Journal of Cardiology (2011) 57, 231—238

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/jjcc

Review

Effect of coronary endothelial function on outcomes in patients undergoing percutaneous coronary intervention

Shuichi Hamasaki (MD, FJCC)*, Chuwa Tei (MD, FJCC)

Department of Cardiovascular, Respiratory and Metabolic Medicine, Graduate School of Medicine, Kagoshima University, 8-35-1 Sakuragaoka, Kagoshima, Japan

Received 9 February 2011; accepted 10 February 2011
Available online 12 March 2011

KEYWORDS
Endothelial function;
Percutaneous coronary intervention;
Drug-eluting stent;
Cardiovascular events

Summary Numerous studies have documented the association between endothelial dysfunction and adverse cardiovascular events. For example, coronary artery disease is associated with functional and structural changes of the coronary arteries, resulting in ischemia or plaque rupture, and is highly associated with endothelial dysfunction. Recent data suggest that implantation of drug-eluting stents (DES) can induce coronary artery endothelial dysfunction at follow-up when compared with bare-metal stents (BMS) and that this endothelial dysfunction may be associated with late stent thrombosis. Indeed, despite the superiority of DES in preventing restenosis, the incidence of death and myocardial infarction is similar when comparing DES with BMS. Medical treatment, such as statins, angiotensin-converting enzyme inhibitors, or angiotensin receptor blockers, can improve endothelial dysfunction. Thus, administration of these drugs along with percutaneous coronary intervention (PCI) may be a low-risk strategy to provide therapeutic benefit by stabilizing unstable plaque or by suppressing new lesion formation in patients undergoing PCI.

Contents

* Corresponding author. Tel.: +81 99 275 5318; fax: +81 99 265 8447.
E-mail address: hamasksh@m.kufm.kagoshima-u.ac.jp (S. Hamasaki).

0914-5087/$ — see front matter © 2011 Japanese College of Cardiology. Published by Elsevier Ltd. All rights reserved.
doi:10.1016/j.jjcc.2011.02.003

Introduction

The endothelium, which lies at the interface between the lumen and the vascular smooth muscle, responds to physical and chemical stimuli (e.g. substances within the blood, hemodynamic forces created by the blood) via membrane receptors, with subsequent release of vasoactive and thromboregulatory molecules [e.g. prostacyclin, nitric oxide (NO), endothelins, endothelial cell growth factors, interleukins, plasminogen inhibitors, and von Willebrand factor]. Thus, the healthy endothelium modulates thrombolysis, platelet and leukocyte interactions with the vessel wall, and vascular tone and growth. By contrast, endothelial dysfunction can lead to a variety of pathophysiologic processes, including vasospasm, vasoconstriction, excessive thrombosis, and abnormal vascular proliferation. Numerous studies have documented the association between endothelial dysfunction and adverse cardiovascular events [1—3]. Conversely, drugs that have beneficial effects on endothelial function, including statins, angiotensin-converting enzyme inhibitors (ACEI), and angiotensin receptor II blockers (ARB), can reduce the incidence of adverse cardiac events.

Coronary artery endothelial dysfunction at non-stented reference segments at follow-up is more frequently seen after implantation of first-generation drug-eluting stents (DES) than after implantation of bare-metal stents (BMS). Furthermore, although DES are associated with lower rates of restenosis, the incidence of death and myocardial infarction (MI) remains similar when comparing DES and BMS [4].

Endothelial function and percutaneous coronary intervention

Restenosis and re-endothelialization

Stent placement frequently produces dissection of the media and adventitia. These events induce focal inflammation in the injured vessel that is followed by neointimal thickening and restenosis [5]. Re-endothelialization of the injured vessel may occur at the stented site, protecting against early-stage thrombotic complications and late restenosis [6].

Recent reports suggest that endothelial progenitor cells mobilized from bone marrow into peripheral blood contribute to endothelial cell regeneration. Additionally, regenerated endothelial cells differentiated from bone marrow-derived endothelial progenitor cells also may contribute to re-endothelialization as part of the process of vascular repair [7]. By contrast, it has been hypothesized that after vascular injury, the inflammatory response triggers smooth muscle progenitor cells mobilization from the bone marrow and that these cells migrate to the site of vascular damage, differentiate into smooth muscle cells, proliferate, and cause neointimal hyperplasia [8]. Therefore, under stimulation by vascular injury such as stenting, bone marrow-derived cells may differentiate into endothelial cells and smooth muscle cells, leading to both re-endothelialization and neointimal thickening/restenosis [9].

Endothelial dysfunction is associated with restenosis. For example, Patti et al. [10] reported that impaired flow-mediated dilation independently predicts occurrence of in-stent restenosis in patients undergoing percutaneous coronary intervention (PCI). However, clinical studies using pharmacological agents that improve endothelial function have not observed a decreased rate of restenosis.

Atherothrombotic process caused by stents

A decrease in the antithrombotic capacity of the endothelium and an increase in production of prothrombotic mediators (e.g. tissue factor and plasminogen activator inhibitor) by the endothelium can result in thrombus formation in the context of the exposure of highly thrombogenic substances from ruptured or erosive plaques. Indeed, several studies have documented leukocyte and platelet activation in stented areas while others have recognized a systemic inflammatory response in patients undergoing PCI [11].

DES and late stent thrombosis

First-generation DES implantation is associated with an increased incidence of late stent thrombosis (LST) and very late stent thrombosis (VLST), especially after discontinuation of dual antiplatelet therapy [12]. Several studies have suggested that delayed arterial healing and poor re-endothelialization may play a major role in the pathogenesis of LST and VLST [13].

A meta-analysis study comparing sirolimus-eluting stents (SES) with BMS showed a similar incidence of death and MI. Although there is a sustained reduction in the need

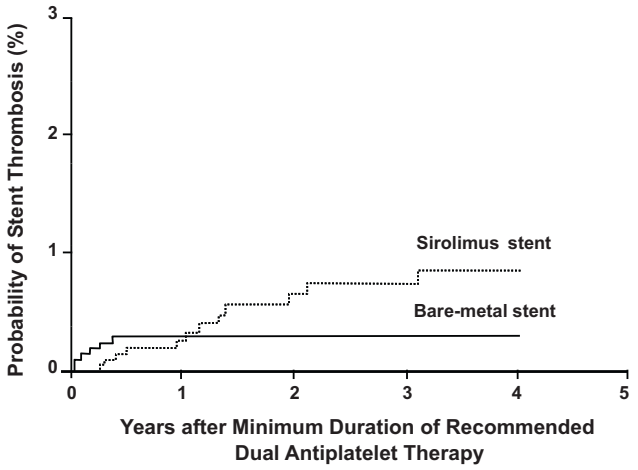

Figure 1 Kaplan—Meier curves for stent thrombosis in the pooled population according to stent type and the duration of dual antiplatelet therapy. The graph shows the probability of stent thrombosis after the use of a trial-defined minimum duration of recommended dual antiplatelet therapy, according to stent type.
Adapted from Kastrati et al. [14].

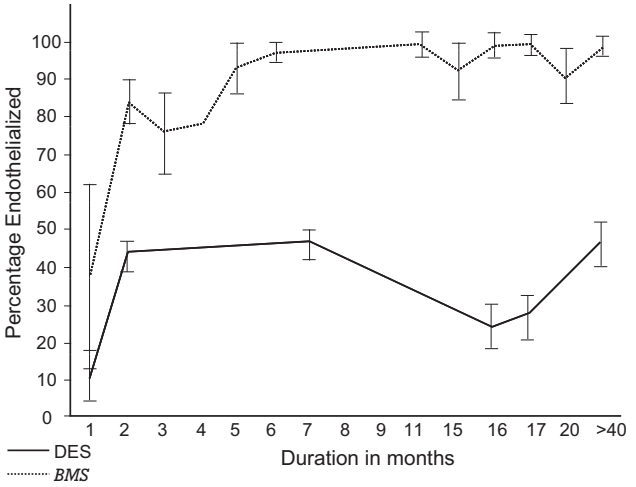

Figure 2 Line chart comparing the percentage of endothelialization in drug-eluting stents (DES) versus bare-metal stent (BMS) as a function of time. Note that DES (solid line) consistently shows less endothelialization when compared with BMS (dashed line), regardless of time point. Even beyond 40 months, DES are not fully endothelialized, whereas BMS are completely endothelialized by six to seven months.
Adapted from Joner et al. [15].

for reintervention after the use of SES, the risk of stent thrombosis with SES is at least as great as that seen with BMS [14] (Fig. 1). Joner et al. [15] reported that first-generation DES caused a significant delay in arterial healing as a result of persistent fibrin deposition and delayed re-endothelialization when compared with BMS implantation. Indeed, LST in the context of first-generation DES is due to a variety of factors, including delayed arterial healing, withdrawal of antiplatelet therapy, malapposition, incomplete apposition, and bifurcation stenting. Finn et al. [16] reported that the most powerful histological predictor of stent thrombosis was endothelial coverage on stent struts (Fig. 2). Non-uniformity of healing is a common finding in first-generation DES with LST and VLST. Thus, incomplete healing of the stented segment may play a major role in the pathophysiology of LST.

DES and coronary endothelial dysfunction

In the first published clinical study of coronary endothelial dysfunction related to first-generation DES, Togni et al. [17] assessed exercise-induced coronary vasodilator function in patients with known coronary artery disease after DES implantation. This study indicated that vasodilatory capacity recovered quickly in atherosclerotic arteries stented with BMS, but not in those stented with SES. Additionally, other studies used an acetylcholine provocation test to show that first-generation DES induced focal dysfunction of endothelium-dependent vasodilation in both proximal and distal non-stented reference segments of coronary arteries for 6—12 months post-stent implantation [18,19]. Obata et al. [20] investigated coronary vasomotor function at two weeks post-SES implantation following successful reperfusion therapy after acute MI. More severe constriction of distal epicardial coronary arteries in response to acetylcholine was seen in patients with SES when compared with those with BMS. Furthermore, coronary blood flow and vascular endothelial growth factor levels were also significantly diminished in patients with SES than in those with BMS. The authors concluded that SES implantation had an adverse effect on endothelium-dependent vasodilation in both epicardial and resistance coronary arteries and reduced vascular endothelial growth factor secretion. Kim et al. [21] reported that paclitaxel-eluting stent (PES) and SES both resulted in greater endothelium-dependent vasoconstriction at corresponding segments when compared with BMS, but that there was no significant difference in endothelium-independent vasodilation when comparing the different stents.

The first-generation DES is associated with increased vasoconstriction when compared with BMS, and this vasoconstriction can have adverse effect on myocardial perfusion. Indeed, severe diffuse coronary artery spasm after either SES or PES has been well documented in clinical case reports [22,23]. Coronary vasoconstriction would result in reduction of coronary blood flow and deterioration of non-laminar flow within the stented vessel, which may be associated with an increase in inflammation and thrombosis.

Secondary prevention in the era of DES

Effect of DES on prevention of cardiac events

DES result in decreased late luminal loss and angiographic restenosis when compared with BMS. This decrease reduces the need for subsequent revascularization procedures [24,25]. In spite of these benefits, DES is associated with several adverse arterial responses, including delayed endothelialization and hypersensitivity to the polymeric coating that regulates drug-dose-and-release kinetics

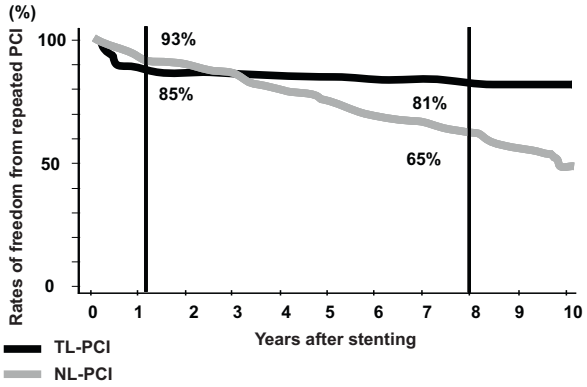

Figure 3 Kaplan—Meier curves showing rates of freedom from repeated percutaneous coronary intervention (PCI) for target lesions (TL) or new lesions (NL). After the initial 14-month period, freedom from TL-PCI reaches a plateau at 84.9 ± 1.8—$80.7 \pm 2.0\%$ over 1—8 years. Although sporadic episodes of late TL-PCI occur beyond five years, late revascularization procedures are predominantly targeted to progressive disease at non-target sites.
Adapted from Kimura et al. [32].

[15,26]. Stone et al. [27] examined the relative safety and efficacy of first-generation DES and BMS in a pooled, patient level analysis of double-blind, randomized trial data. They reported that although the number of episodes of stent thrombosis within the first year was identical among patients with SES and PES and those with BMS, LST between one and four years after implantation was more common with either SES or PES than with BMS. SES and PES were both associated with a marked reduction in target-lesion revascularization, and there were no significant differences in the cumulative rate of death or MI at four years when comparing SES, PES, and BMS.

The adverse events resulting from LST may counteract the reduction in the rates of death or MI that otherwise might result from prevention of restenosis by DES. Indeed, myocardial infarction may be a common clinical presentation of restenosis among patients whose follow-up angiogram is performed for clinical reasons, and MI may occur more frequently in patients with in-stent restenosis than in those with restenosis without stenting [28,29]. Since the majority of episodes of stent thrombosis present as death or MI [30,31], a large reduction in restenosis may counteract the small increase in stent thrombosis.

Most target lesions in patients undergoing re-PCI after stent implantation are new lesions rather than restenotic lesions. Indeed, Kimura et al. [32] reported that late angiography/PCI typically identified/addressed new lesions, which were regarded as the culprit lesions, rather than identifying/addressing late in-stent restenosis (Fig. 3). Thus, new lesions may have a more serious impact on long-term prognosis than restenotic lesions, and prevention of new lesions and stabilization of plaques are critical to reduce coronary events after stent implantation.

New-generation DES and endothelial function

Although first-generation DES have resulted in reduction of in-stent restenosis, long-term safety issues persist. To avoid undesirable side effects, biocompatible and bioabsorbable polymers as well as polymer-free DES have been developed. The zotarolimus-eluting stent (ZES) (Endeavor stent, Medtronic Corporation, Minneapolis, MN, USA) is a tetrazole-containing macrocyclic immunosuppressant that has very low water solubility. Hamilos et al. [33] examined the influence of BMS and four types of DES on endothelium-dependent vasodilation. They reported that SES and PES caused impaired vasodilation, while ZES and biolimus-eluting stents (BES) (Terumo Corporation, Tokyo, Japan) resulted in vasodilatory responses that were similar to BMS. They concluded that the first-generation DES seem to induce endothelial dysfunction of the stented coronary artery, whereas ZES and BES preserved endothelial function to a degree similar to that seen with BMS (Fig. 4). Other studies [34,35] also reported that ZES showed no significant impairment of endothelial function.

The everolimus-eluting stent (EES) (Xience, Abbott Corporation, Abbott Park, IL, USA) is composed of thin cobalt—chromium struts and more biocompatible fluoropolymer with another analogue of rapamycin. Joner et al. [36] investigated the endothelial surface coverage in various polymeric DES using a rabbit peripheral artery. EES showed a greater extent of endothelial coverage on struts at two weeks when compared with ZES, PES, and SES. If stent designs could be improved with thinner struts, more biocompatible polymers, or complete elimination of polymers, it may produce a favorable impact on drug-elution profiles, endothelial coverage, and functional recovery.

Medical therapy with DES implantation

The main goal after PCI is to prevent restenosis, thrombotic occlusion, and cardiac events. Although a variety of drugs have been employed in an effort to prevent restenosis after PCI, none has proven effective. In respect of preventing thrombotic occlusion after stenting, dual antiplatelet therapy using aspirin and thienopyridine derivatives is the standard of care. LST after cessation of the antiplatelet drugs remains an area of intense investigation. Since DES has become the dominant therapy for coronary artery disease, the question of how to prevent coronary events after DES implantation has become a critical issue for medical treatment.

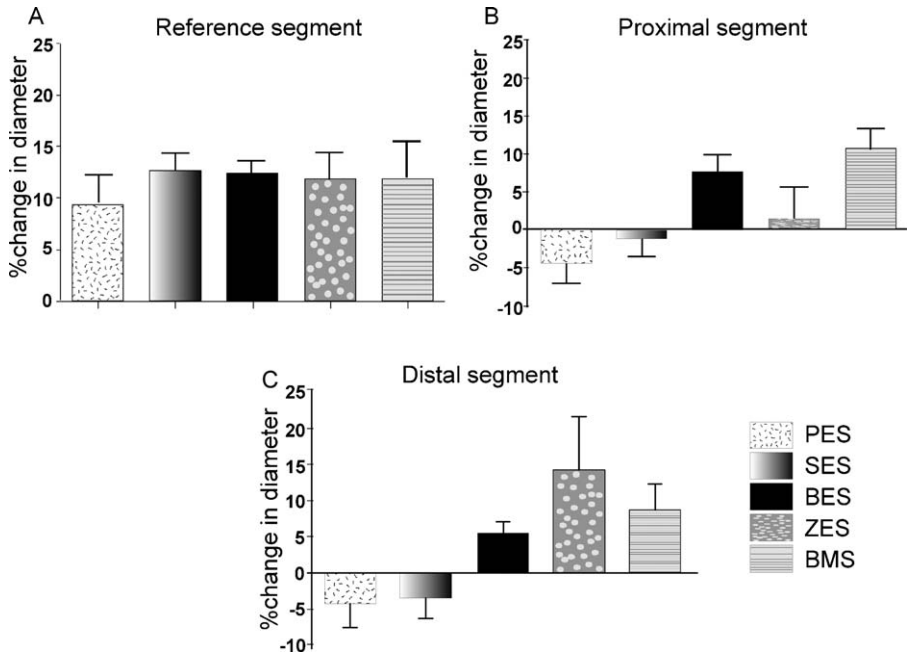

Figure 4 Percent changes in mean diameter from baseline (mean ± SEM) in all stent groups, at reference (A), proximal (B), and distal (C) segment. PES, paclitaxel-eluting stents; SES, sirolimus-eluting stents; BES, biolimus-eluting stent; ZES, zotarolimus-eluting stents; BMS, bare-metal stents.
Adapted from Hamilos et al. [33].

Statins, ACEI/ARB, antiplatelets, and beta-blockers can reduce cardiovascular events and mortality in patients after PCI. These medications have been documented to have long-term benefits in patients with stable coronary artery disease, in patients with acute coronary syndrome, and in patients after PCI [37].

Statins

Secondary prevention trials using statins have shown a significant reduction in cardiovascular events at follow-up after PCI. Chan et al. [38] reported that statin treatment at the time of PCI was associated with a lower 30-day and 6-month all-cause mortality. The Atorvastatin for Reduction of Myocardial Damage during Angioplasty (ARMYDA) study [39] demonstrated a beneficial effect of statins in preventing myocardial damage after PCI in patients undergoing PCI for stable angina. A significant reduction in postprocedural MI was detected in patients receiving atorvastatin. Multivariate regression analysis demonstrated that treatment with atorvastatin was independently associated with a low risk of periprocedural creatine kinase-MB fraction (CK-MB). A meta-analysis by Mood et al. [40] that collected data from six randomized trials showed a significantly reduced incidence of MI in patients undergoing PCI who were treated with statins. In addition, all-cause mortality was significantly lower in the statin group than in the control group. The ''pleiotropic effect'' of statins includes inhibition of inflammation, modulation of endothelium, and attenuation of thrombosis, all of which may provide a clinical benefit in the setting of PCI by preventing postprocedural myocardial damage and cardiovascular events.

ACEI/ARB

Several studies have shown that blockade of the renin—angiotensin system can reduce cardiovascular events [41—43]. However, it is unclear whether ACEI and ARB have vascular protective characteristics that are independent of their effects on blood pressure. ACEI and ARB can prevent cardiovascular events even in high-risk patients undergoing PCI. Kondo et al. [44] demonstrated that the ARB, candesartan, effectively reduced cardiovascular events in patients with coronary artery disease, even when used at a low dose that did not have an effect on blood pressure. Their study focused on patients with coronary artery disease who had a history of PCI, and they suggested that candesartan produced vascular protective effects that were independent of any effect on blood pressure. It has been assumed that prevention of cardiovascular events by ACEI may be due to increases in NO and to increase prostacyclin levels induced by elevated bradykinin concentrations [45]. The specific cardioprotective effects of ARB may be mediated by improvements in endothelial function, inhibition of vasoconstriction, stabilization of vulnerable plaques, inhibition of sympathetic hyperactivity, and reduction of oxidative stress [44].

Antiplatelet therapy

The benefits of long-term antiplatelet therapy with aspirin have been well documented in patients undergoing PCI [37]. Continuation of dual antiplatelet therapy for at least 1 year with aspirin and clopidogrel after PCI leads to a significant reduction in thrombotic events, which has been verified in

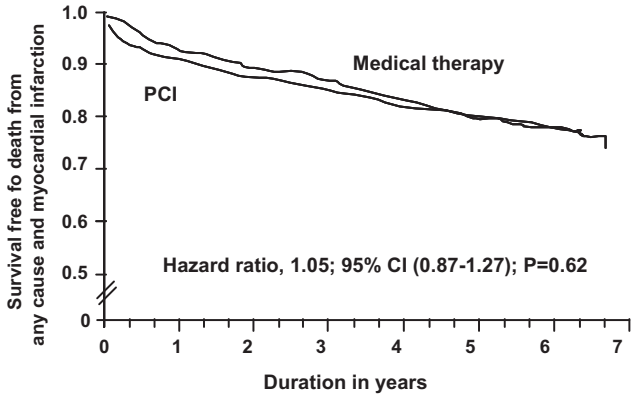

Figure 5 Kaplan—Meier survival curves. The estimated 4.6-year rate of the composite primary outcome of death from any cause and nonfatal myocardial infarction was 19.0% in the percutaneous coronary intervention (PCI) group and 18.5% in the medical-therapy group.
Adapted from Boden et al. [48].

the CREDO trial [46]. Studies have also demonstrated that administration of a 300-mg loading dose of clopidogrel more than 6 h prior to PCI could offer substantial benefit and that long-term dual antiplatelet therapy was relatively safe with efficacy that applied to a broad population of patients undergoing PCI.

Beta-blockers

Beta-blocker therapy is the most effective class of medication against sudden cardiac death and produces a significant long-term survival benefit in patients undergoing PCI. Chan et al. [47] conducted a prospective analysis of PCI in patients treated with beta-blockers at the time of the procedure and reported that beta-blocker therapy was associated with a significant reduction in mortality at 1 year. They also reported that the benefits of beta-blockers are largely proportional to the number of adverse risk factors, such as prior MI, prior coronary artery bypass grafting, left ventricular ejection fraction <35%, multi-vessel coronary artery disease, and multi-vessel PCI. Thus, beta-blockers and PCI should be utilized as complementary therapies.

Adding PCI to optimal medical therapy

The COURAGE trial [48] investigated whether an initial management strategy of PCI with intensive pharmacologic therapy and lifestyle intervention (optimal medical therapy) is superior to optimal medical therapy alone in reducing the risk of cardiovascular events. In patients with stable coronary artery disease, adding PCI to optimal medical therapy did not reduce the risk of death, MI, or the major vascular events when compared with optimal medical therapy alone (Fig. 5). These results suggest that medical therapy is very important when treating patients with coronary artery disease.

Conclusions

Most long-term follow-up analyses show that there is no significant difference in the incidence of death and MI when comparing DES and BMS, and it remains to be determined whether endothelial dysfunction caused by first-generation DES has an effect on these endpoints. The optimal DES should be designed to produce minimal endothelial dysfunction, promote faster recovery of endothelial structure, and maximally inhibit proliferation and migration of smooth muscle cell.

PCI is not as effective when used to address coronary events caused by plaque rupture in new lesions. Therefore, reducing risk factors by optimizing medical therapy may have a more profound effect on preventing cardiovascular events, even in patients undergoing PCI. In-hospital initiation of lipid-lowering therapy using statins along with ACEI/ARB, antiplatelet agents, and beta-blockers is now recommended as the standard care in patients undergoing PCI [3].

References

[1] Lerman A, Zeiher AM. Endothelial function: cardiac events. Circulation 2005;111:363—8.
[2] Suwaidi JA, Hamasaki S, Higano ST, Nishimura RA, Holmes Jr DR, Lerman A. Long-term follow-up of patients with mild coronary artery disease and endothelial dysfunction. Circulation 2000;101:948—54.
[3] Schachinger V, Britten MB, Zeiher AM. Prognostic impact of coronary vasodilator dysfunction on adverse long-term outcome of coronary heart disease. Circulation 2000;101:1899—906.
[4] Stettler C, Wandel S, Allemann S. Outcomes associated with drug-eluting and bare-metal stents: a collaborative network meta-analysis. Lancet 2007;370:937—48.
[5] Well FG, Rogers C. Inflammation and restenosis in the stent era. Arterioscler Thromb Vasc Biol 2002;22:1769—76.
[6] Rogers C, Parikh S, Scifert P, Edelman ER. Endogenous cell seeding: remnant endothelium after stenting enhances vascular repair. Circulation 1996;94:2909—14.
[7] Asahara T, Murohra T, Sullivan A, Silver M, van der Zee R, Li T, Witzenbichler B, Schatteman G, Isner JM. Isolation of putative progenitor endothelial cells for angiogenesis. Science 1997;275:964—6.
[8] Caplice NM, Bunch TJ, Stalboerger PG, Wang S, Simper D, Miller DV, Russel SJ, Litzow MR, Edwards WD. Smooth muscle cells in human coronary atherosclerosis can originate from cells administered at marrow transplantation. Proc Natl Acad Sci USA 2003;100:4754—9.
[9] Inoue T, Sata M, Hikichi Y, Sohma R, Fukuda D, Uchida T, Shimizu M, Komada H, Node K. Mobilization of CD34-positive bone marrow-derived cells after coronary stent implantation: impact on restenosis. Circulation 2007;115:553—61.
[10] Patti G, Pasceri V, Melfi R, Goffredo C, Chello M, D'Ambrosio A, Montesanti R, Sciascio GD. Impaired flow-mediated dilation and risk of restenosis in patients undergoing coronary stent implantation. Circulation 2005;111:70—5.
[11] Serrano Jr CV, Ramires JA, Venturinelli M, Arie S, D'Amico E, Zweiler JL, Pileggi F, da Luz PL. Coronary angioplasty results in leucocyte and platelet activation with adhesion molecule expression. Evidence of inflammatory responses in coronary angioplasty. J Am Coll Cardiol 1997;29:1276—83.
[12] Daemen J, Wenaweser P, Tsuchida K, Abrecht L, Vaina S, Morger C, Kukreja N, Juni P, Sianos G, Hellige G, van Domburg RT, Hess

OM, Boersma E, Meier B, Windecker S, et al. Early and late coronary stent thrombosis of sirolimus-eluting and paclitaxel-eluting stents in routine clinical practice: data from a large two-institutional cohort study. Lancet 2007;369:667—78.
[13] Finn AV, Nakazawa G, Joner M, Kolodgie FD, Mont EK, Gold HK, Virmani R. Vascular responses to drug eluting stents: importance of delayed healing. Arterioscler Thromb Vasc Biol 2007;27:1500—10.
[14] Kastrati A, Mehilli J, Pache J, Kaiser C, Valgimigli M, Kelbaek H, Menichelli M, Sabate M, Suttorp MJ, Baumgart D, Seyfarth M, Pfisterer ME, Schomig A. Analysis of 14 trials comparing sirolimus-eluting stents with bare-metal stents. N Engl J Med 2007;356:1030—9.
[15] Joner M, Finn AV, Farb A, Mont EK, Kolodgie FD, Ladich E, Kutys R, Skorija K, Gold HK, Virmani R. Pathology of drug-eluting stents in humans: delayed healing and late thrombotic risk. J Am Coll Cardiol 2006;48:193—202.
[16] Finn AV, Joner M, Nakazawa G, Kolodgie F, Newell J, John MC, Gold HK, Virmani R. Pathological correlates of late drug-eluting stent thrombosis. Strut coverage as a marker of endothelialization. Circulation 2007;115:2435—41.
[17] Togni M, Windecker S, Cocchia R, Wenaweser P, Cook S, Billinger M, Meier B, Hess OM. Sirolimus-eluting stents associated with paradoxic coronary vasoconstriction. J Am Coll Cardiol 2005;46:231—6.
[18] Hofma SH, van der Glessen WJ, van Dalen BM, Lemos PA, McFadden EP, Sianos G, Ligthart JM, van Essen D, de Feyter PJ, Serruys PW. Indication of long-term endothelial dysfunction after sirolimus-eluting stent implantation. Eur Heart J 2006;27:166—70.
[19] Fuke S, Maekawa K, Kawamoto K, Saito H, Sato T, Hioka T, Ohe T. Impaired endothelial vasomotor function after sirolimus-eluting stent implantation. Circ J 2007;71:220—5.
[20] Obata JE, Kitta Y, Takano H, Kodama Y, Nakamura T, Mende A, Kawabata K, Saitoh Y, Fujioka D, Kobayashi T, Yano T, Kugiyama K. Sirolimus-eluting stent implantation aggravates endothelial vasomotor dysfunction in the infarct-related coronary artery in patients with acute myocardial infarction. J Am Coll Cardiol 2007;50:1305—9.
[21] Kim JW, Suh SY, Choi CU. Six-month comparison of coronary endothelial dysfunction associated with sirolimus-eluting stent versus paclitaxel-eluting stent. J Am Coll Cardiol Intv 2008;1:65—71.
[22] Brott BC, Anayiotos AS, Chapman GD, Anderson PG, Hillegass WB. Severe diffuse coronary artery spasm after drug-eluting stent placement. J Invasive Cardiol 2006;18:284—92.
[23] Maekawa K, Kawamoto K, Fuke S, Yoshioka R, Saito H, Sato T, Hioka T. Images in cardiovascular medicine. Severe endothelial dysfunction after sirolimus-eluting stent implantation. Circulation 2006;113:e850—1.
[24] Morice MC, Serruys PW, Sousa JE, Fajadet J, Ban Hayashi E, Perin M, Colombo A, Schuler G, Barragan P, Guagliumi G, Molnar F, Falotico R, RAVEL Study Group. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. N Engl J Med 2002;346:1773—80.
[25] Stone GW, Ellis SG, Cox DA, Hermiller J, O'Shaughnessy C, Mann JT, Turco M, Caputo R, Bergin P, Greenberg J, Popma JJ, Russell ME, Taxus-IV Investigators. A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. N Engl J Med 2004;350:221—31.
[26] Virmani R, Guagliumi G, Farb A, Musumeci G, Grieco N, Motta T, Mihalcsik L, Tespili M, Valsecchi O, Kolodgie FD. Localized hypersensitivity and late coronary thrombosis secondary to a sirolimus-eluting stent: should we be cautious? Circulation 2004;109:701—5.
[27] Stone GW, Moses JW, Ellis SG, Schoffer J, Dawkins KD, Morice MC, Colombo A, Schampaert E, Grube E, Kirtane AJ, Cutlip DE, Fahy M, Pocock SJ, Mehran R, Leon B. Safety and efficacy of sirolimus- and paclitaxel-eluting coronary stents. N Engl J Med 2007;356:998—1008.
[28] Walters DL, Harding SA, Walsh CR, Wong P, Pomeranstev E, Jang IK. Acute coronary syndrome is a common clinical presentation of in-stent restenosis. Am J Cardiol 2002;89:491—4.
[29] Nayak AK, Kawamura A, Nesto RW, Davis G, Jarbeau J, Pyne CT, Gossman DE, Piemonte TC, Riskalla N, Chauhan MS. Myocardial infarction as a presentation of clinical in-stent restenosis. Circ J 2006;70:1026—9.
[30] Iakovou I, Schmidt T, Bonizzoni E, Ge L, Sangiorgi GM, Stankovic G, Airoldi F, Chieffo A, Montorfano M, Carino M, Michev I, Corvaja N, Briguori C, Gerckens U, Grube E, et al. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. JAMA 2005;293:2126—30.
[31] Ong AT, Hoye A, Aoki J, van Mieghem CA, Rodriguez Granillo GA, Sonnenschein K, Reger E, McFadden EP, Sianos G, van der Giessen WJ, de Jaegere PP, de Feyter P, van Domburg RT, Serruys PW. 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.
[32] Kimura T, Abe K, Shizuta S, Odashiro K, Yoshida Y, Sakai K, Kaitani K, Inoue K, Nakagawa Y, Yokoi H, Iwabuchi M, Hamasaki N, Nosaka H, Nobuyoshi M. Long-term clinical and angiographic follow-up after coronary stent placement in native coronary arteries. Circulation 2002;105:2986—91.
[33] Hamilos M, Sarma J, Ostojic M, Cuisset T, Sarno G, Melikian N, Ntalianis A, Muller O, Barbato E, Beleslin B, Sagic D, De Bruyne B, Bartunek J, Wijns W. Interference of drug-eluting stents with endothelium-dependent coronary vasomotion: evidence for device-specific responses. Circ Cardiovasc Interv 2008;1:193—200.
[34] Shin DI, Seung KB, Kim PJ, Chang K, Choi JK, Jeon DS, Kim MJ, Lee MY, Chung WS. Long-term coronary endothelial function after zotarolimus-eluting stent implantation. A 9 month comparison between zotarolimus-eluting and sirolimus-eluting stents. Int Heart J 2008;49:639—52.
[35] Kim JW, Seo HS, Park JH, Na JO, Choi CU, Lim HE, Kim EJ, Rha SW, Park CG, Oh DJ. 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.
[36] Joner M, Nakazawa G, Finn AV, Quee SC, Coleman L, Acampado E, Wilson PS, Skorija K, Cheng Q, Xu X, Gold HK, Kolodgie FD, Virmani R. Endothelial cell recovery between comparator polymer-based drug-eluting stents. J Am Coll Cardiol 2008;52:333—42.
[37] Braunwald E, Antman EM, Beasley JW, Califf RM, Cheitlin MD, Hochman JS, Jones RH, Kereiakes D, Kupersmith J, Levin TN, Pepine CJ, Schaeffer JW, Smith 3rd EE, Steward DE, Theroux P, et al. ACC/AHA guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction—2002: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2002;106:1893—900.
[38] Chan AW, Bhatt DL, Chew DP, Quinn MJ, Moliterno DJ, Topol EJ, Ellis SG. Early and sustained survival benefit associated with statin therapy at the time of percutaneous coronary intervention. Circulation 2002;105:691—6.
[39] Pasceri V, Patti G, Nusca A, Pristipino C, Richichi G, Di Sciascio G, ARMYDA Investigators. Randomized trial of atorvastatin for reduction of myocardial damage during coronary intervention: results from the ARMYDA study. Circulation 2004;110:674—8.
[40] Mood GR, Bavry AA, Roukoz H, Bhatt DL. Meta-analysis of the role of statin therapy in reducing myocardial infarction follow-

ing elective percutaneous coronary intervention. Am J Cardiol 2007;100:919—23.
[41] Yasuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. N Engl J Med 2000;342:145—53.
[42] Fox KM. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomized, double-blind, placebo-controlled, multicentre trial (the EUROPA study). Lancet 2003;362:782—8.
[43] ONTARGET Investigators, Yusuf S, Teo KK, Pogue J, Dyal L, Copland I, Schumacher H, Dagenais G, Sleight P, Anderson C. Telmisartan, ramipril, or both in patients at high risk for vascular events. N Engl J Med 2008;358:1547—59.
[44] Kondo J, Sone T, Mukawa H, Morishima I, Uesugi M, Kono T, Kosaka T, Yoshida T, Numaguchi Y, Matsui H, Murohara T, Okumura K. Effects of low-dose angiotensin II receptor blocker candesartan on cardiovascular events in patients with coronary artery disease. Am Heart J 2003;146:e20.
[45] Dzau VJ. Theodore Cooper Lecture: tissue angiotensin and pathobiology of vascular disease: a unifying hypothesis. Hypertension 2001;37:1047—52.
[46] Steinhubl SR, Berger PB, Mann 3rd JT, Fry ET, DeLago A, Wilmer C, Topol EJ, CREDO Investigators. Clopidogrel for the Reduction of Events During Observation. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. JAMA 2002;288:2411—20.
[47] Chan AW, Quinn MJ, Bhatt DL, Chew DP, Moliterno DJ, Topol EJ, Ellis SG. Mortality benefit of beta-blockade after successful elective percutaneous coronary intervention. J Am Coll Cardiol 2002;40:669—75.
[48] Boden WE, O'Rourke RA, Teo KK, Hartigan PM, Maron DJ, Kostuk WJ, Knudtson M, Dada M, Casperson P, Harris CL, Chaitman BR, Shaw L, Gosselin G, Nawaz S, Title LM, et al. Optimal medical therapy with or without PCI for stable coronary disease. N Engl J Med 2007;356:1503—16.