ORIGINAL RESEARCH

Left Internal Mammary Artery Versus Coronary Stents: Impact on Downstream Coronary Stenoses and Conduit Patency

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***Background*—**The study compared downstream coronary and conduit disease progression in the left anterior descending coronary artery treated with coronary artery bypass grafting using the left internal mammary artery (LIMA) versus percutaneous coronary intervention with bare metal stent (BMS) or drug eluting stent (DES).

***Methods and Results*—**A total of 12 301 consecutive patients underwent isolated primary coronary revascularization, of which 2386 met our inclusion criteria (Percutaneous coronary intervention, n=1450; coronary artery bypass grafting, n=936). Propensity score analysis matched 628 patients, of which 468 were treated to the left anterior descending with coronary artery bypass grafting with LIMA (n=314), percutaneous coronary intervention with BMS (n=94), and DES (n=60). Coronary angiograms were analyzed by quantitative coronary angiography (QCA; n=433). Cumulative downstream coronary and conduit disease progression were estimated by Kaplan–Meier method and effect of treatment type by Cox proportional hazard models. Patients treated with LIMA had significantly lower risk of downstream coronary disease progression at follow-up angiogram compared with BMS and DES (hazard ratio [HR] [95% CI], 0.34; [0.20–0.59]; P=0.0002; and HR [95% CI], 0.39; [0.20–0.79]; P=0.01, respectively). LIMA was associated with a lower risk of conduit disease progression compared to BMS and DES (HR [95% CI], 0.18; [0.12–0.28]; P<0.001; and HR [95% CI], 0.27; [0.16–0.46]; P<0.001, respectively). BMS was associated with higher HR for downstream coronary and conduit disease progression compared with DES, but the difference did not reach statistical significance (HR [95% CI], 1.13; [0.57–2.36]; P=0.73; and HR [95% CI], 1.46; [0.88–2.50]; P=0.14, respectively).

***Conclusions*—**LIMA grafting to left anterior descending is associated with significantly lower risk of downstream coronary and conduit disease progression compared to percutaneous coronary intervention with BMS and DES. **(*J Am Heart Assoc*. 2016;5: e003568 doi: 10.1161/JAHA.116.003568)**

Key Words: bare metal stent • conduit stenosis • coronary disease • drug eluting stent • left internal mammary artery • revascularization

Percutaneous coronary intervention (PCI) with stent deployment and coronary artery bypass grafting (CABG) have evolved as the standard modes of treatment in the management of coronary artery disease (CAD).[1] However, their effectiveness is limited by the recurrence of symptoms caused either by graft or stent failure or by progression of atherosclerosis in the native coronary vessels. Factors associated with long-term event-free survival post–coronary revascularization include the patient's preprocedural status and comorbidities, conduit patency, and the downstream atherosclerosis disease progression in the native coronary.[2] Conduit patency is related to the type of conduit and the mode of intervention used, endothelial function, and various risk factor modifications.[3,4] The superior patency rate of the internal mammary artery (IMA) compared with saphenous vein graft (SVG) is extensively described in the literature.[5] The unique biological properties and histological characteristics of IMA conduits used in CABG have been proposed as main factors contributing to the reduced susceptibility to atherosclerosis and superior long-term graft patency of IMA.[2,6]

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PCI with coronary stenting is currently the more-common treatment in patients with obstructive CAD. However, sufficient evidence illustrates the association between catheter-based coronary interventions and arterial injury, leading to endothelial dysfunction.[7,8] During stenting, endothelial cells are partially or completely destroyed along with medial wall injury and stretching, which promotes activation of platelets, and thrombus formation accompanied by inflammatory reaction.[9] Those reactions may have serious long-term clinical outcomes.[10]

Downstream coronary patency is important to maintain myocardial perfusion and prevent recurrence of symptoms and repeat interventions. Progression of downstream CAD and consequently, the increase in rates of repeat intervention might, as a result, decrease long-term survival rates of patients undergoing coronary revascularization. Previous studies have focused on the patency rate of CABGs and percutaneous coronary stents, but their effect on downstream vessel disease progression have been sparsely studied. The purpose of this study is to compare the effect of CABG with left internal mammary artery (LIMA) to the left anterior descending (LAD) coronary artery versus PCI using either bare metal stent (BMS) or drug eluting stent (DES) on downstream coronary atherosclerosis disease progression in multivessel CAD patients undergoing isolated primary coronary revascularization. We hypothesized that LIMA is associated with a lesser degree of downstream coronary and conduit disease progression compared with percutaneous coronary stents.

Methods

Between 1993 to 2012, 12 301 consecutive multivessel CAD patients underwent isolated primary coronary revascularization, either by CABG (n=8621) or PCI (n=3680). Only the first eligible revascularization record (index procedure) for each patient was analyzed. All patients were screened for follow-up angiograms at a minimum of 6 months after the index procedure. Exclusion criteria included age less than 18 years old, past coronary interventions, concomitant cardiac surgical procedures, isolated left main disease, single-vessel disease, coronary anomalies, absence of eligible follow-up angiogram, patients with myocardial infarction (MI) leading to sudden death and those with noncardiac causes of death preceding a follow-up angiogram, valvular heart disease, significant arrhythmias, and heart failure. Included in the study were 2386 patients (1450 PCI and 936 CABG patients) who met our inclusion criteria. To adjust for differences in

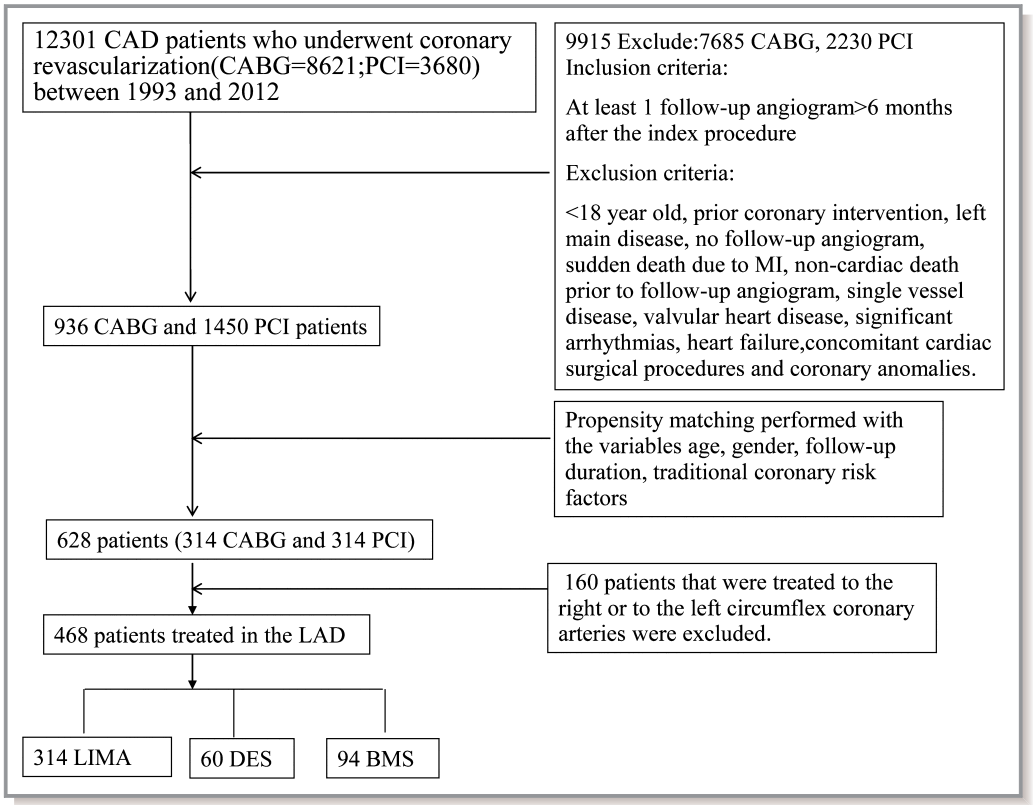

Figure 1. Patient selection flow. BMS indicates bare metal stent; CABG, coronary artery bypass grafting; CAD, coronary artery disease; DES, drug eluting stent; LAD, left anterior descending; LIMA, left internal mammary artery; MI, myocardial infarction; PCI, percutaneous coronary intervention.

baseline patient's characteristics, a propensity-score–matched analysis was performed and 628 patients were matched (314 in each group). Our investigation focused on intervention to the LAD only; hence, of the 628 matched patients, 160 that were treated to the right or to the left circumflex coronary arteries were excluded. We investigated 468 matched patients in 3 groups: CABG with LIMA to the LAD (n=314); PCI with BMS to the LAD (n=94); and PCI with DES to the LAD (n=60). Figure 1 summarizes the patient selection process.

Table 1. Patient Characteristics

Variable	LIMA (N=314)	BMS (N=94)	DES (N=60)	*P* Value
Age, y	65.6±9.2	65.4±8.4	65.0±10.6	0.92
Sex, N (%)				0.93
Female	74 (24)	24 (24)	14 (23)	
Male	240 (76)	70 (75)	46 (77)	
Left main disease, N (%)	11 (4)	2 (2)	2 (3)	0.74
No. of diseased vessels, N (%)				0.20
2	63 (20)	17 (18)	18 (30)	
3	245 (80)	77 (82)	42 (70)	
BMI	30.2±5.1	30.2±5.7	29.6±4.5	0.66
Diabetes Mellitus, N (%)	112 (36)	27 (29)	27 (45)	0.12
HTN, N (%)	246 (78)	73 (78)	44 (73)	0.70
Current smoking, N (%)	32 (10)	6 (6)	6 (10)	0.50
Dyslipidemia, N (%)	283 (90)	79 (84)	55 (92)	0.22
F/H CAD, N (%)	126 (40)	33 (35)	17 (28)	0.18
PVD, N (%)	54 (17)	10 (11)	4 (7)	0.04
Renal failure, N (%)	27 (9)	4 (4)	3 (5)	0.02
RS (mg/dL), median (Q1, Q3)	113.0 (100.0, 133.5)	111.0 (102, 133)	112.0 (101.0, 137.0)	0.95
Creatinine (mg/dL), median (Q1, Q3)	1.1 (1.0, 1.4)	1.1 (1.0, 1.3)	1.1 (0.9, 1.4)	0.18
BUN, median (Q1, Q3)	20.0 (16.0, 27.0)	19.0 (17.0, 23.0)	20.0 (15.0, 24.0)	0.03
TC (mg/dL), median (Q1, Q3)	150.0 (129.0, 175.2)	157.5 (136.5, 175.5)	159.5 (130.5, 174.8)	0.62
TG (mg/dL), median (Q1, Q3)	115.0 (84.8, 171.5)	125.0 (89.3, 173.0)	138.5 (94.3, 184.8)	0.21
LDL (mg/dL), median (Q1, Q3)	78.0 (61.8, 99.3)	85.0 (69.0, 99.5)	78.5 (62.3, 92.8)	0.15
HDL (mg/dL), median (Q1, Q3)	43.0 (36.0, 52.0)	42.5 (37.3, 55.8)	45.0 (37.3, 55.8)	0.56
Aspirin, N (%)	304 (97)	92 (98)	59 (98)	0.74
Clopidogrel, N (%)	104 (33)	39 (42)	41 (68)	<0.001
Beta-blockers, N (%)	262 (83)	82 (87)	56 (93)	0.08
ACEI/ARB, N (%)	223 (71)	68 (72)	42 (70)	0.95
CCBs, N (%)	185 (59)	50 (53)	36 (60)	0.58
Nitrates, N (%)	169 (54)	48 (51)	32 (53)	0.90
Statins, N (%)	306 (97)	89 (95)	59 (98)	0.35
Diuretics, N (%)	71 (23)	14 (15)	12 (20)	0.25
Insulin, N (%)	103 (33)	24 (26)	23 (38)	0.22
Oral hypoglycemics, N (%)	75 (24)	23 (25)	18 (30)	0.62
Mean follow-up duration	5.4±0.2	4.5±0.3	4.4±0.4	0.02

Numbers are presented as median (Q1, Q3) or mean±SD. Thirty-five patients had total conduit occlusion at follow-up and were therefore excluded from the quantitative coronary angiography analysis. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blockers; BMI, body mass index; BMS, bare metal stent; BUN, blood urea nitrogen; CCBs, calcium-channel blockers; DES, drug eluting stent; DM, diabetes mellitus; F/H CAD, family history of coronary artery disease; HDL-C, high-density lipoprotein-cholesterol; HTN, hypertension; LDL-C, low-density lipoprotein-cholesterol; LIMA, left internal mammary artery; PVD, peripheral arterial disease; RS, random glucose; TC, total cholesterol; TG, triglyceride.

Definitions of Terms and Data Collection

With approval of the Mayo Clinic Institutional Review Board (IRB 14-001228) and after obtaining patients' consent, data were collected retrospectively by conducting a review of the patient's clinical charts, the percutaneous transluminal coronary angioplasty registry, and the cardiac surgery computerized database. Patient data and definitions followed the American College of Cardiology database definitions and guidelines and the Society of Thoracic Surgeons National Cardiac Surgery database.

Quantitative and Qualitative Coronary Angiography Analysis

Patients' medical records were screened for follow-up angiograms. Indications for follow-up angiogram included typical cardiac chest pain with or without serum biomarker elevation, electrocardiographical evidence of ischemia or infarction, and a positive stress test. Follow-up angiograms were accepted to be included if performed after 6 months from the index procedure. Data collected from follow-up coronary angiogram included the date of the procedure, follow-up duration, diameter stenosis distal to the site of index procedural intervention, and the mode of intervention. Coronary artery percent stenosis at follow-up angiogram was evaluated by the performing physician.

Both baseline and follow-up coronary angiograms were analyzed with quantitative coronary angiography (QCA) by a single trained investigator (M.Z.) blinded to each patient using QAngio XA software (Version 7.3; Medis Medical Imaging System BV, Leiden, The Netherlands). In order for a lesion to be eligible for analysis, the following was required: reference vessel diameter ≥1.5 mm; diameter reduction of ≥30% at either baseline or follow-up angiogram; and a target vessel

Table 2. QCA Analysis for Downstream Segment

Variable	LIMA (N=291)	BMS (N=87)	DES (N=55)	*P* Value
Reference diameter, mm				
Baseline	1.9±0.4	2.2±0.4	2.2±0.4	<0.001
Follow-up	1.8±0.4	2.2±0.5	2.2±0.5	<0.001
P value	0.11	0.68	0.89	
Δ reference diameter	−0.01 (−0.1, 0.1)	0 (−0.2, 0.2)	0.04 (−0.1, 0.1)	0.33
Obstructive diameter, mm				
Baseline	1.6 (1.3, 1.8)	1.9 (1.5, 2.2)	1.9 (1.6, 2.2)	<0.001
Follow-up	1.4±0.4	1.5±0.5	1.5±0.5	0.35
P value	<0.001	<0.001	<0.001	
Δ obstructive diameter	−0.1 (−0.3, 0.01)	−0.3 (−0.7, −0.01)	−0.2 (−0.7, 0.02)	0.0002
Diameter stenosis (%)				
Baseline	13.7 (10.6, 17.2)	15.5 (12.1, 22.0)	12.6 (10.3, 16.4)	0.001
Follow-up	19.0 (13.8, 26.8)	32.5 (17.0, 46.7)	23.8 (14.7, 47.3)	<0.001
P value	<0.001	<0.001	<0.001	
Δ diameter stenosis (%)	4.1 (0.5, 12)	15.6 (2.0, 29.0)	10.8 (2.0, 31.0)	<0.0001
Area stenosis (%)				
Baseline	25.6 (20.1, 31.8)	28.5 (22.7, 38.8)	23.6 (19.5, 29.5)	0.0003
Follow-up	34.1 (25.7, 46.3)	54.5 (31.1, 71.6)	41.9 (27.3, 72.7)	<0.001
P value	<0.001	<0.001	<0.001	
Δ area stenosis (%)	7.2 (1.1, 19.1)	23.0 (3.8, 40.3)	10.8 (3.4, 42)	<0.0001
Obstruction length, mm				
Baseline	3.0 (2.3, 4.0)	3.4 (2.8, 4.7)	3.0 (2.3, 3.7)	0.01
Follow-up	3.66 (2.8, 5.0)	3.7 (2.7, 5.9)	4.4 (3.1, 7.4)	<0.001
P value	<0.001	<0.001	<0.001	
Δ obstruction length	0.45 (−0.3, 1.9)	1.36 (0.01, 4.1)	1.4 (−0.003, 3.8)	<0.0001

Numbers are presented as median (Q1, Q3) or mean±SD. BMS indicates bare metal stent; DES, drug eluting stent; LIMA, left internal mammary artery; QCA, quantitative coronary angiography.

that was adequately visualized in similar projections at both baseline and follow-up angiogram.

We examined disease progression in both the conduit and in the segment downstream to the conduit's touchdown by QCA analysis. In order to eliminate the anastomosis site and stent edge effects, we excluded the vessel segment 5 mm from the anastomosis and distal stent edge. The degree of progression in percent diameter stenosis and the progression of downstream coronary disease were defined as: (1) 30% luminal diameter reduction; (2) progression of any lesion to total occlusion; and (3) "new" lesions with a 30% diameter reduction in a segment that was normal at the first angiogram. Conduit patency was defined as less than 30% vessel stenosis (stent or graft).[11]

Statistical Analysis

The propensity score matching was developed using logistic regression and modeling treatment group with age, sex, age-sex interaction, diabetes mellitus, hypertension, dyslipidemia, current smoking, peripheral vascular disease, basal metabolic index, and number of diseased vessels. Matching was based on the propensity score (within 0.25 of the SD), age (within 5 years), sex, and index procedure date (within 2 years). We matched 628 patients between CABG and PCI groups (314 in each group). A total of 468 patients that were treated to the LAD only were included. Continuous data are summarized as mean (SD) or for skewed data median (25th, 75th percentile). Discrete data are summarized as frequency and percentage.

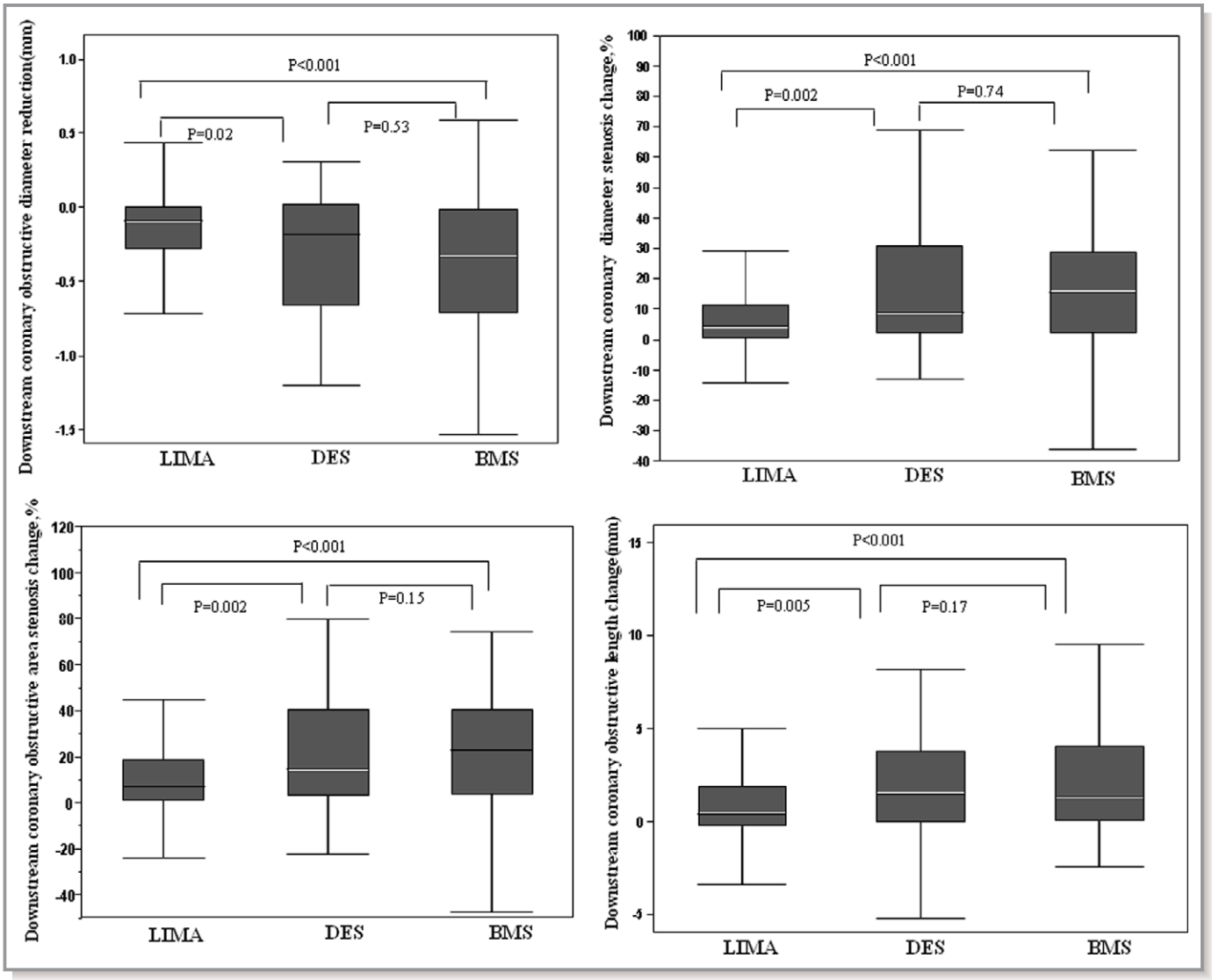

Figure 2. Change in obstructive diameter, percent diameter stenosis, percent area stenosis, and obstruction length in the downstream coronary segment from baseline to follow-up compared between LIMA versus BMS versus DES. (Among 468 patients, 35 had total conduit occlusion at follow-up and were therefore excluded from the analysis.) BMS indicates bare metal stent; DES, drug eluting stent; LIMA, left internal mammary artery.

Group comparisons between LIMA, BMS, and DES were performed with 2-way ANOVA for continuous variables followed by Student *t* test with post-hoc Bonferroni correction and Pearson chi-squared for categorical variables. Significant difference from control value was indicated by $P<0.05$. Continuous variables were compared between postprocedure and follow-up using 2-tailed, paired *t* tests, or, if parameters were not normally distributed, then using Wilcoxon test. Kaplan–Meier survival curves were generated and the log-rank test was used to assess differences in survival. Multivariate Cox proportional models were developed to determine the hazards ratios (HRs) for downstream coronary and conduit disease progression in patients with LIMA compared with BMS and DES, after adjusting for the following variables: age, sex, age-sex interaction, diabetes mellitus, hypertension, dyslipidemia, current smoking, peripheral vascular disease, basal metabolic index, and number of diseased vessels. All statistical analyses were performed using JMP software (version 9; SAS Institute Inc., Cary, NC).

Results

Baseline Patient Characteristics

Characteristics of patients treated with LIMA, BMS, and DES are shown in Table 1. CABG patients (patients treated with LIMA) had significantly more peripheral vascular disease and renal failure. Among PCI patients, clopidogrel treatment was significantly more common. Mean follow-up duration from index procedure to follow-up angiogram was similar between CABG and PCI groups (5.4±3.4 vs 5.3±3.4 years, respectively; $P=0.67$).

Downstream Coronary Disease Progression in Patients With Revascularization of the LAD

Downstream coronary disease progression in the LAD was assessed by follow-up angiogram. Among 468 patients, 35 (7.5%) had total conduit occlusion at follow-up and were therefore excluded from the analysis. We evaluated downstream disease progression by measuring obstructive diameter (vessel diameter at the narrowest point of the obstructive lesion, in millimeters [mm]), percentage of diameter stenosis (obstructive diameter/reference diameter [%]), percentage of area stenosis (obstructive lesion area/reference vessel area [%]), and obstruction length (maximal longitudinal length of the obstructive lesion, [mm]) using QCA. Compared to baseline, follow-up angiograms for the distal segment showed that obstructive diameter significantly decreased ($P<0.001$), whereas percentage diameter stenosis, area stenosis, and obstruction length significantly increased ($P<0.001$, respectively; Table 2).

Table 3. Hazard Ratios* for Downstream Coronary Disease Progression in Patients Who Underwent Revascularization of LAD

Description	HR	95% CI	*P* Value
LIMA vs BMS	0.34	0.20 to 0.59	0.0002
LIMA vs DES	0.39	0.20 to 0.79	0.01
BMS vs DES	1.13	0.57 to 2.36	0.73

LIMA (n=314), BMS (n=94), and DES (n=60). BMS indicates bare metal stent; DES, drug eluting stent; HR, hazard ratio; LAD, left anterior descending; LIMA, left internal mammary artery.
*Adjusted for age, sex, age-sex interaction, diabetes mellitus, hypertension, dyslipidemia, current smoking, peripheral vascular disease, basal metabolic index, and number of diseased vessels.

There was a significant difference between LIMA, BMS, and DES in the change occurring in obstructive diameter, percentage diameter stenosis, area stenosis, and obstruction length. Compared to LIMA, BMS and DES showed a significant reduction in obstructive diameter (−0.1 vs −0.3 and −0.2 mm, $P=0.0002$, respectively), and a significant increase in percent diameter stenosis (4.1% vs 15.6% and 10.8%, $P<0.001$, respectively), percent area stenosis (7.2% vs 23.0% and 10.8%, $P=0.0002$, respectively), and obstruction length (0.45 vs 1.36 and 1.43 mm, $P<0.0001$, respectively; Figure 2).

We performed qualitative analysis according to our previous definition.[11] At follow-up angiogram, 68 patients (15.7%), treated with LIMA (n=31), BMS (n=25), and DES (n=12), developed downstream coronary disease progression in the LAD. Downstream coronary stenoses were found to be less frequent with LIMA compared with BMS and DES (10.7% vs 28.7% and 21.1%, respectively; $P=0.0003$). Revascularization

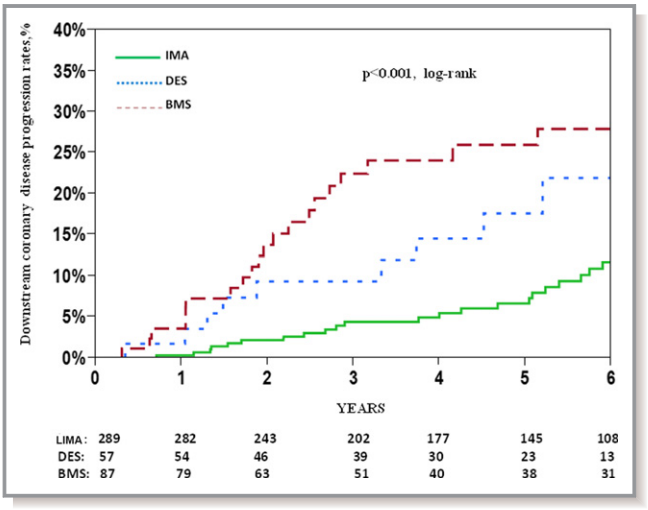

Figure 3. Kaplan–Meier estimated cumulative downstream coronary disease progression rates in patients who underwent revascularization of LAD (LIMA vs BMS vs DES; log-rank test, $P<0.001$). BMS indicates bare metal stent; DES, drug eluting stent; IMA, internal mammary artery; LAD, left anterior descending; LIMA, left internal mammary artery.

with LIMA was associated with significantly lower HR for downstream disease progression compared with BMS and DES (HR [95% CI], 0.34 [0.20–0.59]; P=0.0002; and HR [95% CI], 0.39 [0.20–0.79]; P=0.01, respectively). Although BMS was associated with a higher HR compared with DES, the difference was not statistically significant (HR [95% CI], 1.13 [0.57–2.36]; P=0.73; Table 3).

Six-year Kaplan–Meier estimated cumulative downstream coronary stenoses rate in the LAD was significantly lower for LIMA versus BMS and DES (log-rank test, P<0.001; Figure 3).

Conduit Disease Progression in Patients With Revascularization of the LAD

At follow-up investigation of conduit segments, the QCA analysis showed that obstructive diameter significantly decreased (P<0.001), whereas percentage diameter stenosis, area stenosis, and obstruction length were significantly increased (P<0.0001, respectively; Table 4).

Changes observed in conduit segment for obstructive diameter, percentage diameter stenosis, area stenosis, and obstruction length were evaluated among LIMA, BMS, and DES. Compared to LIMA, BMS and DES showed significant obstructive diameter reduction (−0.01 vs −0.7 and −0.3 mm; P<0.001), whereas there was significantly increased percentage diameter stenosis (1.0% vs 20.4% and 6.9%, P<0.001, respectively), percent area stenosis (2.0% vs 28.8% and 11.4%, P<0.001, respectively), and obstruction length (0.2 vs 2.9 and 1.1 mm, P<0.0001, respectively) increase (Figure 4).

We also performed qualitative analysis for conduit progression based on our QCA measurement. One hundred six patients (22.7%) treated with LIMA (n=36), BMS (n=49), and DES (n=21) developed conduit disease progression. LIMA was

Table 4. QCA Analysis for Conduit Segment

	LIMA (N=291)	BMS (N=87)	DES (N=55)	*P* Value
Reference diameter, mm				
Baseline	2.7±0.6	2.9±0.6	3.2±0.6	<0.001
Follow-up	2.7±0.6	2.9±0.5	3.1±0.7	<0.001
P value	0.53	0.10	0.36	
Δ reference diameter	0.01 (−0.1, 0.7)	−0.1 (−0.3, 0.2)	0.01 (0.2, 0.1)	0.08
Obstructive diameter, mm				
Baseline	2.5±0.5	2.5±0.5	2.8±0.6	<0.001
Follow-up	2.4±0.6	1.9±0.1	2.3±0.8	<0.001
P value	<0.001	<0.001	<0.001	
Δ obstructive diameter	−0.01 (−0.1, 0.04)	−0.7 (−1.0, −0.2)	−0.3 (−1.0, 0.03)	<0.0001
Diameter stenosis (%)				
Baseline	8.5 (6.5, 10.3)	13.2 (9.2, 16.3)	11.5 (8.4, 14.3)	<0.001
Follow-up	9.1 (6.9, 13.2)	36 (20.5, 47.3)	19.1 (11.8, 42.1)	<0.001
P value	<0.001	<0.001	<0.001	
Δ diameter stenosis (%)	1.0 (−0.8, 3.4)	20.4 (7.7, 35.0)	6.9 (1.7, 31.1)	<0.0001
Area stenosis (%)				
Baseline	16.1 (12.5, 20.4)	24.2 (17.6, 29.9)	21.6 (16.1, 26.5)	<0.001
Follow-up	17.4 (13.4, 25.0)	58.7 (36.5, 70.8)	34.6 (22.2, 65.5)	<0.001
P value	<0.001	<0.001	<0.001	
Δ area stenosis (%)	2.0 (−1.3, 6.2)	28.8 (11.8, 48.0)	11.4 (3.1, 43.0)	<0.0001
Obstruction length, mm				
Baseline	3.3 (2.6, 4.4)	3.5 (2.4, 4.5)	3.0 (2.1, 4.2)	<0.001
Follow-up	3.5 (2.8, 4.4)	6.0 (4.1, 9.2)	4.0 (2.9, 6.2)	<0.001
P value	0.05	<0.001	0.001	
Δ obstruction length	0.2 (−0.9, 1.3)	2.9 (0.4, 5.4)	1.1 (−0.1, 2.2)	<0.0001

Numbers are presented as median (Q1, Q3) or mean±SD. BMS indicates bare metal stent; DES, drug eluting stent; LIMA, left internal mammary artery; QCA, quantitative coronary angiography.

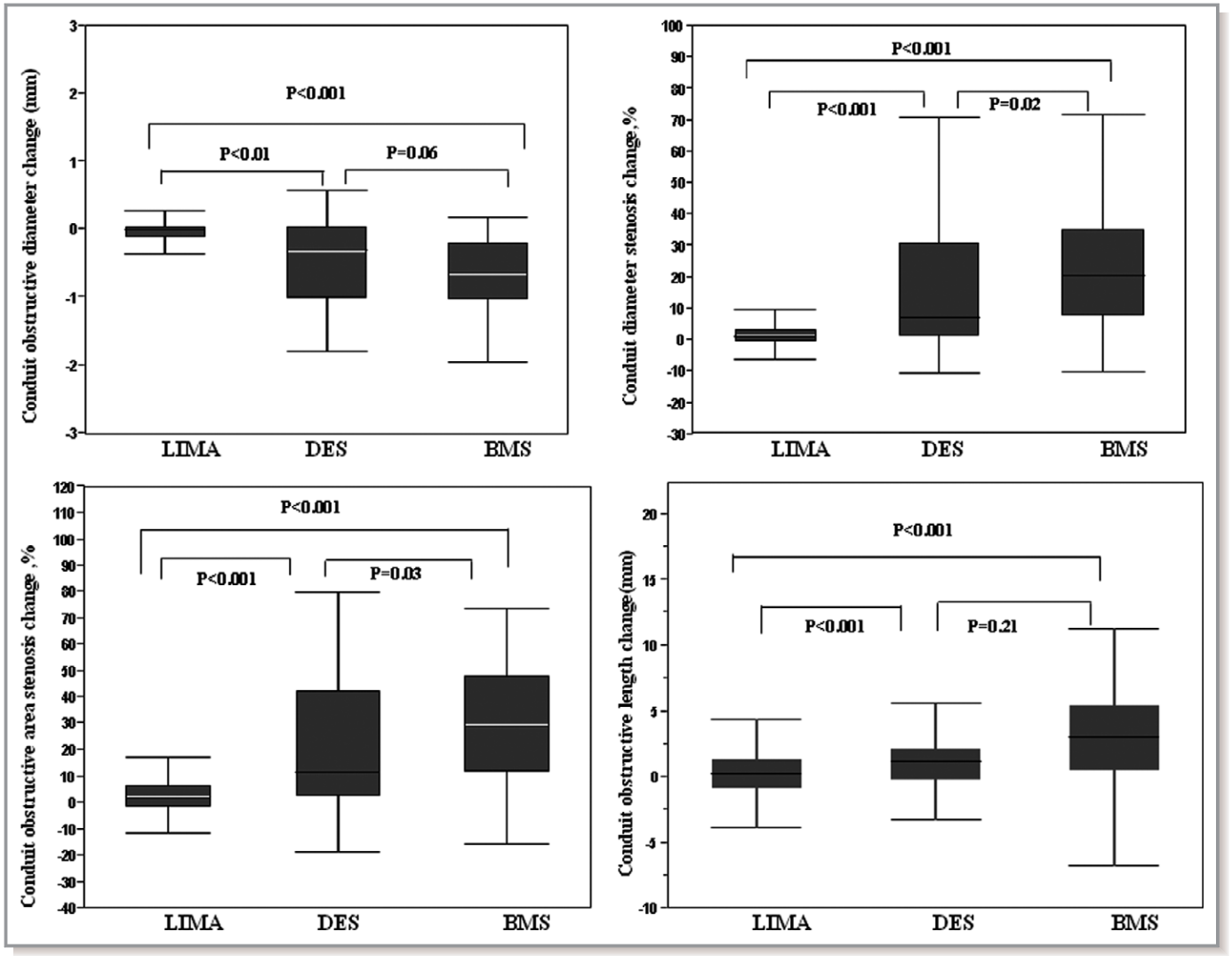

Figure 4. Change in obstructive diameter, percent diameter stenosis, percent area stenosis, and obstruction length in the conduit segment from baseline to follow-up compared between LIMA versus BMS versus DES. (Among 468 patients, 35 had total conduit occlusion at follow-up and were therefore excluded from the analysis.) BMS indicates bare metal stent; DES, drug eluting stent; LIMA, left internal mammary artery.

associated with significantly lower risk for conduit disease progression as compared with BMS and DES (HR [95% CI], 0.18 [0.12–0.28]; $P<0.001$; and HR [95% CI], 0.27 [0.16–0.46]; $P<0.001$, respectively). BMS was associated with a higher HR for conduit disease progression compared with DES, but the difference was not statistically significant (HR [95% CI], 1.46 [0.88–2.50]; $P=0.14$; Table 5).

Seven-year Kaplan–Meier estimated cumulative conduit disease progression rate was also significantly lower for LIMA versus BMS and DES (log-rank test, $P<0.001$; Figure 5).

Discussion

This study, which involved patients treated for multivessel CAD, has shown that patients treated with CABG with LIMA to the LAD had significantly lower risk of downstream coronary and conduit disease progression compared to PCI patients treated with either BMS or DES. These findings may provide important clinical insight into the superior long-term graft patency, decreased repeat revascularization rate, and increased event-free long-term survival benefit exhibited in patients undergoing CABG with the use of 1 or more IMAs.

Significant evolvements in the field of PCI have led to a rising preference for PCI procedures in the management of obstructive CAD over CABG.[1] However, in a meta-analysis of trials for multivessel CAD, repeat revascularization was significantly more frequent in PCI patients compared with patients undergoing CABG.[12] Factors leading to repeat revascularization include both conduit restenosis and/or native vessel disease progression.[13,14] Goy et al evaluated 10-year clinical outcome in the SIMA (Stent versus Internal Mammary Artery Grafting) trial. They demonstrated excellent similar long-term outcomes for patients treated with either mode of revascularization; however, coronary stents were

Table 5. Hazard Ratios* for Conduit Disease Progression in Patients Who Underwent Revascularization of LAD

Description	HR	95% CI	*P* Value
LIMA vs BMS	0.18	0.12 to 0.28	<0.001
LIMA vs DES	0.27	0.16 to 0.46	<0.001
BMS vs DES	1.46	0.88 to 2.50	0.14

LIMA (n=314), BMS (n=94), DES (n=60). BMS indicates bare metal stent; DES, drug eluting stent; HR, hazard ratio; LAD, left anterior descending; LIMA, left internal mammary artery.
*Adjusted for age, sex, age-sex interaction, diabetes mellitus, hypertension, dyslipidemia, current smoking, peripheral vascular disease, basal metabolic index, and number of diseased vessels.

significantly associated with an increased need for repeat interventions.[15]

Most studies investigating target vessel disease progression after revascularization procedures focused mainly on conduit patency, as opposed to downstream disease progression of the native vessels. Our findings suggest that the LIMA, in addition to maintaining improved self-patency, is also associated with a lesser degree of downstream distal vessel disease progression as compared with BMS and DES. This finding might explain the mounting evidence in recent literature, showing increased event-free long-term survival in patients treated with CABG as compared to those treated with PCI in complex multivessel CAD.[13,14] Our results support previous findings, which demonstrated that use of multiarterial grafts in CABG may provide a strong protective effect against native CAD progression and excellent conduit patency and survival rates in patients undergoing CABG.[16]

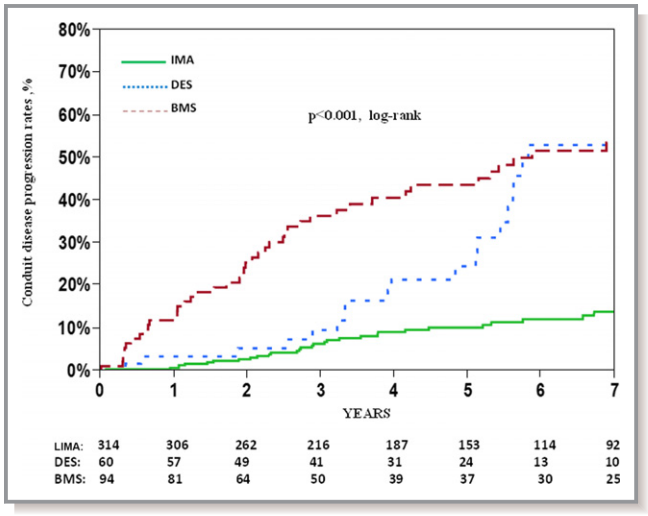

Figure 5. Kaplan–Meier estimated cumulative conduit disease progression rates in patients who underwent revascularization of LAD (LIMA vs BMS vs DES; log-rank test, *P*<0.001). BMS indicates bare metal stent; DES, drug eluting stent; IMA, internal mammary artery; LAD, left anterior descending; LIMA, left internal mammary artery.

The mechanism by which LIMA confers protection against CAD progression was extensively investigated. The biological properties of the endothelium and vascular smooth muscle significantly contribute to the function and patency of coronary bypass grafts, whereas the internal mammary artery has near-ideal characteristics.[5,11] Lüscher et al and others reported that both basal release of nitric oxide and endothelium-derived hyperpolarizing factor (EDHF)-mediated hyperpolarization were significantly greater in IMA.[17–19] Further studies demonstrated that release of endothelium-derived nitric oxide and prostacyclin from bypass grafts into the lumen could promote the vasodilatation of distal coronary arterial beds, enhancing myocardial perfusion.[20] In addition, the presence of smooth muscle layer in the arterial wall enables the conduit to adjust its caliber to the amount of coronary flow in the native coronary, which, in turn, creates less turbulence at the distal anastomosis.[21] The presence of active and functional endothelium protects graft vessels from vasoconstriction and atherosclerosis by regulation of vasoactive substances and, consequently, long-term conduit patency and improved graft survival.[17,22]

On the contrary, restenosis after angioplasty and stent implantation has been long considered as arguably the most significant obstacle in coronary interventional treatment.[23] DES has substantially reduced the rate of restenosis and target lesion revascularization compared with BMS. However, some rate of in-stent restenosis after deployment of DES into the coronary artery still remains, and this was reported to occur in the range of 3% to 20% of patients, depending on the patient and lesion characteristics and the type of DES used.[24] The length of treatment with dual antiplatelet therapy and the risk of long-term stent thrombosis associated with DES are also increased.[25] Additional possible mechanisms for the inferior patency of stents are implied by their interference with pathways in the process of impaired endothelial repair, inflammation, and neointimal proliferation.[24,26]

In accord to the above-mentioned studies, our results suggest that coronary stents are associated with a higher risk of conduit disease progression as compared with the LIMA graft.

More important, our study results demonstrated a significant difference in the rate of downstream coronary disease progression among different types of conduits (LIMA vs DES vs BMS) in patients undergoing revascularization to the LAD. The LIMA clearly exhibited less downstream atherosclerotic disease progression in the LAD compared with PCI stents. These results may suggest that the initial selection of conduits might have a more-important impact on late outcome than other factors appearing later after the intervention, including progression of the atherosclerotic disease in treated and untreated coronaries.[15]

Our study found no significant difference between DES and BMS on distal vessel progression. Although previous studies

have investigated the impact of type of stent on downstream coronary disease progression, the conclusions from these studies are conflicting.[27,28] Of note, in our study, the number of vessels revascularized by DES was relatively small compared with BMS and LIMA. This may have influenced the results, and therefore further research involving larger number of patients is warranted in order to confirm our findings.

Limitation

Our study had several limitations. It is retrospective and from a single center and involves a relatively small matched cohort. Although we were able to control for all known differences among the study groups with propensity-score–matched analysis, and to adjust for multiple risk factors that may potentially affect disease progression, this form of analysis may be limited by inherent selection bias. In addition, if we would match the cohort by the type of vessel or by the segment treated and referenced by angiographic criteria, our study sample would decrease substantially. Another limitation was the difference in location of the conduit in the coronary artery; in patients receiving stents in proximal LAD lesions, the coronary segment distal to the conduit is relatively longer than the segment distal to the LIMA anastomosis, and this may increase the risk of coronary disease progression.

Additionally, the patients must have had a follow-up angiogram to be included in the study. Acquisition of follow-up angiograms was symptom driven and was not always confirmed by stress testing. Last, the study was not designed to measure clinical outcomes related to distal vessel disease progression and it extended over a long period of time, during which both CABG and PCI procedures evolved. Nonetheless, we do think that further studies with a larger number of patients included, and enabling more-complete adjustment for angiographic criteria, are warranted in the future.

Conclusions

LIMA graft to the LAD coronary artery reduces significantly the risk of downstream coronary and conduit disease progression compared with PCI with BMS and DES in patients treated for multivessel coronary disease. This may explain the increased long-term graft patency, decreased repeat revascularization, and improved event-free long-term survival rates of patients undergoing CABG with the LIMA grafted to the LAD as compared to PCI-treated patients.

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Disclosures

None.

References

1. Sipahi I, Akay MH, Dagdelen S, Blitz A, Alhan C. Coronary artery bypass grafting vs percutaneous coronary intervention and long-term mortality and morbidity in multivessel disease: meta-analysis of randomized clinical trials of the arterial grafting and stenting era. *JAMA Intern Med*. 2014;174:223–230.
2. Tranbaugh RF, Dimitrova KR, Friedmann P, Geller CM, Harris LJ, Stelzer P, Cohen B, Hoffman DM. Radial artery conduits improve long-term survival after coronary artery bypass grafting. *Ann Thorac Surg*. 2010;90:1165–1172.
3. Matsuzawa Y, Lerman A. Endothelial dysfunction and coronary artery disease: assessment, prognosis, and treatment. *Coron Artery Dis*. 2014;25:713–724.
4. Gutiérrez E, Flammer AJ, Lerman LO, Elízaga J, Lerman A, Fernández-Avilés F. Endothelial dysfunction over the course of coronary artery disease. *Eur Heart J*. 2013;34:3175–3181.
5. Otsuka F, Yahagi K, Sakakura K, Virmani R. Why is the mammary artery so special and what protects it from atherosclerosis? *Ann Cardiothorac Surg*. 2013;2:519–526.
6. Cheng A, Slaughter MS. How I choose conduits and configure grafts for my patients-rationales and practices. *Ann Cardiothorac Surg*. 2013;2:527–532.
7. Leroy F, McFadden EP, Lablanche JM, Bauters C, Quandalle P, Bertrand ME. Prognostic significance of silent myocardial ischaemia during maximal exercise testing after a first acute myocardial infarction. *Eur Heart J*. 1993;14:1471–1475.
8. Mc Fadden EP, Bauters C, Lablanche JM, Quandalle P, Leroy F, Bertrand ME. Response of human coronary arteries to serotonin after injury by coronary angioplasty. *Circulation*. 1993;88:2076–2085.
9. Chaabane C, Otsuka F, Virmani R, Bochaton-Piallat ML. Biological responses in stented arteries. *Cardiovasc Res*. 2013;99:353–363.
10. 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;71:220–225.
11. Zouridakis EG, Schwartzman R, Garcia-Moll X, Cox ID, Fredericks S, Holt DW, Kaski JC. Increased plasma endothelin levels in angina patients with rapid coronary artery disease progression. *Eur Heart J*. 2001;22:1578–1584.
12. Daemen J, Boersma E, Flather M, Booth J, Stables R, Rodriguez A, Rodriguez-Granillo G, Hueb WA, Lemos PA, Serruys PW. Long-term safety and efficacy of percutaneous coronary intervention with stenting and coronary artery bypass surgery for multivessel coronary artery disease: a meta-analysis with 5-year patient-level data from the ARTS, ERACI-II, MASS-II, and SoS trials. *Circulation*. 2008;118:1146–1154.
13. Head SJ, Davierwala PM, Serruys PW, Redwood SR, Colombo A, Mack MJ, Morice MC, Holmes DR Jr, Feldman TE, Ståhle E, Underwood P, Dawkins KD, Kappetein AP, Mohr FW. Coronary artery bypass grafting vs. percutaneous coronary intervention for patients with three-vessel disease: final five-year follow-up of the SYNTAX trial. *Eur Heart J*. 2014;35:2821–2830.
14. Morice MC, Serruys PW, Kappetein AP, Feldman TE, Ståhle E, Colombo A, Mack MJ, Holmes DR, Choi JW, Ruzyllo W, Religa G, Huang J, Roy K, Dawkins KD, Mohr F. Five-year outcomes in patients with left main disease treated with either percutaneous coronary intervention or coronary artery bypass grafting in the synergy between percutaneous coronary intervention with taxus and cardiac surgery trial. *Circulation*. 2014;129:2388–2394.
15. Goy JJ, Kaufmann U, Hurni M, Cook S, Versaci F, Ruchat P, Bertel O, Pieper M, Meier B, Chiarello L, Eeckhout E; SIMA Investigators. 10-year follow-up of a prospective randomized trial comparing bare-metal stenting with internal mammary artery grafting for proximal, isolated de novo left anterior coronary artery stenosis the SIMA (Stenting versus Internal Mammary Artery grafting) trial. *J Am Coll Cardiol*. 2008;52:815–817.
16. Locker C, Schaff HV, Dearani JA, Joyce LD, Park SJ, Burkhart HM, Suri RM, Greason KL, Stulak JM, Li Z, Daly RC. Multiple arterial grafts improve late survival of patients undergoing coronary artery bypass graft surgery: analysis of 8622 patients with multivessel disease. *Circulation*. 2012;126:1023–1030.
17. Lüscher TF. Vascular biology of coronary bypass grafts. *Curr Opin Cardiol*. 1991;6:868–876.

18. Lüscher TF, Diederich D, Siebenmann R, Lehmann K, Stulz P, von Segesser L, Yang ZH, Turina M, Grädel E, Weber E. Difference between endothelium-dependent relaxation in arterial and in venous coronary bypass grafts. *N Engl J Med*. 1988;319:462–467.
19. Liu ZG, Ge ZD, He GW. Difference in endothelium-derived hyperpolarizing factor-mediated hyperpolarization and nitric oxide release between human internal mammary artery and saphenous vein. *Circulation*. 2000;102:III296–III301.
20. Pearson PJ, Evora PR, Discigil B, Schaff HV. Hypoxia increases vasodilator release from internal mammary artery and saphenous vein grafts. *Ann Thorac Surg*. 1998;65:1220–1225.
21. Verhoeff BJ, Siebes M, Meuwissen M, Atasever B, Voskuil M, de Winter RJ, Koch KT, Tijssen JG, Spaan JA, Piek JJ. Influence of percutaneous coronary intervention on coronary microvascular resistance index. *Circulation*. 2005;111:76–82.
22. Lüscher TF. Endothelium-derived nitric oxide: the endogenous nitrovasodilator in the human cardiovascular system. *Eur Heart J*. 1991;12(suppl E):2–11.
23. Stettler C, Wandel S, Allemann S, Kastrati A, Morice MC, Schömig A, Pfisterer ME, Stone GW, Leon MB, de Lezo JS, Goy JJ, Park SJ, Sabaté M, Suttorp MJ, Kelbaek H, Spaulding C, Menichelli M, Vermeersch P, Dirksen MT, Cervinka P, Petronio AS, Nordmann AJ, Diem P, Meier B, Zwahlen M, Reichenbach S, Trelle S, Windecker S, Jüni P. Outcomes associated with drug-eluting and bare-metal stents: a collaborative network metaanalysis. *Lancet*. 2007;370:937–948.
24. Dangas GD, Claessen BE, Caixeta A, Sanidas EA, Mintz GS, Mehran R. In-stent restenosis in the drug-eluting stent era. *J Am Coll Cardiol*. 2010;56:1897–1907.
25. Holmes DR Jr, Kereiakes DJ, Garg S, Serruys PW, Dehmer GJ, Ellis SG, Williams DO, Kimura T, Moliterno DJ. Stent thrombosis. *J Am Coll Cardiol*. 2010;56:1357–1365.
26. Van der Heiden K, Gijsen FJ, Narracott A, Hsiao S, Halliday I, Gunn J, Wentzel JJ, Evans PCL. The effects of stenting on shear stress: relevance to endothelial injury and repair. *Cardiovasc Res*. 2013;99:269–275.
27. Krasuski RA, Cater GM, Devendra GP, Wolski K, Shishehbor MH, Nissen SE, Oberti C, Ellis SG. Downstream coronary effects of drug-eluting stents. *Am Heart J*. 2011;162:764–771.
28. Wakabayashi K, Mintz GS, Weissman NJ, Stone GW, Ellis SG, Grube E, Ormiston JA, Turco MA, Pakala R, Xue Z, Desale S, Laynez-Carnicero A, Romaguera R, Sardi G, Pichard AD, Waksman R. Impact of drug-eluting stents on distal vessels. *Circ Cardiovasc Interv*. 2012;5:211–219.