

Percutaneous coronary intervention for unprotected left main coronary artery stenosis

Seung-Jung Park, Young-Hak Kim

Seung-Jung Park, Young-Hak Kim, Cardiac Center, Asan Medical Center, University of Ulsan College of Medicine, Seoul 138-736, South Korea

Author contributions: Park SJ designed the study, wrote the manuscript and was involved in editing the manuscript; Kim YH collected the data of clinical studies and was also involved in editing the manuscript.

Correspondence to: Seung-Jung Park, MD, PhD, Cardiac Center, Asan Medical Center, University of Ulsan College of Medicine, 388-1 Pungnap-dong, Songpa-gu, Seoul 138-736, South Korea. sjpark@amc.seoul.kr

Telephone: +82-2-30104812 Fax: +82-2-4865918

Received: March 19, 2010 Revised: April 5, 2010

Accepted: April 9, 2010

Published online: April 26, 2010

© 2010 Baishideng. All rights reserved.

Key words: Bypass surgery; Left main; Prognosis; Restenosis; Stent

Peer reviewer: Paul Erne, MD, Professor, Head, Department of Cardiology, Luzerner Kantonsspital, CH-6000 Luzern 16, Switzerland

Park SJ, Kim YH. Percutaneous coronary intervention for unprotected left main coronary artery stenosis. *World J Cardiol* 2010; 2(4): 78-88 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v2/i4/78.htm> DOI: <http://dx.doi.org/10.4330/wjc.v2.i4.78>

Abstract

Hemodynamically significant left main coronary artery stenosis (LMCA) is found in around 4% of diagnostic coronary angiograms and is known as unprotected LMCA stenosis if the left coronary artery and left circumflex artery has no previous patent grafts. Previous randomized studies have demonstrated a significant reduction in mortality when revascularization by coronary artery bypass graft (CABG) surgery was undertaken compared with medical treatment. Therefore, current practice guidelines do not recommend percutaneous coronary intervention (PCI) for such a lesion because of the proven benefit of surgery and high rates of restenosis with the use of bare metal stents. However, with the advent of drug-eluting stents (DES), the long term outcomes of PCI with DES to treat unprotected LMCA stenoses have been acceptable. Therefore, apart from the current guidelines, PCI for treatment of unprotected LMCA stenosis is often undertaken in individuals who are at a very high risk of CABG or refuse to undergo a sternotomy. Future randomized studies comparing CABG vs PCI using DES for treatment of unprotected LMCA stenosis would be a great advance in clinical knowledge for the adoption of appropriate treatment.

INTRODUCTION

Because of the long-term benefit of coronary artery bypass graft (CABG) surgery with reference to medical therapy, CABG has been the standard treatment for unprotected left main coronary artery (LMCA) stenosis^[1-3]. However, with the advancement of techniques and equipment, the percutaneous interventional approach for implantation of coronary stents has been shown to be feasible for patients with unprotected LMCA stenosis^[3]. In particular, the recent introduction of drug-eluting stents (DES), together with advances in periprocedural and postprocedural adjunctive pharmacotherapies, have improved the outcome of percutaneous coronary interventions (PCI) for these complex coronary lesions^[4-29]. Nonetheless, PCI for unprotected LMCA stenosis is still indicated for patients at high surgical risk or with emergent clinical situations, such as bailout procedure or acute myocardial infarction (MI), as an alternative therapy to CABG, because a recent randomized study failed to prove superiority or at least non-inferiority of DES placement for unprotected LMCA stenosis compared with CABG^[21,30,31]. In contrast, there is a concern about the long-term safety of DES. The incidence of late stent

thrombosis has been reported to be higher with DES compared with bare-metal stent (BMS) implantation^[32-36]. Indeed, the United States Food and Drug Administration has warned that the risk of stent thrombosis may outweigh the benefits of DES in off-label use, such as for unprotected LMCA stenosis^[37].

Patients with LMCA stenosis have been traditionally classified into two subgroups: protected (a previous patient CABG surgery graft to one or more major branches of the left coronary artery) and unprotected LMCA diseases (without such bypasses). In this review, we evaluated the current outcomes of PCI with DES in a series of research studies conducted across several countries.

DEFINITION OF SIGNIFICANT LMCA STENOSIS

Coronary angiography has been the standard tool to determine the severity of coronary artery disease. Although the traditional cutoff for significant coronary stenosis has been a diameter stenosis of 70% in non-LMCA lesions, this cutoff in LMCA has been a diameter stenosis of 50%. However, because the conventional coronary angiogram is only a lumenogram providing information about lumen diameter but yielding little insight into lesion and plaque characteristics themselves, it has several limitations due to peculiar anatomic and hemodynamic factors. In addition, the LMCA segment is the least reproducible of any coronary segment with the largest reported intraobserver and interobserver variabilities^[38-40]. Therefore, intravascular ultrasound (IVUS) is often used to assess the severity of LMCA stenosis.

A decision of significant stenosis at the LMCA necessitating revascularization should be determined by the absolute luminal area, not by the degree of plaque burden or area stenosis. Because of remodeling, a larger plaque burden can exist in the absence of lumen compromise^[41]. Abizaid *et al.*^[42] reported a 1-year follow-up in 122 patients with LMCA. The minimal lumen diameter by IVUS was the most important predictor of cardiac events with a 1-year event rate of 14% in patients with a minimal luminal diameter < 3.0 mm. Fassa *et al.*^[43] reported that the long-term outcome of patients having LMCA with a minimal lumen area < 7.5 mm² without revascularization was considerably worse than those who were revascularized. Jasti *et al.*^[44] compared fractional flow reserve (FFR) and IVUS in patients with an angiographically ambiguous LMCA stenosis. However, accurate assessment of ostial LMCA is not always possible. Practically, it is important to keep the IVUS catheter coaxial with the LMCA and to disengage the guiding catheter from the ostium so that the guiding catheter is not mistaken for a calcific lesion with a lumen dimension equal to the inner lumen of the guiding catheter. When assessing distal LMCA disease, it is important to begin imaging in the most co-axial branch vessel. Nevertheless, distribution of plaque in the distal LMCA is not always

uniform; and it may be necessary to image from more than one branch back into the LMCA.

FFR may play an adjunctive role in determining significant stenosis at the LMCA. FFR is the ratio of the maximal blood flow achievable in a stenotic vessel to the normal maximal flow in the same vessel^[45]. A FFR value of < 0.75 is considered a reliable indicator of significant stenosis producing inducible ischemia^[46]. In patients with an angiographically equivocal LMCA stenosis, a strategy of revascularization vs medical therapy based on an FFR cut-point of 0.75 was associated with an excellent survival and freedom from events for up to 3 years of follow-up^[44].

OUTCOMES OF DES

Safety in terms of the risk of death, MI or stent thrombosis

Although there are disputes regarding the long-term safety of DES, the possibility of late or very late thrombosis is still the major factor limiting global use of DES, especially for unprotected LMCA stenosis. Table 1 depicts the results of recent studies demonstrating the outcomes of DES implantation for unprotected LMCA stenosis. It is clear that none of the clinical studies showed a significant increase in the cumulative rates of death or MI following DES implantation for unprotected LMCA, as compared with BMS. In three early pilot studies which compared the outcomes of DES with those of BMS, the incidence of death, MI or stent thrombosis were comparable in the two stent types during the procedure and at follow-up^[4-6]. Of interest, in the study by Valgimigli *et al.*^[6], DES was associated with a significant reduction in both the rate of MI [hazard ratio (HR) = 0.22, *P* = 0.006] and the composite of death or MI (HR = 0.26, *P* = 0.004) compared with BMS. Considering that restenosis can lead to an acute MI in 3.5% to 19.4%, a significant reduction in restenosis achieved by DES might contribute to the better outcome seen with DES. In fact, a previous study suggested that restenosis at the BMS in LMCA could present as late mortality^[47]. In addition, more frequent repeat revascularizations to treat BMS restenosis, in which CABG is the standard of care for unprotected LMCA, may also be related to an increase in complications compared with DES. A recent meta-analysis supported the safety of DES which did not increase the risk of death, MI, or stent thrombosis compared with BMS^[18]. In this meta-analysis of 1278 patients with unprotected LMCA stenosis, during a median of 10 mo, the mortality rate in DES-based PCI was only 5.5% (3.4% to 7.7%) and was not higher than BMS-based PCI.

Recently, 3 studies assessed the risk of safety outcomes following the use of DES compared with BMS over 2 years^[25-27]. After rigorous adjustment using propensity score or the IPTW (inverse-probability-of-treatment weighting) method to avoid selection bias, which was an inherent limitation of the studies, DES was not associated with a long-term increase in death or MI. Of

Table 1 Outcomes of drug-eluting stents for unprotected left main coronary artery stenosis

	Chieffo <i>et al.</i> ^[41]		Valgimigli <i>et al.</i> ^[61]		Park <i>et al.</i> ^[51]		de Lezo <i>et al.</i> ^[28]	Price <i>et al.</i> ^[11]	Kim <i>et al.</i> ^[20]	Meliga <i>et al.</i> ^[29]	Mehilli <i>et al.</i> ^[48]	
Stent type	SES, PES	BMS	SES, PES	BMS	SES	BMS	SES	SES	SES, PES	SES, PES	PES	SES
Design	Single center study		Single center study		Single center study		Single center study	Single center study	Single center study	Multicenter DELFT study	Multicenter randomized study	
No. of patient	85	64	95	86	102	121	52	50	63	358	302	305
Age (yr)	63	66	64	66	60	58	63	69	67	66	69	69
Ejection fraction (%)	51 ^a	57	41	42	60	62	57	NA	50	49	53	54
Acute myocardial infarction (%)	NA	NA	17	20 ^a	9.8	6.6	NA	NA	5	8.4	NA	NA
Bifurcation involvement (%)	81 ^a	58	65	66	71 ^a	43	42	94	54	74	63	63
Two-stent technique (%)	74	NA	40 ^a	15	41 ^a	18	18	89	17	43	51	49
Initial clinical outcomes	In-hospital		30 d		In-hospital		In-hospital	In-hospital	In-hospital	In-hospital	30 d	
Death (%)	0	0	11	7	0	0	0	0	0	3	1	2
Myocardial infarction (%)	6	8	4	9	7	8	4	8	10	7	4	4
Stent thrombosis (%)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	4.0	0.0	NA	0.3	0.7
TVR (%)	0.0	2.0	0.0	2.0	0.0	0.0	0.0	6.0	0.0	0.8	0.3 (TLR)	0.7 (TLR)
Any events, %	NA	NA	15.0	19.0	7.0	8.0	4.0	10.0	10.0	11.0	5.0	4.6
Long-term outcomes (%)	Cumulative		Cumulative		Cumulative		Cumulative	After discharge	Cumulative	3 yr	2 yr	
Mean follow-up (mo)	6	6	17	12	12	12	12	9	11	NA	NA	NA
Death (%)	4	14	14	16	0	0	0	10	5	9	10	9
Myocardial infarction (%)	NA	NA	4 ^a	12	7	8	4	2	11	9	5	5
Stent thrombosis (%)	0.1	0.0	NA	NA	0.0	0.0	0.0	0.0	0.2	0.6	0.3	0.7
TVR (%)	19	31	6 ^a	12	2 ^a	17	2	38	19	14	9 (TLR)	11 (TLR)
Any MACE (%)	NA	NA	24 ^a	45	8 ^a	26	NA	44	29	32	21	21

^a*P* < 0.05 between drug-eluting stent (SES and/or PES) *vs* BMS. BMS: Bare metal stent; NA: Not available; MACE: Major adverse cardiac events including death, myocardial infarction, and TVR; PES: Paclitaxel-eluting stent; SES: Sirolimus-eluting stent; TVR: Target vessel revascularization; DELFT: Drug Eluting stent for left main.

interest, Palmerini *et al.*^[26] showed a survival benefit of DES over 2 years. These studies supported previous pilot studies in that elective PCI with DES for unprotected LMCA stenosis seems to be a safe alternative to CABG.

With regard to the risk of stent thrombosis, in the series of LMCA DES studies, the incidence of stent thrombosis at 1 year ranged from 0% to 4% and was not statistically different from that with BMS^[4-6]. Recently, a multicenter study confirmed this finding, where the incidence of definite stent thrombosis at 2 years was only 0.5% in 731 patients treated with DES^[19]. In addition, the Drug Eluting stent for left main multicenter study, which included 358 patients undergoing LMCA stenting with DES, reported that the incidence of definite, probable, and possible stent thrombosis was 0.6%, 1.1% and 4.4%, respectively, at 3 years^[29]. In recent large multicenter studies for the ISAR-LEFT-MAIN (Intracoronary Stenting and Angiographic Results: Drug-Eluting Stents for Unprotected Coronary Left Main Lesions) study or MAIN-COMPARE (Comparison of Percutaneous Coronary Angioplasty Versus Surgical Revascularization) study, the

incidence of definite or probable stent thrombosis was less than 1%^[21,48]. However, because these studies were underpowered to completely exclude the possibility of an increased risk of stent thrombosis over this long time period, further research needs to be performed. Previous studies assessing the long-term outcomes of DES for complex lesions showed inhomogeneous outcomes. For example, recent large trials evaluating the safety of DES for complex lesions showed comparable risks of death or MI for the two stent types^[49,50]. The recent large NHLBI (National Heart, Lung, and Blood Institute) study in the United States reported that, the off-label use of DES, compared with BMS, for similar indications was associated with a comparable 1-year risk of death and a lower 1-year risk of MI after adjustment^[49]. Of interest, a large study of 13353 patients in Ontario found that the 3-year mortality rate in a propensity-matched population was significantly higher with BMS than with DES^[50]. The comparable or lower incidence of death or MI using DES compared with BMS may be due, at least in part, to the off-setting risks of restenosis *vs* stent thrombosis.

Prognostic factors

Several attempts have been made to predict the long-term outcome of complex LMCA intervention. Predictably, periprocedural and long-term mortality strongly depend on the patient's clinical presentation. In the ULTIMA (Unprotected Left Main Trunk Investigation Multicenter Assessment) multicenter study, which included 279 patients treated with BMS, 46% of whom were inoperable or high surgical risk, the in-hospital mortality was 13.7%, and the 1-year incidence of all-cause mortality was 24.2%^[51]. On the other hand, in the 32% of patients with low surgical risk (age < 65 years and ejection fraction > 30%), there were no periprocedural deaths and the 1-year mortality was 3.4%. Similarly, in patients with DES implantation, high surgical risk represented by high EuroSCORE or Parsonnet score, was the independent predictor of death or MI^[13,52]. Therefore, it is recommended that continued attention should be paid to this procedure in patients at high surgical risk. More recently, the 'SYNTAX (Synergy between PCI with Taxus and Cardiac Surgery score)', which was an angiographic risk stratification model, has been created to predict long-term outcome after coronary revascularization with either PCI or CABG^[30]. In the recent SYNTAX study comparing PCI with paclitaxel-eluting stent *vs* CABG for multivessel or LMCA disease, the long-term mortality was significantly associated with the SYNTAX score^[30]. Therefore, for patients with high clinical risk profiles or complex lesion morphologies, who are defined using these risk stratification models, the PCI procedures need to be performed by experienced interventionalists with the aid of IVUS, mechanical hemodynamic support, and optimal adjunctive pharmacotherapies, after judicious selection of patients.

Recurrent revascularization

Compared with BMS, DES reduced the incidence of angiographic restenosis and subsequently the need for repeat revascularization in unprotected LMCA stenosis. In early pilot studies, the 1-year incidence of repeat revascularization following DES implantation was 2%-19% as compared with 12%-31% following BMS implantation (Table 1)^[4-6]. Fortunately, in a long-term study of 3 years, the incidence of repeat revascularization remained steady without significant observation of the "late catch-up" phenomenon of late restenosis noted after coronary brachytherapy^[21]. Recently, two larger studies confirmed the efficacy of DES^[25,27]. The risk of target lesion revascularization over 3 years was reduced by 60% with use of DES^[27].

The risk of restenosis was significantly influenced by lesion location. DES treatment for ostial and shaft LMCA lesions had a very low incidence of angiographic or clinical restenosis^[14]. In a study which included 144 patients with ostial or shaft stenosis in three cardiac centers, angiographic restenosis and target vessel revascularization at 1 year occurred in only 1 (1%) and 2 (1%) patients, respectively. Although, in those studies, the lack

of availability of DES sizes larger than 3.5 mm imposed an overdilation strategy to match the LMCA reference diameter, there were no cardiac deaths, MI or stent thrombosis in this study.

In contrast, PCI for LMCA bifurcation has been more challenging although the prevalence was more than 60% in previous studies^[4-6,10,21]. However, repeat revascularization was exclusively performed in patients with PCI for bifurcation stenosis^[4-6]. A recent study assessing the outcomes of LMCA DES showed that the risk of target vessel revascularization was 6-fold (95% CI: 1.2-29) in bifurcation stenosis compared with non-bifurcation stenosis (13% *vs* 3%)^[13]. The risk of bifurcation stenosis was highlighted in a recent study by Price *et al*^[11] where the target lesion revascularization rate after sirolimus-eluting stent implantation was 38% (11). In this study, 94% (47/50) of patients had lesions at the bifurcation and 98% underwent serial angiographic follow-up at 3 and/or 9 mo. This discouraging result questioned the efficacy of DES and suggested the need for meticulous surveillance using angiographic follow-up in PCI for LMCA bifurcation stenosis. However, this study was limited by the exclusive use of a complex stenting strategy (two stents in both branches) in 84% of patients, which may have increased the need for repeat revascularization. Although, there is an ongoing debate^[53], a recent report proposed that the complex stenting technique might be associated with the high occurrence of restenosis compared with the simple stenting technique^[8]. A subgroup analysis of a large Italian study supported this hypothesis that a single stenting strategy for bifurcation LMCA lesions had a comparable long-term outcome to that for non-bifurcation lesions^[24]. Taken together, these findings suggest that the simple stenting approach (LMCA to left anterior descending artery with optional treatment in the circumflex artery) is primarily recommended in patients with a relatively patent or diminutive circumflex artery. Furthermore, future stent platforms specifically designed for LMCA bifurcation lesions may provide better scaffolding and more uniform drug delivery to the bifurcation LMCA stenosis.

With regard to the differential benefit of the type of DES used for the prevention of restenosis, the two most widely used DESs, sirolimus- and paclitaxel-eluting stents, were evaluated in previous studies. In an early study, the research trial, which compared these two DESs, a comparable incidence of major adverse cardiac events was shown with 25% in the sirolimus- (55 patients) and 29% in the paclitaxel-eluting stent (55 patients)^[12]. The recent ISAR-Left-Main study compared 305 patients receiving sirolimus- and 302 patients receiving paclitaxel-eluting stents in a prospective randomized design^[48]. At 1 year, major adverse events occurred in 13.6% of the paclitaxel- and 15.8% of the sirolimus-eluting stent groups with 16.0% and 19.4% of restenosis, respectively (*P* = NS). The use of a second generation DES is being evaluated in many studies.

Table 2 Features favoring PCI or CABG

	Indications in favor of PCI	Indications in favor of CABG
Absolute	Suitable coronary anatomy for stenting with preserved left ventricular function ($\geq 40\%$) Patient who refuses surgery	Patient who refuses PCI Contraindication to antiplatelet therapy including aspirin, heparin, and thienopyridine (ticlopidine or clopidogrel) History of serious allergic reaction to stainless steel, drugs on drug-eluting stents, and contrast agent History of known coagulopathy or bleeding diathesis Pregnant women
Relative	Lesion restricted to the LMCA ostium or shaft Isolated LMCA lesion Bail-out procedure (e.g. dissection at the LMCA complicated during angiography or PCI) Acute myocardial infarction at the LMCA, in which emergent revascularization is necessary Cardiogenic shock due to LMCA stenosis, in which emergent revascularization is necessary Age ≥ 80 yr Serious co-morbid disease (e.g. chronic lung disease, poor general performance, <i>etc.</i>) Limited life expectancy of less than 1 yr Prior CABG Coronary anatomy, unsuitable for CABG (e.g. poor distal run-off)	Complex coronary anatomies at LMCA, unsuitable for stenting (e.g. severe calcification, severe tortuosity, <i>etc.</i>) Total occlusions at other major epicardial coronary arteries (≥ 2) Multivessel stenosis except LMCA Decreased left ventricular dysfunction ($< 40\%$) Extensive peripheral vascular disease, in which placement of guiding catheter or intra-aortic balloon pump is not likely to be performed In-stent restenosis at the LMCA, in which repeat PCI is not likely to be performed

CABG: Coronary artery bypass graft surgery; LMCA: Left main coronary artery; PCI: Percutaneous coronary intervention.

COMPARISON WITH CORONARY ARTERY BYPASS SURGERY

It is surprising to note that current guidelines for unprotected LMCA treatment, in which elective PCI for patients who are treatable with bypass surgery is a contraindication, is based mostly on 20-year-old clinical trials^[1-3]. These studies demonstrated a definite benefit of survival with CABG in LMCA stenosis compared with medical treatment. However, application of these results to current practice seems inappropriate because surgical technique as well as medical treatment in these studies is outdated by today's standards and no randomization studies between PCI and CABG with enough power have been conducted. The lack of data on the current CABG procedure used in unprotected LMCA stenosis further precludes a theoretical comparison of the two revascularization strategies. Table 2 lists the patient and lesion characteristics favoring PCI or CABG based on current expert opinion and evidence.

Recently, several non-randomized studies comparing the safety and efficacy of DES treatment for unprotected LMCA stenosis, compared with CABG, were published (Table 3). Chieffo *et al.*^[7] compared retrospectively the outcomes of 107 patients undergoing DES placement with 142 patients undergoing CABG. They showed that DES was associated with a non-significant mortality benefit (odds ratio = 0.331, $P = 0.167$) and a significantly lower incidence of composites of death or MI (0.260, $P = 0.0005$) and death, MI, or cerebrovascular accident (odds ratio = 0.385, $P = 0.01$) at 1-year follow-up. Conversely, CABG was correlated with a lower occurrence

of target vessel revascularization (3.6% *vs* 19.6%, $P = 0.0001$). These findings were supported by Lee *et al.*^[9], in 50 patients with DES placement and 123 patients with CABG. In this study, although the DES group had slightly higher surgical risk, the rate of mortality or MI at 30 d was comparable between the two treatments. At 1-year follow-up, DES patients had a non-significantly better clinical outcome compared with CABG, reflected by overall survival (96% *vs* 85%) and survival freedom from death, MI, target vessel revascularization, or adverse cerebrovascular events (83% *vs* 75%). However, the survival freedom from repeat revascularization at 1 year remained non-significantly higher for CABG compared to the DES (95% *vs* 87%). The results of a recent multicenter study were in agreement with the previous two reports with regard to the safety outcomes^[10]. The PCI group treated with BMS or DES (60%) had a similar incidence of death and/or MI, but a higher incidence of target lesion revascularization compared with the CABG group. Similar safety with PCI compared with CABG was observed in older patients (age ≥ 75 years) by Palmerini *et al.*^[15]. Recently, a randomized study comparing PCI ($n = 52$) *vs* CABG ($n = 53$) was undertaken in 105 patients with unprotected LMCA stenosis^[17]. PCI was performed using either BMS (65%) or DES (35%). The primary end point was the change in left ventricular ejection fraction 12 mo after the intervention. A significant increase in ejection fraction was noted only in the PCI group ($3.3\% \pm 6.7\%$ after PCI *vs* $0.5\% \pm 0.8\%$ after CABG, $P = 0.047$). In contrast, at 1-year after the procedure, repeat revascularization was significantly lower in the CABG group ($n = 5$) than in the PCI group ($n =$

Table 3 Comparison of drug-eluting stents to coronary artery bypass surgery for unprotected left main coronary artery stenosis

	Chieffo <i>et al</i> ^[7]		Lee <i>et al</i> ^[9]		Palmerini <i>et al</i> ^[15]		Buszman <i>et al</i> ^[17]		Seung <i>et al</i> ^[21]	
Study design	Registry		Registry		Registry		Randomized study		Registry	
Treatment type	PCI with SES, PES	CABG	PCI with SES	CABG	PCI with SES	CABG	PCI with BMS, DES	CABG	PCI with BMS, DES	CABG
No. of patient	107	142	50	123	157	154	52	53	1102	1138
Age (yr)	64	68	72	70	73 ^a	69	61	61	62	64
Ejection fraction (%)	52	52	51	52	52	55	54	54	62	60
EuroSCORE or Parsonnet score (Lee)	4.4	4.3	18.0 ^a	13.0	6.0 ^a	5.0	3.3	3.5	NA	NA
Initial clinical outcomes	In-hospital		30 d		30 d		30 d		NA	
Death (%)	0.0	2.0	2.0	5.0	3.2	4.5	0.0	0.0	NA	NA
Myocardial infarction (%)	9.0	26.0	0.0	2.0	4.5	1.9	1.9	3.8	NA	NA
TVR (%)	0.0	2.0	0.0	1.0	0.6	0.6	1.9	0.0	NA	NA
Any MACE (%)	NA	NA	0.0	8.0	NA	NA	NA	NA	NA	NA
Cerebrovascular accident	0.0	1.4	2.0 ^a	17.0	NA	NA	0.0	2.0	NA	NA
Long-term clinical outcomes	Cumulative after discharge		Kaplan-Meier		Cumulative		At 1 yr		Kaplan-Meier at 3 yr for propensity-matched cohort	
Mean follow-up (mo)	12.0	12.0	6.0	6.0	14.0	14.0	NA	NA	33.9	38.4
Death (%)	2.8	6.4	4.0	13.0	13.4	12.3	1.9	7.5	7.9	7.8
Myocardial infarction (%)	0.9	1.4	NA	NA	8.3	4.5	1.9	5.7	NA	NA
TVR (%)	19.6 ^a	3.6	7.0	1.0	25.5 ^a	2.6	28.8 ^a	9.4	12.6	2.6
Cerebrovascular accident (%)	0.9	0.7	NA	NA	NA	NA	0.0	3.8	NA	NA
Any events (%)	NA	NA	11.0	17.0	NA	NA	NA	NA	NA	NA

^a*P* < 0.05 between PCI *vs* CABG.

15), although the incidence of death or MI was comparable between the two groups. However, this study was underpowered to assess the long-term clinical effectiveness of PCI compared with CABG.

Stronger evidence for the feasibility of PCI as an alternative to CABG comes from a recent large trial, the MAIN-COMPARE study^[21]. In this study, data were analyzed from 2240 patients with unprotected LMCA disease treated at 12 medical centers in Korea. Of these, 318 were treated with BMS, 784 were treated with DES, and 1138 underwent CABG. To avoid bias due to the non-randomized study design, a novel adjustment was performed using propensity-score matching in the overall population at separate periods. In the first and second waves, BMS and DES were exclusively used, respectively. The outcome of stenting in the overall population and each wave were compared with those of concurrent CABG. During 3 years of follow-up, patients treated with stenting were nearly 4 times as likely to need a repeat revascularization compared to those who underwent CABG (HR = 4.76, 95% CI: 2.80-8.11). However, the rates of death (HR = 1.18, 95% CI: 0.77-1.80) and the combined rates of death, MI and stroke (HR = 1.10, 95% CI: 0.75-1.62) were not significantly higher with stenting compared with CABG. A similar pattern was also observed in patients treated with DES or BMS. Another interesting finding in this study was that the majority of repeat revascularizations in PCI patients were treated with repeat PCI instead of CABG. Given the fact that the recommendation for CABG for unprotected LMCA disease was based mostly on survival benefit compared with medical treatment, the lack of a statistically significant difference in mortality may support PCI

as an alternative option to bypass surgery. In addition, the current recommendation of routine angiographic surveillance at 6-9 mo after PCI for unprotected LMCA stenosis might increase the unnecessary need for repeat revascularization due to 'oculo-stenotic' reflex.

The ultimate proof of the relative values of PCI *vs* CABG for unprotected LMCA stenosis clearly depends on the results of randomized clinical trials comparing the two treatment strategies. The trials involve a number of technical considerations that could significantly alter angioplasty outcomes. The SYNTAX trial compared the outcomes of PCI with paclitaxel-eluting stents *vs* CABG for unprotected LMCA stenosis in a subgroup from the randomized study cohort^[30]. As shown in the subset of patients with LMCA disease comprising 348 patients receiving CABG and 357 receiving PCI, PCI (15.8%) demonstrated equivalent 1-year clinical outcomes of major adverse cardiac and cerebrovascular events including death, MI, stroke and repeat revascularization compared with CABG (13.7%, *P* = 0.44). When the patients were stratified according to the vascular involvement, the event rate in the PCI group was numerically higher for patients with 2-vessel (19.8% *vs* 14.4%, *P* = 0.29) and 3-vessel (19.3% *vs* 15.4%, *P* = 0.42) disease. However, the incidence of these events were numerically lower in the PCI group for patients with isolated LMCA (7.1% *vs* 8.5%, *P* = 1.0) or 1-vessel disease (7.5% *vs* 13.2%, *P* = 0.27). Of interest, the higher rate of repeat revascularization with PCI (11.8% *vs* 6.5%, *P* = 0.02) was offset by a higher incidence of stroke with CABG (2.7% *vs* 0.3%, *P* = 0.01). However, it should be noted that the analysis for LMCA disease was not the primary objective analysis but the post-

hoc analysis, which is hypothesis-generating. Therefore, further randomized studies are warranted to provide a definite answer to this question for a specific cohort of patients having unprotected LMCA stenosis. Another randomized study, the PRECOMBAT (Premier of Randomized Comparison of Bypass Surgery *vs* Angioplasty using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease) trial, performed in Korea randomized 600 patients with unprotected LMCA to either CABG or PCI with sirolimus-eluting stents. This study has a non-inferiority design with the primary end point of major adverse cardiac and cerebrovascular events at a mean of 2 years. A more global randomized trial, the EXCEL (Evaluation of XIENCE PRIME™ *vs* Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization), is also being carried out to compare PCI and CABG for approximately 2500 patients with unprotected LMCA stenosis.

TECHNICAL ISSUES

Stenting techniques

Stenting for ostial or body LMCA lesions seems very simple as the other stenting technique for non-LMCA coronary lesions. For instance, a brief stent expansion is required to obtain optimal stent expansion and to avoid ischemic complications. In ostial LMCA lesions, the coronary stent is generally positioned outside the LMCA for complete lesion coverage of the ostium. Stenting for bifurcation LMCA lesions, however, are technically demanding and should be performed by experienced operators. In general, the selection of an appropriate stenting strategy is dependent on the plaque configuration surrounding the LMCA. However, in spite of recent randomized studies comparing single-stent *vs* two-stent treatment for bifurcation coronary lesions^[54,55], the optimal stenting strategy for LMCA bifurcation lesions has not yet been determined. The current consensus is that the two-stent strategy does not have long-term advantages in terms of the incidence of any major cardiac events compared with the single-stent strategy. Therefore, systemic treatment with the two-stent strategy for all LMCA bifurcation lesions, such as T-stenting, Kissing stenting, Crush technique, or Culotte technique is not generally recommended. Instead, a provisional stenting strategy should be considered as the first-line treatment for LMCA bifurcations without significant side branch stenosis.

IVUS

IVUS is considered a useful invasive diagnostic modality in determining anatomical configuration, selecting treatment strategy, and defining optimal stenting outcomes in either the BMS or DES era^[56]. Although a retrospective study showed that the clinical impact of IVUS-guided stenting for LMCA with DES did not show a significant clinical long-term benefit compared with the angiography-guided procedure^[57], the usefulness of IVUS guided-

stenting may not be hampered by this underpowered retrospective study. The information gathered by IVUS may be crucial for the optimal stenting procedure in unprotected LMCA stenosis with excellent intraclass correlation in the measurement of area and plaque^[58]. In fact, angiography has a limitation in assessing the true luminal size of the LMCA because this artery is often short and lacks a normal segment for comparison. Therefore, the severity of LMCA stenosis is often underestimated by misinterpretation of the normal segment adjacent to focal stenosis. In addition to the actual assessment of LMCA lesions before a procedure, use of IVUS is very helpful to obtain an adequate expansion of the DES, to prevent stent inapposition, and to achieve full lesion coverage with the DES.

A recent subgroup analysis from the MAIN-COMPARE study reported a very interesting finding in that IVUS-guidance was associated with improved long-term mortality compared with the conventional angiography-guided procedure^[23]. With an adjustment using propensity-score matching for 201 matched pairs, there was a strong tendency for a lower risk of 3-year mortality with IVUS-guidance compared with angiography-guidance (6.3% *vs* 13.6%, log-rank $P = 0.063$, HR = 0.54, 95% CI: 0.28-1.03). In particular, for 145 pairs of patients receiving DES, the 3-year incidence of mortality was lower with IVUS-guidance compared with angiography-guidance (4.7% *vs* 16.0%, log-rank $P = 0.048$, HR = 0.39, 95% CI: 0.15-1.02). Of interest, mortality started to diverge 1 year after the procedure. Therefore, in spite of inherent limitations of the non-randomized study design, this study indicated that IVUS-guidance may play a role in reducing very late stent thrombosis and subsequent long-term mortality. In fact, IVUS evaluations of stent underexpansion, incomplete lesion coverage, small stent area, large residual plaque and inapposition have been found to predict stent thrombosis after DES placement^[59-63]. Therefore, we strongly recommend the mandatory use of IVUS in PCI for unprotected LMCA.

Debulking atherectomy

In the BMS era, debulking coronary atherectomy before stenting had been used widely in an attempt to reduce restenosis by removal of plaque burden. However, following the introduction of DES, the role of debulking was restricted due to the dramatic benefit of restenosis reduction. One study suggested a viable role for debulking atherectomy even in the DES era for 99 patients with coronary bifurcations^[64]. Of interest, debulking in the main branch and side branch for LMCA stenoses allowed single-stenting in 60 of the 63 LMCA bifurcation stenoses. Surprisingly, during the 1-year follow-up, no serious adverse events occurred. This study indicated that debulking may be preferred in LMCA bifurcations in order to aid a provisional single stenting strategy. In addition, debulking still plays a limited role in facilitating stent delivery. Debulking is used to remove plaque in the LMCA which inhibited advancement of the wire into

the left anterior descending artery. Similarly, a rotablator has been used prior to stenting when calcification in the proximal segment prevents stent delivery or the calcified target lesion is not sufficiently dilated. Therefore, although the data is limited, debulking atherectomy or rotablator still have a limited role even in DES treatment to improve lesion compliance.

Hemodynamic support

Patients in an unstable hemodynamic condition need pharmacological- or device-based hemodynamic support during the procedure for LMCA stenosis. Old age, MI, cardiogenic shock and decreased left ventricular ejection fraction are common clinical conditions requiring elective or provisional hemodynamic support. Hemodynamic support devices include the intra-aortic balloon pump, percutaneous hemodynamic support devices, and left ventricular assist devices. The intra-aortic balloon pump has been used most frequently. Although there is no doubt that the provisional use of an intra-aortic balloon pump in patients with hemodynamic compromise is necessary for a successful procedure, from the literature, the planned use of the balloon pump ranges widely. A study recently suggested the role of intra-aortic balloon pump support in 219 elective LMCA interventions^[65]. These authors used a prophylactic balloon pump for a broad range of patients with distal LMCA bifurcation lesions, low ejection fraction of < 40%, use of debulking devices, unstable angina, and critical right coronary artery disease. In that study, interestingly, although the patients receiving elective intra-aortic balloon pump support had more complex clinical risk profiles, the rate of procedural complications was lower than in those not receiving intra-aortic balloon pump support (1.4% *vs* 9.3%, $P = 0.032$). Therefore, the elective use of intra-aortic balloon pump support needs to be considered in patients at a high risk with multivessel disease, complex LMCA anatomy, low ejection fraction or unstable presentations. Hopefully, the new support devices, such as Tandem-Heart (CardiacAssist, Pittsburgh, Pennsylvania, USA) or the Impella Recover LP 2.5 System (Impella Cardio-Systems, Aachen, Germany) may improve the feasibility of implementation and the complication rate related to these devices.

Antithrombotics

Although the reported incidence of stent thrombosis in DES treatment for LMCA lesions is very low^[66], the fear of stent thrombosis remains a major concern and prevents the more generalized use of DES. Therefore, careful administration of antiplatelet agents is very important to prevent the occurrence of stent thrombosis. In fact, premature discontinuation of clopidogrel was strongly associated with stent thrombosis in several studies^[32,67]. Therefore, as generally recommended, dual antiplatelet therapy including aspirin and clopidogrel (or ticlopidine) should be maintained for 1 year. If the patients are at high risk, a high loading dose (600 mg) or lifelong admin-

istration of clopidogrel needs to be considered. A recent study added the benefit of aggressive use of clopidogrel in the early period after DES implantation^[68]. After stopping clopidogrel between 31 and 180 d, the hazard of cardiac death or MI was 4.20 ($P = 0.009$) compared with stopping clopidogrel between 181 and 36 d. Furthermore, in some institutions in Asian countries, the adjunctive administration of cilostazol has been used to reduce thrombotic complications^[69].

Aggressive use of antithrombotics should also be considered for complex lesion anatomy or unstable coronary conditions. For example, as shown in previous studies, the use of glycoprotein II b/III inhibitor may play a role in reducing procedure-related thrombotic complications including death or MI^[70]. However, the additive role of the glycoprotein II b/II a inhibitor, cilostazol, low molecular weight heparin, direct thrombin inhibitor or other new drugs in DES treatment for LMCA lesions needs to be investigated in future research. Until evidence is accumulated, we have to consider an aggressive combination of antithrombotic drugs before, during or after the procedure to avoid thrombotic complications in high risk patients. Although the features of high risk are not well delineated, off-label use of DES, such as in diabetes mellitus, multiple stenting, long DES, chronic renal failure, or presentation with MI, is a good index of a high risk procedure^[71].

CONCLUSION

The current studies, although they are limited by the non-randomized study design, small sample size, and short-term follow-up, have demonstrated the promising procedural and mid-term safety and effectiveness of DES compared with BMS or CABG. With these findings, in our opinion, PCI with DES will progressively increase and can be recommended as the reliable alternative to bypass surgery for patients with unprotected LMCA stenosis, especially as the first line-therapy for ostial or shaft stenosis. Although bifurcation stenosis remains challenging using the percutaneous approach, we are still optimistic as further research into novel procedural techniques, new dedicated stent platforms, and optimal pharmacotherapies may improve patient outcome. Furthermore, we hope, with the upcoming results from randomized clinical trials comparing PCI to CABG for unprotected LMCA stenosis, more confidence in the long-term safety, durability, and efficacy of PCI will be accrued in the near future.

REFERENCES

- 1 Takaro T, Hultgren HN, Lipton MJ, Detre KM. The VA cooperative randomized study of surgery for coronary arterial occlusive disease II. Subgroup with significant left main lesions. *Circulation* 1976; **54**: III107-III117
- 2 Chaitman BR, Fisher LD, Bourassa MG, Davis K, Rogers WJ, Maynard C, Tyras DH, Berger RL, Judkins MP, Ringqvist I, Mock MB, Killip T. Effect of coronary bypass surgery on survival patterns in subsets of patients with left

- main coronary artery disease. Report of the Collaborative Study in Coronary Artery Surgery (CASS). *Am J Cardiol* 1981; **48**: 765-777
- 3 **Park SJ**, Mintz GS. Left main stem disease. 1st ed. Seoul: Informa Healthcare, 2006
 - 4 **Chieffo A**, Stankovic G, Bonizzoni E, Tsagalou E, Iakovou I, Montorfano M, Airolidi F, Michev I, Sangiorgi MG, Carlino M, Vitrella G, Colombo A. Early and mid-term results of drug-eluting stent implantation in unprotected left main. *Circulation* 2005; **111**: 791-795
 - 5 **Park SJ**, Kim YH, Lee BK, Lee SW, Lee CW, Hong MK, Kim JJ, Mintz GS, Park SW. Sirolimus-eluting stent implantation for unprotected left main coronary artery stenosis: comparison with bare metal stent implantation. *J Am Coll Cardiol* 2005; **45**: 351-356
 - 6 **Valgimigli M**, van Mieghem CA, Ong AT, Aoki J, Granillo GA, McFadden EP, Kappetein AP, de Feyter PJ, Smits PC, Regar E, Van der Giessen WJ, Sianos G, de Jaegere P, Van Domburg RT, Serruys PW. Short- and long-term clinical outcome after drug-eluting stent implantation for the percutaneous treatment of left main coronary artery disease: insights from the Rapamycin-Eluting and Taxus Stent Evaluated At Rotterdam Cardiology Hospital registries (RESEARCH and T-SEARCH). *Circulation* 2005; **111**: 1383-1389
 - 7 **Chieffo A**, Morici N, Maisano F, Bonizzoni E, Cosgrave J, Montorfano M, Airolidi F, Carlino M, Michev I, Melzi G, Sangiorgi G, Alfieri O, Colombo A. Percutaneous treatment with drug-eluting stent implantation versus bypass surgery for unprotected left main stenosis: a single-center experience. *Circulation* 2006; **113**: 2542-2547
 - 8 **Kim YH**, Park SW, Hong MK, Park DW, Park KM, Lee BK, Song JM, Han KH, Lee CW, Kang DH, Song JK, Kim JJ, Park SJ. Comparison of simple and complex stenting techniques in the treatment of unprotected left main coronary artery bifurcation stenosis. *Am J Cardiol* 2006; **97**: 1597-1601
 - 9 **Lee MS**, Kapoor N, Jamal F, Czer L, Aragon J, Forrester J, Kar S, Dohad S, Kass R, Eigler N, Trento A, Shah PK, Makkar RR. Comparison of coronary artery bypass surgery with percutaneous coronary intervention with drug-eluting stents for unprotected left main coronary artery disease. *J Am Coll Cardiol* 2006; **47**: 864-870
 - 10 **Palmerini T**, Marzocchi A, Marrozzini C, Ortolani P, Saia F, Savini C, Bacchi-Reggiani L, Gianstefani S, Virzi S, Manara F, Kiros Weldeab M, Marinelli G, Di Bartolomeo R, Branzi A. Comparison between coronary angioplasty and coronary artery bypass surgery for the treatment of unprotected left main coronary artery stenosis (the Bologna Registry). *Am J Cardiol* 2006; **98**: 54-59
 - 11 **Price MJ**, Cristea E, Sawhney N, Kao JA, Moses JW, Leon MB, Costa RA, Lansky AJ, Teirstein PS. Serial angiographic follow-up of sirolimus-eluting stents for unprotected left main coronary artery revascularization. *J Am Coll Cardiol* 2006; **47**: 871-877
 - 12 **Valgimigli M**, Malagutti P, Aoki J, Garcia-Garcia HM, Rodriguez Granillo GA, van Mieghem CA, Ligthart JM, Ong AT, Sianos G, Regar E, Van Domburg RT, De Feyter P, de Jaegere P, Serruys PW. Sirolimus-eluting versus paclitaxel-eluting stent implantation for the percutaneous treatment of left main coronary artery disease: a combined RESEARCH and T-SEARCH long-term analysis. *J Am Coll Cardiol* 2006; **47**: 507-514
 - 13 **Valgimigli M**, Malagutti P, Rodriguez-Granillo GA, Garcia-Garcia HM, Polad J, Tsuchida K, Regar E, Van der Giessen WJ, de Jaegere P, De Feyter P, Serruys PW. Distal left main coronary disease is a major predictor of outcome in patients undergoing percutaneous intervention in the drug-eluting stent era: an integrated clinical and angiographic analysis based on the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) and Taxus-Stent Evaluated At Rotterdam Cardiology Hospital (T-SEARCH) registries. *J Am Coll Cardiol* 2006; **47**: 1530-1537
 - 14 **Chieffo A**, Park SJ, Valgimigli M, Kim YH, Daemen J, Sheiban I, Truffa A, Montorfano M, Airolidi F, Sangiorgi G, Carlino M, Michev I, Lee CW, Hong MK, Park SW, Moretti C, Bonizzoni E, Rogacka R, Serruys PW, Colombo A. Favorable long-term outcome after drug-eluting stent implantation in nonbifurcation lesions that involve unprotected left main coronary artery: a multicenter registry. *Circulation* 2007; **116**: 158-162
 - 15 **Palmerini T**, Barlocco F, Santarelli A, Bacchi-Reggiani L, Savini C, Baldini E, Alessi L, Ruffini M, Di Credico G, Piovaccari G, Di Bartolomeo R, Marzocchi A, Branzi A, De Servi S. A comparison between coronary artery bypass grafting surgery and drug eluting stent for the treatment of unprotected left main coronary artery disease in elderly patients (aged > or =75 years). *Eur Heart J* 2007; **28**: 2714-2719
 - 16 **Sheiban I**, Meliga E, Moretti C, Biondi-Zoccai GG, Rosano G, Sciuto F, Marra WG, Omedè P, Gerasimou A, Trevi GP. Long-term clinical and angiographic outcomes of treatment of unprotected left main coronary artery stenosis with sirolimus-eluting stents. *Am J Cardiol* 2007; **100**: 431-435
 - 17 **Buszman PE**, Kiesz SR, Bochenek A, Peszek-Przybyla E, Szkrobka I, Debinski M, Bialkowska B, Dudek D, Gruszka A, Zurawski A, Milewski K, Wilczynski M, Rzeszutko L, Buszman P, Szymaszal J, Martin JL, Tenders M. Acute and late outcomes of unprotected left main stenting in comparison with surgical revascularization. *J Am Coll Cardiol* 2008; **51**: 538-545
 - 18 **Biondi-Zoccai GG**, Lotrionte M, Moretti C, Meliga E, Agostoni P, Valgimigli M, Migliorini A, Antoniucci D, Carriè D, Sangiorgi G, Chieffo A, Colombo A, Price MJ, Teirstein PS, Christiansen EH, Abbate A, Testa L, Gunn JP, Burzotta F, Laudito A, Trevi GP, Sheiban I. A collaborative systematic review and meta-analysis on 1278 patients undergoing percutaneous drug-eluting stenting for unprotected left main coronary artery disease. *Am Heart J* 2008; **155**: 274-283
 - 19 **Chieffo A**, Park SJ, Meliga E, Sheiban I, Lee MS, Latib A, Kim YH, Valgimigli M, Sillano D, Magni V, Zoccai GB, Montorfano M, Airolidi F, Rogacka R, Carlino M, Michev I, Lee CW, Hong MK, Park SW, Moretti C, Bonizzoni E, Sangiorgi GM, Tobis J, Serruys PW, Colombo A. Late and very late stent thrombosis following drug-eluting stent implantation in unprotected left main coronary artery: a multicentre registry. *Eur Heart J* 2008; **29**: 2108-2115
 - 20 **Kim YH**, Dangas GD, Solinas E, Aoki J, Parise H, Kimura M, Franklin-Bond T, Dasgupta NK, Kirtane AJ, Moussa I, Lansky AJ, Collins M, Stone GW, Leon MB, Moses JW, Mehran R. Effectiveness of drug-eluting stent implantation for patients with unprotected left main coronary artery stenosis. *Am J Cardiol* 2008; **101**: 801-806
 - 21 **Seung KB**, Park DW, Kim YH, Lee SW, Lee CW, Hong MK, Park SW, Yun SC, Gwon HC, Jeong MH, Jang Y, Kim HS, Kim PJ, Seong IW, Park HS, Ahn T, Chae IH, Tahk SJ, Chung WS, Park SJ. Stents versus coronary-artery bypass grafting for left main coronary artery disease. *N Engl J Med* 2008; **358**: 1781-1792
 - 22 **Tamburino C**, Di Salvo ME, Capodanno D, Marzocchi A, Sheiban I, Margheri M, Maresta A, Barlocco F, Sangiorgi G, Piovaccari G, Bartorelli A, Briguori C, Ardissino D, Di Pede F, Ramondo A, Inglese L, Petronio AS, Bolognese L, Benassi A, Palmieri C, Patti A, De Servi S. Are drug-eluting stents superior to bare-metal stents in patients with unprotected non-bifurcational left main disease? Insights from a multicentre registry. *Eur Heart J* 2009; **30**: 1171-1179
 - 23 **Park SJ**, Kim YH, Park DW, Lee SW, Kim WJ, Suh J, Yun SC, Lee CW, Hong MK, Lee JH, Park SW. Impact of intravascular ultrasound guidance on long-term mortality in stenting for unprotected left main coronary artery stenosis. *Circ Cardiovasc Interv* 2009; **2**: 167-177
 - 24 **Palmerini T**, Sangiorgi D, Marzocchi A, Tamburino C,

- Sheiban I, Margheri M, Vecchi G, Sangiorgi G, Ruffini M, Bartorelli AL, Briguori C, Vignali L, Di Pede F, Ramondo A, Inglese L, De Carlo M, Bolognese L, Benassi A, Palmieri C, Filippone V, Barlocco F, Lauria G, De Servi S. Ostial and midshaft lesions vs. bifurcation lesions in 1111 patients with unprotected left main coronary artery stenosis treated with drug-eluting stents: results of the survey from the Italian Society of Invasive Cardiology. *Eur Heart J* 2009; **30**: 2087-2094
- 25 **Tamburino C**, Di Salvo ME, Capodanno D, Palmerini T, Sheiban I, Margheri M, Vecchi G, Sangiorgi G, Piovaccari G, Bartorelli A, Briguori C, Ardissino D, Di Pede F, Ramondo A, Inglese L, Petronio AS, Bolognese L, Benassi A, Palmieri C, Filippone V, De Servi S. Comparison of drug-eluting stents and bare-metal stents for the treatment of unprotected left main coronary artery disease in acute coronary syndromes. *Am J Cardiol* 2009; **103**: 187-193
- 26 **Palmerini T**, Marzocchi A, Tamburino C, Sheiban I, Margheri M, Vecchi G, Sangiorgi G, Santarelli A, Bartorelli A, Briguori C, Vignali L, Di Pede F, Ramondo A, Inglese L, De Carlo M, Bolognese L, Benassi A, Palmieri C, Filippone V, Sangiorgi D, De Servi S. Two-year clinical outcome with drug-eluting stents versus bare-metal stents in a real-world registry of unprotected left main coronary artery stenosis from the Italian Society of Invasive Cardiology. *Am J Cardiol* 2008; **102**: 1463-1468
- 27 **Kim YH**, Park DW, Lee SW, Yun SC, Lee CW, Hong MK, Park SW, Seung KB, Gwon HC, Jeong MH, Jang Y, Kim HS, Seong IW, Park HS, Ahn T, Chae IH, Tahk SJ, Chung WS, Park SJ. Long-term safety and effectiveness of unprotected left main coronary stenting with drug-eluting stents compared with bare-metal stents. *Circulation* 2009; **120**: 400-407
- 28 **de Lezo JS**, Medina A, Pan M, Delgado A, Segura J, Pavlovic D, Melián F, Romero M, Burgos L, Hernández E, Ureña I, Herrador J. Rapamycin-eluting stents for the treatment of unprotected left main coronary disease. *Am Heart J* 2004; **148**: 481-485
- 29 **Meliga E**, Garcia-Garcia HM, Valgimigli M, Chieffo A, Biondi-Zoccai G, Maree AO, Cook S, Reardon L, Moretti C, De Servi S, Palacios IF, Windecker S, Colombo A, van Domburg R, Sheiban I, Serruys PW. Longest available clinical outcomes after drug-eluting stent implantation for unprotected left main coronary artery disease: the DELFT (Drug Eluting stent for LeFT main) Registry. *J Am Coll Cardiol* 2008; **51**: 2212-2219
- 30 **Serruys PW**, Morice MC, Kappetein AP, Colombo A, Holmes DR, Mack MJ, Ståhle E, Feldman TE, van den Brand M, Bass EJ, Van Dyck N, Leadley K, Dawkins KD, Mohr FW. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *N Engl J Med* 2009; **360**: 961-972
- 31 **Patel MR**, Dehmer GJ, Hirshfeld JW, Smith PK, Spertus JA. ACCF/SCAI/STS/AATS/AHA/ASNC 2009 Appropriateness Criteria for Coronary Revascularization: a report by the American College of Cardiology Foundation Appropriateness Criteria Task Force, Society for Cardiovascular Angiography and Interventions, Society of Thoracic Surgeons, American Association for Thoracic Surgery, American Heart Association, and the American Society of Nuclear Cardiology Endorsed by the American Society of Echocardiography, the Heart Failure Society of America, and the Society of Cardiovascular Computed Tomography. *J Am Coll Cardiol* 2009; **53**: 530-553
- 32 **Iakovou I**, Schmidt T, Bonizzoni E, Ge L, Sangiorgi GM, Stankovic G, Airolidi F, Chieffo A, Montorfano M, Carlino M, Michev I, Corvaja N, Briguori C, Gerckens U, Grube E, Colombo A. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. *JAMA* 2005; **293**: 2126-2130
- 33 **Lagerqvist B**, James SK, Stenestrand U, Lindbäck J, Nilsson T, Wallentin L. Long-term outcomes with drug-eluting stents versus bare-metal stents in Sweden. *N Engl J Med* 2007; **356**: 1009-1019
- 34 **Spaulding C**, Daemen J, Boersma E, Cutlip DE, Serruys PW. A pooled analysis of data comparing sirolimus-eluting stents with bare-metal stents. *N Engl J Med* 2007; **356**: 989-997
- 35 **Stone GW**, Moses JW, Ellis SG, Schofer J, Dawkins KD, Morice MC, Colombo A, Schampaert E, Grube E, Kirtane AJ, Cutlip DE, Fahy M, Pocock SJ, Mehran R, Leon MB. Safety and efficacy of sirolimus- and paclitaxel-eluting coronary stents. *N Engl J Med* 2007; **356**: 998-1008
- 36 **Park DW**, Park SW, Lee SW, Kim YH, Lee CW, Hong MK, Kim JJ, Park SJ. Frequency of coronary arterial late angiographic stent thrombosis (LAST) in the first six months: outcomes with drug-eluting stents versus bare metal stents. *Am J Cardiol* 2007; **99**: 774-778
- 37 **Farb A**, Boam AB. Stent thrombosis redux--the FDA perspective. *N Engl J Med* 2007; **356**: 984-987
- 38 **Arnett EN**, Isner JM, Redwood DR, Kent KM, Baker WP, Ackerstein H, Roberts WC. Coronary artery narrowing in coronary heart disease: comparison of cineangiographic and necropsy findings. *Ann Intern Med* 1979; **91**: 350-356
- 39 **Fisher LD**, Judkins MP, Lesperance J, Cameron A, Swaye P, Ryan T, Maynard C, Bourassa M, Kennedy JW, Gosselin A, Kemp H, Faxon D, Wexler L, Davis KB. Reproducibility of coronary arteriographic reading in the coronary artery surgery study (CASS). *Cathet Cardiovasc Diagn* 1982; **8**: 565-575
- 40 **Isner JM**, Kishel J, Kent KM, Ronan JA Jr, Ross AM, Roberts WC. Accuracy of angiographic determination of left main coronary arterial narrowing. Angiographic-histologic correlative analysis in 28 patients. *Circulation* 1981; **63**: 1056-1064
- 41 **Gerber TC**, Erbel R, Gorge G, Ge J, Rupprecht HJ, Meyer J. Extent of atherosclerosis and remodeling of the left main coronary artery determined by intravascular ultrasound. *Am J Cardiol* 1994; **73**: 666-671
- 42 **Abizaid AS**, Mintz GS, Abizaid A, Mehran R, Lansky AJ, Pichard AD, Satler LF, Wu H, Kent KM, Leon MB. One-year follow-up after intravascular ultrasound assessment of moderate left main coronary artery disease in patients with ambiguous angiograms. *J Am Coll Cardiol* 1999; **34**: 707-715
- 43 **Fassa AA**, Wagatsuma K, Higano ST, Mathew V, Barsness GW, Lennon RJ, Holmes DR Jr, Lerman A. Intravascular ultrasound-guided treatment for angiographically indeterminate left main coronary artery disease: a long-term follow-up study. *J Am Coll Cardiol* 2005; **45**: 204-211
- 44 **Jasti V**, Ivan E, Yalamanchili V, Wongpraparut N, Leesar MA. Correlations between fractional flow reserve and intravascular ultrasound in patients with an ambiguous left main coronary artery stenosis. *Circulation* 2004; **110**: 2831-2836
- 45 **Pijls NH**, Van Gelder B, Van der Voort P, Peels K, Bracke FA, Bonnier HJ, el Gamal MI. Fractional flow reserve. A useful index to evaluate the influence of an epicardial coronary stenosis on myocardial blood flow. *Circulation* 1995; **92**: 3183-3193
- 46 **Pijls NH**, De Bruyne B, Peels K, Van Der Voort PH, Bonnier HJ, Bartunek J, Koolen JJ, Koolen JJ. Measurement of fractional flow reserve to assess the functional severity of coronary-artery stenoses. *N Engl J Med* 1996; **334**: 1703-1708
- 47 **Takagi T**, Stankovic G, Finci L, Toutouzas K, Chieffo A, Spanos V, Liistro F, Briguori C, Corvaja N, Albero R, Sivieri G, Paloschi R, Di Mario C, Colombo A. Results and long-term predictors of adverse clinical events after elective percutaneous interventions on unprotected left main coronary artery. *Circulation* 2002; **106**: 698-702
- 48 **Mehilli J**, Kastrati A, Byrne RA, Bruskina O, Iijima R, Schulz S, Pache J, Seyfarth M, Massberg S, Laugwitz KL, Dirschinger J, Schömig A. Paclitaxel- versus sirolimus-eluting stents for unprotected left main coronary artery disease. *J Am Coll Cardiol* 2009; **53**: 1760-1768
- 49 **Marroquin OC**, Selzer F, Mulukutla SR, Williams DO, Vla-

- chos HA, Wilensky RL, Tanguay JF, Holper EM, Abbott JD, Lee JS, Smith C, Anderson WD, Kelsey SF, Kip KE. A comparison of bare-metal and drug-eluting stents for off-label indications. *N Engl J Med* 2008; **358**: 342-352
- 50 **Tu JV**, Bowen J, Chiu M, Ko DT, Austin PC, He Y, Hopkins R, Tarride JE, Blackhouse G, Lazzam C, Cohen EA, Goeree R. Effectiveness and safety of drug-eluting stents in Ontario. *N Engl J Med* 2007; **357**: 1393-1402
- 51 **Tan WA**, Tamai H, Park SJ, Plokker HW, Nobuyoshi M, Suzuki T, Colombo A, Macaya C, Holmes DR Jr, Cohen DJ, Whitlow PL, Ellis SG. Long-term clinical outcomes after unprotected left main trunk percutaneous revascularization in 279 patients. *Circulation* 2001; **104**: 1609-1614
- 52 **Kim YH**, Ahn JM, Park DW, Lee BK, Lee CW, Hong MK, Kim JJ, Park SW, Park SJ. EuroSCORE as a predictor of death and myocardial infarction after unprotected left main coronary stenting. *Am J Cardiol* 2006; **98**: 1567-1570
- 53 **Valgimigli M**, Malagutti P, Rodriguez Granillo GA, Tsuchida K, Garcia-Garcia HM, van Mieghem CA, Van der Giessen WJ, De Feyter P, de Jaegere P, Van Domburg RT, Serruys PW. Single-vessel versus bifurcation stenting for the treatment of distal left main coronary artery disease in the drug-eluting stenting era. Clinical and angiographic insights into the Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital (RESEARCH) and Taxus-Stent Evaluated at Rotterdam Cardiology Hospital (T-SEARCH) registries. *Am Heart J* 2006; **152**: 896-902
- 54 **Colombo A**, Moses JW, Morice MC, Ludwig J, Holmes DR Jr, Spanos V, Louvard Y, Desmedt B, Di Mario C, Leon MB. Randomized study to evaluate sirolimus-eluting stents implanted at coronary bifurcation lesions. *Circulation* 2004; **109**: 1244-1249
- 55 **Steigen TK**, Maeng M, Wiseth R, Erglis A, Kumsars I, Narbutė I, Gunnes P, Mannsverk J, Meyerderks O, Rotevatn S, Niemelä M, Kervinen K, Jensen JS, Galløe A, Nikus K, Vikman S, Ravkilde J, James S, Aarøe J, Ylitalo A, Helqvist S, Sjögren I, Thayssen P, Virtanen K, Puhakka M, Airaksinen J, Lassen JF, Thuesen L. Randomized study on simple versus complex stenting of coronary artery bifurcation lesions: the Nordic bifurcation study. *Circulation* 2006; **114**: 1955-1961
- 56 **Mintz GS**, Nissen SE, Anderson WD, Bailey SR, Erbel R, Fitzgerald PJ, Pinto FJ, Rosenfield K, Siegel RJ, Tuzcu EM, Yock PG. American College of Cardiology Clinical Expert Consensus Document on Standards for Acquisition, Measurement and Reporting of Intravascular Ultrasound Studies (IVUS). A report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents. *J Am Coll Cardiol* 2001; **37**: 1478-1492
- 57 **Agostoni P**, Valgimigli M, Van Mieghem CA, Rodriguez-Granillo GA, Aoki J, Ong AT, Tsuchida K, McFadden EP, Ligthart JM, Smits PC, de Jaegere P, Sianos G, Van der Giessen WJ, De Feyter P, Serruys PW. Comparison of early outcome of percutaneous coronary intervention for unprotected left main coronary artery disease in the drug-eluting stent era with versus without intravascular ultrasonic guidance. *Am J Cardiol* 2005; **95**: 644-647
- 58 **Suter Y**, Schoenenberger AW, Toggweiler S, Jamshidi P, Resink T, Erne P. Intravascular ultrasound-based left main coronary artery assessment: comparison between pullback from left anterior descending and circumflex arteries. *J Invasive Cardiol* 2009; **21**: 457-460
- 59 **Sonoda S**, Morino Y, Ako J, Terashima M, Hassan AH, Bonneau HN, Leon MB, Moses JW, Yock PG, Honda Y, Kuntz RE, Fitzgerald PJ. Impact of final stent dimensions on long-term results following sirolimus-eluting stent implantation: serial intravascular ultrasound analysis from the sirius trial. *J Am Coll Cardiol* 2004; **43**: 1959-1963
- 60 **Costa MA**, Gigliotti OS, Zenni MM, Gilmore PS, Bass TA. Synergistic use of sirolimus-eluting stents and intravascular ultrasound for the treatment of unprotected left main and vein graft disease. *Catheter Cardiovasc Interv* 2004; **61**: 368-375
- 61 **Fujii K**, Carlier SG, Mintz GS, Yang YM, Moussa I, Weisz G, Dangas G, Mehran R, Lansky AJ, Kreps EM, Collins M, Stone GW, Moses JW, Leon MB. Stent underexpansion and residual reference segment stenosis are related to stent thrombosis after sirolimus-eluting stent implantation: an intravascular ultrasound study. *J Am Coll Cardiol* 2005; **45**: 995-998
- 62 **Cook S**, Wenaweser P, Togni M, Billinger M, Morger C, Seiler C, Vogel R, Hess O, Meier B, Windecker S. Incomplete stent apposition and very late stent thrombosis after drug-eluting stent implantation. *Circulation* 2007; **115**: 2426-2434
- 63 **Okabe T**, Mintz GS, Buch AN, Roy P, Hong YJ, Smith KA, Torguson R, Gevorkian N, Xue Z, Satler LF, Kent KM, Pichard AD, Weissman NJ, Waksman R. Intravascular ultrasound parameters associated with stent thrombosis after drug-eluting stent deployment. *Am J Cardiol* 2007; **100**: 615-620
- 64 **Tsuchikane E**, Aizawa T, Tamai H, Igarashi Y, Kawajiri K, Ozawa N, Nakamura S, Oku K, Kijima M, Suzuki T. Pre-drug-eluting stent debulking of bifurcated coronary lesions. *J Am Coll Cardiol* 2007; **50**: 1941-1945
- 65 **Briguori C**, Airolidi F, Chieffo A, Montorfano M, Carlino M, Sangiorgi GM, Morici N, Michev I, Iakovou I, Biondi-Zoccai G, Colombo A. Elective versus provisional intraaortic balloon pumping in unprotected left main stenting. *Am Heart J* 2006; **152**: 565-572
- 66 **Chieffo A**, Park SJ, Meliga E, Sheiban I, Lee MS, Latib A, Kim YH, Valgimigli M, Sillano D, Magni V, Zoccai GB, Montorfano M, Airolidi F, Rogacka R, Carlino M, Michev I, Lee CW, Hong MK, Park SW, Moretti C, Bonizzoni E, Sangiorgi GM, Tobis J, Serruys PW, Colombo A. Late and very late stent thrombosis following drug-eluting stent implantation in unprotected left main coronary artery: a multicentre registry. *Eur Heart J* 2008; **29**: 2108-2115
- 67 **Park DW**, Park SW, Park KH, Lee BK, Kim YH, Lee CW, Hong MK, Kim JJ, Park SJ. Frequency of and risk factors for stent thrombosis after drug-eluting stent implantation during long-term follow-up. *Am J Cardiol* 2006; **98**: 352-356
- 68 **Palmerini T**, Marzocchi A, Tamburino C, Sheiban I, Margheri M, Vecchi G, Sangiorgi G, Santarelli A, Bartorelli AL, Briguori C, Vignali L, Di Pede F, Ramondo A, Inglese L, De Carlo M, Bolognese L, Benassi A, Palmieri C, Filippone V, Sangiorgi D, Barlocco F, Lauria G, De Servi S. Temporal pattern of ischemic events in relation to dual antiplatelet therapy in patients with unprotected left main coronary artery stenosis undergoing percutaneous coronary intervention. *J Am Coll Cardiol* 2009; **53**: 1176-1181
- 69 **Lee SW**, Park SW, Hong MK, Kim YH, Lee BK, Song JM, Han KH, Lee CW, Kang DH, Song JK, Kim JJ, Park SJ. Triple versus dual antiplatelet therapy after coronary stenting: impact on stent thrombosis. *J Am Coll Cardiol* 2005; **46**: 1833-1837
- 70 **Cura FA**, Bhatt DL, Lincoff AM, Kapadia SR, L'Allier PL, Ziada KM, Wolski KE, Moliterno DJ, Brener SJ, Ellis SG, Topol EJ. Pronounced benefit of coronary stenting and adjunctive platelet glycoprotein IIb/IIIa inhibition in complex atherosclerotic lesions. *Circulation* 2000; **102**: 28-34
- 71 **Pinto Slottow TL**, Waksman R. Overview of the 2006 Food and Drug Administration Circulatory System Devices Panel meeting on drug-eluting stent thrombosis. *Catheter Cardiovasc Interv* 2007; **69**: 1064-1074

S- Editor Cheng JX L- Editor Webster JR E- Editor Zheng XM