metal stents in patients with diabetes mellitus. Eur Heart J 2007;28:26-32.
29. Ortolani P, Balducelli M, Marzaroli P, Piovaccari G, Menozzi A, Guiducci V, et al. Two-year clinical outcomes with drug-eluting stents for diabetic patients with de novo coronary lesions: results from a real-world multicenter registry. Circulation 2008;117: 923-30.
30. Iakovou I, Schmidt T, Bonizzoni E, Ge L, Sangiorgi GM, Stankovic G, et al. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. JAMA 2005;293: 2126-30.
31. Mauri L, Hsieh WH, Massaro JM, Ho KK, D'Agostino R, Cutlip DE. Stent thrombosis in randomized clinical trials of drug-eluting stents. N Engl J Med 2007;356:1020-9.
32. Stettler C, Wandel S, Allemann S, Kastrati A, Morice MC, Schömig A, et al. Outcomes associated with drug-eluting and bare-metal stents: a collaborative network meta-analysis. Lancet 2007;370:937-48.
33. Wenaweser P, Daemen J, Zwahlen M, van Domburg R, Jüni P, Vaina S, et al. Incidence and correlates of drug-eluting stent thrombosis in routine clinical practice. 4-year results from a large 2-institutional cohort study. J Am Coll Cardiol 2008;52:1134-40.
34. Joner M, Finn AV, Farb A, Mont EK, Kolodgie FD, Ladich E, et al. Pathology of drug-eluting stents in humans: delayed healing and late thrombotic risk. J Am Coll Cardiol 2006;48:193-202.
35. Finn AV, Joner M, Nakazawa G, Kolodgie F, Newell J, John MC, et al. Pathological correlates of late drug-eluting stent thrombosis: strut coverage as a marker of endothelialization. Circulation 2007;115:2435-41.
36. Awata M, Kotani J, Uematsu M, Morozumi T, Watanabe T, Onishi T, et al. Serial angioscopic evidence of incomplete neointimal coverage after sirolimus-eluting stent implantation: comparison with bare-metal stents. Circulation 2007;116:910-6.
37. Kotani J, Awata M, Nanto S, Uematsu M, Oshima F, Minamiguchi H, et al. Incomplete neointimal coverage of sirolimus-eluting stents: angioscopic findings. J Am Coll Cardiol 2006;47:2108-11.
38. Nebeker JR, Virmani R, Bennett CL, Hoffman JM, Samore MH, Alvarez J, et al. Hypersensitivity cases associated with drug-eluting coronary stents: a review of available cases from the Research on Adverse Drug Events and Reports (RADAR) project. J Am Coll Cardiol 2006;47:175-81.
39. Virmani R, Guagliumi G, Farb A, Musumeci G, Grieco N, Motta T, et al. Localized hypersensitivity and late coronary thrombosis secondary to a sirolimus-eluting stent: should we be cautious? Circulation 2004;109:701-5.
40. Jeong MH. Current status of the development of new-drug eluting stents. Korean J Med 2009;76:544-8.
41. Räber L, Wohlwend L, Wigger M, Togni M, Wandel S, Wenaweser P, et al. Five-year clinical and angiographic outcomes of a randomized comparison of sirolimus-eluting and paclitaxel-eluting stents: results of the Sirolimus-Eluting Versus Paclitaxel-Eluting Stents for Coronary Revascularization LATE trial. Circulation 2011;123:2819-28.
42. Kim HK, Jeong MH. Prevention of intracoronary stent thrombosis; in Stent thrombosis: epidermiology, prevention, and management. In: De luca C, ed. New York, NY, USA: Nova publisher, Hauppauge, 2012.
43. Pache J, Kastrati A, Mehilli J, Schühlen H, Dotzer F, Hausleiter J, et al. Intracoronary stenting and angiographic results: strut thickness effect on restenosis outcome (ISAR-STEREO-2) trial. J Am Coll Cardiol 2003;41:1283-8.
44. Kastrati A, Mehilli J, Dirschinger J, Dotzer F, Schühlen H, Neumann FJ, et al. Intracoronary stenting and angiographic results: strut thickness effect on restenosis outcome (ISAR-STEREO) trial. Circulation 2001;103:2816-21.
45. Kolandaivelu K, Swaminathan R, Gibson WJ, Kolachalama VB, Nguyen-Ehrenreich KL, Giddings VL, et al. Stent thrombogenicity early in high-risk interventional settings is driven by stent design and deployment and protected by polymer-drug coatings. Circulation 2011;123:1400-9.
46. Lewis AL, Tolhurst LA, Stratford PW. Analysis of a phosphorylcholine-based polymer coating on a coronary stent pre- and post-implantation. Biomaterials 2002;23:1697-706.
47. Xie X, Guidoin R, Nutley M, Zhang Z. Fluoropassivation and gelatin sealing of polyester arterial prostheses to skip preclotting and constrain the chronic inflammatory response. J Biomed Mater Res B Appl Biomater 2010;93:497-509.
48. Gutiérrez-Chico JL, van Geuns RJ, Regar E, van der Giessen WJ, Kelbæk H, Saunamäki K, et al. Tissue coverage of a hydrophilic polymer-coated zotarolimus-eluting stent vs. a fluoropolymer-coated everolimus-eluting stent at 13-month follow-up: an optical coherence tomography substudy from the RESOLUTE All Comers trial. Eur Heart J 2011;32:2454-63.
49. Joner M, Nakazawa G, Finn AV, Quee SC, Coleman L, Acampado E, et al. Endothelial cell recovery between comparator polymer-based drug-eluting stents. J Am Coll Cardiol 2008;52:333-42.
50. Kim JW, Seo HS, Park JH, Na JO, Choi CU, Lim HE, et al. A prospective, randomized, 6-month comparison of the coronary vasomotor response associated with a zotarolimus- versus a sirolimus-eluting stent: differential recovery of coronary endothelial dysfunction. J Am Coll Cardiol 2009;53:1653-9.
51. Kim JS, Jang IK, Kim JS, Kim TH, Takano M, Kume T, et al. Optical coherence tomography evaluation of zotarolimus-eluting stents at 9-month follow-up: comparison with sirolimus-eluting stents. Heart 2009;95:1907-12.
52. Guagliumi G, Musumeci G, Sirbu V, Bezerra HG, Suzuki N, Fiocca L, et al; ODESSA Trial Investigators. Optical coherence tomography assessment of in vivo vascular response after implantation of overlapping bare- metal and drug-eluting stents. JACC Cardiovasc Interv 2010;3: 531-9.
53. Awata M, Nanto S, Uematsu M, Morozumi T, Watanabe T, Onishi T, et al. Angioscopic comparison of neointimal coverage between zotarolimus- and sirolimus-eluting stents. J Am Coll Cardiol 2008;52:789-90.
54. Leon MB, Mauri L, Popma JJ, Cutlip DE, Nikolsky E, O'Shaughnessy C, et al; ENDEAVOR IV Investigators. 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.
55. Park DW, Kim YH, Yun SC, Kang SJ, Lee SW, Lee CW, et al. Comparison of zotarolimus-eluting stents with sirolimus- and paclitaxel-eluting stents for coronary revascularization: the ZEST (comparison of the efficacy and safety of zotarolimus-eluting stent with sirolimus-eluting and paclitaxel-eluting stent for coronary lesions) randomized trial. J Am Coll Cardiol 2010;56:1187-95.
56. Rasmussen K, Maeng M, Kaltoft A, Thayssen P, Kelbaek H, Tilsted HH, et al; SORT OUT III study group. 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.
57. Kim HK, Jeong MH, Ahn YK, Kim JH, Chae SC, Kim YJ, et al; Korea Acute Myocardial Infarction Registry Investigators. Comparison of outcomes between Zotarolimus- and sirolimus-eluting stents in patients with ST-segment elevation acute myocardial infarction. Am J Cardiol 2010;105:813-8.
58. Leon MB, Nikolsky E, Cutlip DE, Mauri L, Liberman H, Wilson H, et al; ENDEAVOR IV Investigators. 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. JACC Cardiovasc Interv 2010;3:1043-50.
59. Kandzari DE, Mauri L, Popma JJ, Turco MA, Gurbel PA, Fitzgerald PJ, 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). JACC Cardiovasc Interv 2011;4:543-50.
60. Hannan EL, Zhong Y, Wu C, Walford G, Holmes DR Jr, Jacobs AK, et al. Everolimus-eluting stents and zotarolimus-eluting stents for percutaneous coronary interventions: Two-year outcomes in new york state. Catheter Cardiovasc Interv 2012 [Epub ahead of print]
61. Serruys PW, Silber S, Garg S, van Geuns RJ, Richardt G, Buszman PE, et al. Comparison of zotarolimus-eluting and everolimus-eluting coronary stents. N Engl J Med 2010;363:136-46.
62. Silber S, Windecker S, Vranckx P, Serruys PW; RESOLUTE All Comers investigators. Unrestricted randomised use of two new generation drug-eluting coronary stents: 2-year patient-related versus stent-related outcomes from the RESOLUTE All Comers trial. Lancet 2011;377:1241-7.
63. von Birgelen C, Basalus MW, Tandjung K, van Houwelingen KG, Stoel MG, Louwerenburg JH, et al. A randomized controlled trial in second-generation zotarolimus-eluting Resolute stents versus everolimus-eluting Xience V stents in real-world patients: the TWENTE trial. J Am Coll Cardiol 2012;59:1350-61.
64. Guagliumi G, Ikejima H, Sirbu V, Bezerra H, Musumeci G, Lortkipanidze N, et al. Impact of drug release kinetics on vascular response to different zotarolimus-eluting stents implanted in patients with long coronary stenoses: the LongOCT study (Optical Coherence Tomography in Long Lesions). JACC Cardiovasc Interv 2011;4:778-85.
65. Kedhi E, Joesoef KS, McFadden E, Wassing J, van Mieghem C, Goedhart D, et al. Second-generation everolimus-eluting and paclitaxel-eluting stents in real-life practice (COMPARE): a randomised trial. Lancet 2010;375:201-9.
66. Stone GW, Rizvi A, Newman W, Mastali K, Wang JC, Caputo R, et al; SPIRIT IV Investigators. Everolimus-eluting versus paclitaxel-eluting stents in coronary artery disease. N Engl J Med 2010;362:1663-74.
67. Kimura T, Morimoto T, Natsuaki M, Shiomi H, Igarashi K, Kadota K, et al; RESET Investigators. Comparison of everolimus-eluting and sirolimus-eluting coronary stents: 1-year outcomes from the Randomized Evaluation of Sirolimus-eluting Versus Everolimus-eluting stent Trial (RESET). Circulation 2012;126:1225-36.
68. Park KW, Chae IH, Lim DS, Han KR, Yang HM, Lee HY, et al. Everolimus-eluting versus sirolimus-eluting stents in patients undergoing percutaneous coronary intervention: the EXCELLENT (Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting) randomized trial. J Am Coll Cardiol 2011;58:1844-54.
69. Byrne RA, Kastrati A, Massberg S, Wieczorek A, Laugwitz KL, Hadamitzky M, et al; ISAR-TEST 4 Investigators. Biodegradable polymer versus permanent polymer drug-eluting stents and everolimus- versus sirolimus-eluting stents in patients with coronary artery disease: 3-year outcomes from a randomized clinical trial. J Am Coll Cardiol 2011;58:1325-31.
70. Park DW, Kim YH, Song HG, Ahn JM, Kim WJ, Lee JY, et al; IRIS-DES Investigators. Outcomes after unrestricted use of everolimus-eluting and sirolimus-eluting stents in routine clinical practice: a multicenter, prospective cohort study. Circ Cardiovasc Interv 2012;5:365-71.
71. Jensen LO, Thayssen P, Hansen HS, Christiansen EH, Tilsted HH, Krusell LR, et al; Scandinavian Organization for Randomized Trials With Clinical Outcome IV (SORT OUT IV) Investigators. Randomized comparison of everolimus- eluting and sirolimus-eluting stents in patients treated with percutaneous coronary intervention: the Scandinavian Organization for Randomized Trials with Clinical Outcome IV (SORT OUT IV). Circulation 2012;125:1246-55.
72. Räber L, Jüni P, Nüesch E, Kalesan B, Wenaweser P, Moschovitis A, et al. Long-term comparison of everolimus-eluting and sirolimus-eluting stents for coronary revascularization. J Am Coll Cardiol 2011;57:2143-51.
73. Sarno G, Lagerqvist B, Fröbert O, Nilsson J, Olivecrona G, Omerovic E, et al. Lower risk of stent thrombosis and restenosis with unrestricted use of 'new-generation' drug-eluting stents: a report from the nationwide Swedish Coronary Angiography and Angioplasty Registry (SCAAR). Eur Heart J 2012;33:606-13.
74. Palmerini T, Biondi-Zoccai G, Della Riva D, Stettler C, Sangiorgi D, D'Ascenzo F, et al. Stent thrombosis with drug-eluting and bare-metal stents: evidence from a comprehensive network meta-analysis. Lancet 2012;379:1393-402.
75. Kim YH, Park DW, Ahn JM, Yun SC, Song HG, Lee JY, et al; PRECOMBAT-2 Investigators. Everolimus-eluting stent implantation for unprotected left main coronary artery stenosis. The PRECOMBAT-2 (Premier of Randomized Comparison of Bypass

Surgery versus Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease) study. JACC Cardiovasc Interv 2012;5:708-17.
76. Pan M, Medina A, Lezo JS, Romero M, Segura J, Martín P, et al. Randomized study comparing everolimus- and sirolimus-eluting stents in patients with bifurcation lesions treated by provisional side-branch stenting. Catheter Cardiovasc Interv 2012. [Epub ahead of print]
77. Claessen BE, Smits PC, Kereiakes DJ, Parise H, Fahy M, Kedhi E, et al. Impact of lesion length and vessel size on clinical outcomes after percutaneous coronary intervention with everolimus- versus paclitaxel-eluting stents pooled analysis from the SPIRIT (Clinical Evaluation of the XIENCE V Everolimus Eluting Coronary Stent System) and COMPARE (Second-generation everolimus-eluting and paclitaxel-eluting stents in real-life practice) Randomized Trials. JACC Cardiovasc Interv 2011;4:1209-15.
78. Song HG, Park DW, Kim YH, Ahn JM, Kim WJ, Lee JY, et al. Randomized trial of optimal treatment strategies for in-stent restenosis after drug-eluting stent implantation. J Am Coll Cardiol 2012;59:1093-100.
79. Hofma SH, Brouwer J, Velders MA, van't Hof AW, Smits PC, Queré M, et al. Second-generation everolimus-eluting stents versus first-generation sirolimus-eluting stents in acute myocardial infarction. 1-year results of the randomized XAMI (XienceV Stent vs. Cypher Stent in Primary PCI for Acute Myocardial Infarction) trial. J Am Coll Cardiol 2012;60:381-7.
80. Kalesan B, Stefanini GG, Räber L, Schmutz M, Baumgartner S, Hitz S, et al. Long-term comparison of everolimus- and sirolimus-eluting stents in patients with acute coronary syndromes. JACC Cardiovasc Interv 2012;5:145-54.
81. Kim WJ, Lee SW, Park SW, Kim YH, Yun SC, Lee JY, et al; ESSENCE-DIABETES Study Investigators. Randomized comparison of everolimus-eluting stent versus sirolimus-eluting stent implantation for de novo coronary artery disease in patients with diabetes mellitus (ESSENCE-DIABETES): results from the ESSENCE-DIABETES trial. Circulation 2011;124:886-92.
82. Grube E, Chevalier B, Guagliumi G, Smits PC, Stuteville M, Dorange C, et al. The SPIRIT V diabetic study: a randomized clinical evaluation of the XIENCE V everolimus-eluting stent vs the TAXUS Liberté paclitaxel-eluting stent in diabetic patients with de novo coronary artery lesions. Am Heart J 2012;163:867-75.e1.
83. Garg S, Serruys PW, Miquel-Hebert K; SPIRIT II Investigators. Four-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. Catheter Cardiovasc Interv 2011;77:1012-7.
84. Wiemer M, Serruys PW, Miquel-Hebert K, Neumann FJ, Piek JJ, Grube E, et al. Five-year long-term 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 FIRST trial. Catheter Cardiovasc Interv 2010;75:997-1003.
85. Garg S, Serruys PW. Coronary stents: looking forward. J Am Coll Cardiol 2010;56(10 Suppl):S43-78.
86. Windecker S, Serruys PW, Wandel S, Buszman P, Trznadel S, Linke A, 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.
87. Barlis P, Regar E, Serruys PW, Dimopoulos K, van der Giessen WJ, van Geuns RJ, et al. An optical coherence tomography study of a biodegradable vs. durable polymer-coated limus-eluting stent: a LEADERS trial sub-study. Eur Heart J 2010;31:165-76.
88. Stefanini GG, Kalesan B, Serruys PW, Heg D, Buszman P, Linke A, et al. Long-term clinical outcomes of biodegradable polymer biolimus-eluting stents versus durable polymer sirolimus-eluting stents in patients with coronary artery disease (LEADERS): 4 year follow-up of a randomised non-inferiority trial. Lancet 2011;378:1940-8.
89. Mehilli J, Byrne RA, Wieczorek A, Iijima R, Schulz S, Bruskina O, et al; Intracoronary Stenting and Angiographic Restenosis Investigators--Test Efficacy of Rapamycin-eluting Stents with Different Polymer Coating Strategies (ISAR-TEST-3). Randomized trial of three rapamycin-eluting stents with different coating strategies for the reduction of coronary restenosis. Eur Heart J 2008;29:1975-82.
90. Byrne RA, Kastrati A, Kufner S, Massberg S, Birkmeier KA, Laugwitz KL, et al; Intracoronary Stenting and Angiographic Results: Test Efficacy of 3 Limus-Eluting Stents (ISAR-TEST-4) Investigators. Randomized, non-inferiority trial of three limus agent-eluting stents with different polymer coatings: the Intracoronary Stenting and Angiographic Results: Test Efficacy of 3 Limus-Eluting Stents (ISAR-TEST-4) Trial. Eur Heart J 2009;30:2441-9.
91. Stefanini GG, Byrne RA, Serruys PW, de Waha A, Meier B, Massberg S, et al. Biodegradable polymer drug-eluting stents reduce the risk of stent thrombosis at 4 years in patients undergoing percutaneous coronary intervention: a pooled analysis of individual patient data from the ISAR-TEST 3, ISAR-TEST 4, and LEADERS randomized trials. Eur Heart J 2012;33:1214-22.
92. Byrne RA, Iijima R, Mehilli J, Pinieck S, Bruskina O, Schömig A, et al. Durability of antirestenotic efficacy in drug-eluting stents with and without permanent polymer. JACC Cardiovasc Interv 2009;2:291-9.
93. Byrne RA, Mehilli J, Iijima R, Schulz S, Pache J, Seyfarth M, et al. A polymer-free dual drug-eluting stent in patients with coronary artery disease: a randomized trial vs. polymer-based drug-eluting stents. Eur Heart J 2009;30:923-31.
94. Byrne RA, Kastrati A, Tiroch K, Schulz S, Pache J, Pinieck S, et al; ISAR-TEST-2 Investigators. 2-year clinical and angiographic outcomes from a randomized trial of polymer-free dual drug-eluting stents versus polymer-based Cypher and Endeavor [corrected] drug-eluting stents. J Am Coll Cardiol 2010;55:2536-43.
95. Massberg S, Byrne RA, Kastrati A, Schulz S, Pache J, Hausleiter J, et al; Intracoronary Stenting and Angiographic Results: Test Efficacy of Sirolimus- and Probucol-Eluting Versus Zotarolimus-Eluting Stents (ISAR-TEST 5) Investigators. Polymer-free sirolimus- and probucol-eluting versus new generation zotarolimus-eluting stents in coronary artery disease: the Intracoronary Stenting and Angiographic Results: Test Efficacy of Sirolimus- and Probucol-Eluting versus Zotarolimus- eluting Stents (ISAR-TEST 5) trial. Circulation 2011;124:624-32.
96. Onuma Y, Serruys PW. Bioresorbable scaffold: the advent of a

new era in percutaneous coronary and peripheral revascularization? Circulation 2011;123:779-97.
97. Serruys PW, Ormiston JA, Onuma Y, Regar E, Gonzalo N, Garcia-Garcia HM, et al. A bioabsorbable everolimus-eluting coronary stent system (ABSORB): 2-year outcomes and results from multiple imaging methods. Lancet 2009;373:897-910.
98. Serruys PW, Onuma Y, Dudek D, Smits PC, Koolen J, Chevalier B, et al. Evaluation of the second generation of a bioresorbable everolimus-eluting vascular scaffold for the treatment of de novo coronary artery stenosis: 12-month clinical and imaging outcomes. J Am Coll Cardiol 2011;58:1578-88.