

Temporal Trends in Revascularization Strategy and Outcomes in Left Main Coronary Artery Stenosis

Data From the Asan Medical Center-Left Main Revascularization Registry

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Background—Changes over time in revascularization strategies and outcomes among patients with unprotected left main coronary artery stenosis remain largely unknown.

Methods and Results—A total of 2618 consecutive patients with unprotected left main coronary artery stenosis who underwent revascularization were identified from the ASAN Medical Center-Left MAIN Revascularization registry and classified by time periods: bare metal stent (wave 1, 1995–1998), early drug-eluting stents (wave 2, 2003–2006), and late drug-eluting stents (wave 3, 2007–2010). Primary end point was major adverse cerebrocardiovascular events (the composite of death, myocardial infarction, repeat revascularization, and stroke). During the study period, 1124 patients underwent percutaneous coronary intervention (PCI) and 1494 patients underwent coronary artery bypass grafting. The proportion of PCI significantly increased from 35% to 52% between waves 1 and 3. In patients receiving PCI, the risk-adjusted incidence rate of major adverse cerebro-cardiovascular events decreased from 20.18 cases per 100 person-years in wave 1 to 6.77 cases per 100 person-years in wave 3 ($P < 0.001$ for trend). Death, the composite of death, myocardial infarction, stroke, and repeat revascularization were also significantly decreased by 40%, 35%, and 46%, respectively. The risk-adjusted incidence rate of major adverse cerebrocardiovascular events did not change in patients receiving coronary artery bypass grafting. The difference major adverse cerebrocardiovascular events risk between PCI and coronary artery bypass grafting progressively reduced (adjusted hazard ratio [95% confidence interval], 0.33 [0.23–0.47]; 0.53 [0.35–0.80]; and 1.01 [0.68–1.49] from wave 1 to wave 3.

Conclusions—The outcomes of unprotected left main coronary artery PCI have significantly improved over time. In addition, more patients received PCI for unprotected left main coronary artery stenosis in recent years. (*Circ Cardiovasc Interv.* 2015;8:e001846. DOI: 10.1161/CIRCINTERVENTIONS.114.001846.)

Key Words: bypass surgery, coronary artery ■ cerebral revascularization ■ coronary artery disease ■ stent

Significant unprotected left main coronary artery (ULMCA) disease is observed in $\approx 5\%$ of patients undergoing coronary angiography.¹ Coronary artery bypass grafting (CABG) has been considered the standard care for such patients. However, since the introduction of percutaneous coronary intervention (PCI), the accumulation of experience, coupled with improved technology and pharmacology, has led to this approach being rapidly evolved and broadly adopted in ULMCA stenosis. In addition, several studies demonstrate that PCI and CABG show comparable long-term incidences of death, myocardial infarction (MI), or stroke.^{2–4} Therefore, ULMCA PCI may be a potential alternative to CABG in selected situations.^{5,6} However, the extent

and time course of changes in revascularization strategies are not well documented, and whether such changes are associated with improved outcome is unknown.

See Editorial by Stone

This retrospective study evaluated temporal trends in revascularization strategies and outcomes in patients from the Asan Medical Center-Left Main Revascularization (ASAN MAIN) registry who received PCI or CABG for significant ULMCA stenosis.

Methods

The study population was from the ASAN MAIN registry and included 2630 patients treated between January 1995 and December 2010.

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WHAT IS KNOWN

- Coronary artery bypass grafting has been considered standard care for patients with significant unprotected left main coronary artery stenosis.
- Recently among selected patients, percutaneous coronary intervention (PCI) has been considered as a potential alternative to coronary artery bypass grafting.

WHAT THE STUDY ADDS

- Comorbidities and the extent of coronary disease have become more complex in unprotected left main coronary artery patients undergoing either PCI or coronary artery bypass grafting over time.
- Nevertheless, rates of adverse events among patients treated with PCI have declined.
- The gap in treatment effect between PCI and coronary artery bypass grafting has decreased, and more patients are receiving PCI for the treatment for unprotected left main coronary artery stenosis.

The ASAN MAIN registry was designed to investigate the real world outcomes of PCI and CABG for patients with significant ULMCA stenosis. The details of the design and the 5-year outcomes for the registry have been reported previously.⁷ Significant ULMCA stenosis was defined as a visually estimated stenosis of >50% diameter. Patients who underwent concomitant valvular or aortic surgery, those who had an acute MI within 24 hours before revascularization, or those who presented with cardiogenic shock were excluded from this analysis. Target patients population was on either elective or urgent situation, but not on emergent situation. The Institutional Review Board of the Asan Medical Center approved the use of clinical data for this study, and all patients provided written informed consent for enrollment in the registry.

From January 1995 to May 2003, coronary stenting was performed exclusively with bare metal stents (BMS), whereas from May 2003 to December 2010, drug-eluting stents (DES) were used exclusively. Therefore, the patients were classified as BMS (wave 1, 1995–1998), early DES (wave 2, 2003–2006), and late DES (wave 3, 2007–2010).

Procedures

Patients underwent PCI instead of CABG because of either the patient's or physician's preference or because of the high risk associated with CABG. Methods of stent implantation for patients with ULMCA disease have been described previously.² All procedures were performed with standard interventional techniques. The use of predilation, intra-aortic balloon pumps, or intravascular ultrasound (IVUS), and the choice of the specific type of stents was at the operator's discretion. Antiplatelet therapy and periprocedural anticoagulation followed standard regimens. After the procedure, aspirin was continued indefinitely. Patients treated with BMS were prescribed ticlopidine (250 mg BID) for ≥1 month, and patients treated with DES were prescribed clopidogrel (75 mg QD) for ≥6 months, regardless of DES type. Treatment beyond this duration was at the discretion of the physician. Surgical revascularization was performed using standard bypass techniques. Complete revascularization was performed when possible with arterial conduits or saphenous vein grafts. Mainly, attempts were made to graft the left internal mammary artery to the left anterior descending artery. On- or off-pump surgery was performed at the surgeon's discretion.⁸

Clinical End Points and Follow-Up

The clinical outcomes of interest were death, the composite of all-cause death, MI, and stroke, any repeat revascularization and the composite of death, MI, stroke and repeat revascularization (MACCE), post-PCI, or CABG. Deaths were considered cardiac unless an unequivocal, noncardiac cause was established. MI was defined as an increase in the creatine kinase myocardial band concentration to >5× the upper limit of the normal range and any of following: new pathological Q waves or new bundle branch block, angiographic documented new graft or new native coronary occlusion, or demonstration of new loss of viable myocardium or new regional wall motion abnormalities if occurring within 48 hours of the procedure, or any increase in creatine kinase myocardial band concentration to greater than the upper limit of the normal range, plus ischemic symptoms or signs if occurring >48 hours after the procedure.⁹ Repeat revascularization included target vessel revascularization, regardless of whether the procedure was clinically or angiographically driven, and nontarget vessel revascularization. Stroke, as indicated by neurological deficits, was established by a neurologist on the basis of imaging studies. All outcomes of interest were carefully verified and adjudicated by independent clinicians.

Statistical Analysis

Clinical, angiographic, procedural, and operative data were summarized for the patient groups as numbers (percentages) for categorical variables and as median (interquartile range) for continuous variables. Differences in the parameters between the groups were compared using the Kruskal–Wallis test for continuous variables, and the χ^2 test for categorical variables.

Initially, we analyzed the trends of outcomes separately for PCI and CABG. We calculated the crude incidence rate per 100 person-year as follows: the crude incidence rate=number of cases/the summation of time spent in the study across all participants×100. Variables with a *P* value ≤0.20 in univariate analyses were candidates for multiple Cox proportional hazards regression model. A backward elimination process was used to develop the final multivariable models, using a threshold of 0.1 for variable elimination. Our independent variable, waves, was included as categorical variable with wave 3 as the reference in the final multivariable models. The results of the final models are provided in the Appendix in the Data Supplement. We multiplied the adjusted hazard ratio for each wave by the crude incidence rate to obtain risk-adjusted incidence rates. We also evaluated waves as continuous variable to obtain adjusted hazard ratio for time trends. For the comparison between PCI and CABG according to the wave, we compared the each outcome between groups in similar ways as described above. Patients without experiencing events were censored at 2 years (720 days).

All reported *P* values were 2 sided, and a value of *P*<0.05 was considered statistically significant. SAS software, version 9.1 (SAS Institute, Inc, Cary, NC), was used for statistical analyses.

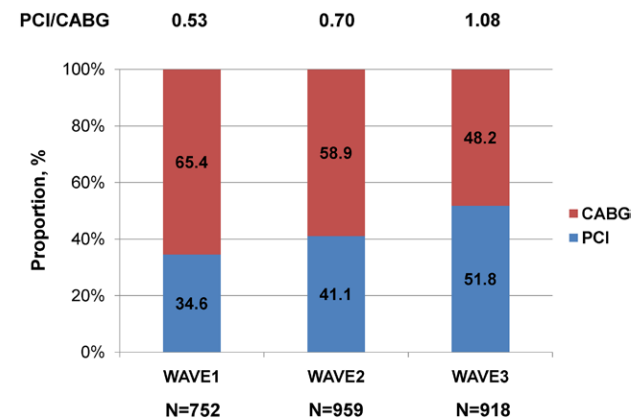


Figure 1. Treatment strategies according to the time period. CABG indicates coronary artery bypass grafting; and PCI, percutaneous coronary intervention.

Table 1. Patient Characteristics*

	Percutaneous Coronary Intervention			P Value	Coronary Artery Bypass Grafting			P Value
	Wave 1† (n=260)	Wave 2 (n=394)	Wave 3 (n=470)		Wave 1 (n=492)	Wave 2 (n=565)	Wave 3 (n=437)	
Age, y	57 (48–64)	62 (52–68)	64 (56–70)	<0.001	63 (56–69)	65 (58–70)	66 (59–72)	<0.001
Male sex	171 (65.8)	285 (72.3)	358 (76.2)	0.011	380 (77.2)	424 (75.0)	332 (76.0)	0.71
Body mass index, kg/m ²	25 (23–27)	24 (23–26)	24 (23–26)	>0.99	25 (23–26)	25 (23–26)	24 (23–26)	0.41
Atrial fibrillation	5 (1.9)	8 (2.0)	11 (2.3)	0.92	13 (2.6)	9 (1.6)	9 (2.1)	0.49
Hypertension	111 (42.7)	214 (54.3)	286 (60.9)	<0.001	260 (52.8)	335 (59.3)	280 (64.1)	0.002
Diabetes mellitus	58 (22.3)	125 (31.7)	176 (37.4)	<0.001	164 (33.3)	230 (40.7)	179 (41.0)	0.02
Smoking	81 (31.2)	104 (26.4)	130 (27.7)	0.40	162 (32.9)	149 (26.4)	115 (26.3)	0.03
Hypercholesterolemia	94 (36.2)	152 (38.6)	265 (56.4)	<0.001	184 (37.4)	271 (48.0)	208 (47.6)	0.001
Previous myocardial infarction	38 (14.6)	34 (8.6)	42 (8.9)	0.024	83 (16.9)	93 (16.5)	52 (11.9)	0.07
Previous coronary intervention	36 (13.8)	74 (18.8)	90 (19.1)	0.16	51 (10.4)	84 (14.9)	65 (14.9)	0.06
Previous cardiac surgery	0	1 (0.3)	6 (1.3)	0.057	0	2 (0.4)	0	0.19
Previous stroke	8 (3.1)	27 (6.9)	41 (8.7)	0.014	42 (8.5)	46 (8.1)	44 (10.1)	0.54
Previous heart failure	11 (4.2)	5 (1.3)	5 (1.1)	0.006	36 (7.3)	29 (5.1)	12 (2.7)	0.007
Chronic lung disease	4 (1.5)	12 (3.0)	10 (2.1)	0.43	9 (1.8)	26 (4.6)	16 (3.7)	0.044
Chronic renal failure	5 (1.9)	9 (2.3)	12 (2.6)	0.86	10 (2.0)	24 (4.2)	22 (5.0)	0.041
Clinical presentation				<0.001				<0.001
Stable angina	77 (29.6)	178 (45.2)	270 (57.4)		59 (12.0)	104 (18.4)	196 (44.9)	
Unstable angina	156 (60.0)	160 (40.6)	148 (31.5)		401 (81.5)	408 (72.2)	202 (46.2)	
NSTEMI	17 (6.5)	25 (6.3)	28 (6.0)		22 (4.5)	37 (6.5)	25 (5.7)	
STEMI	4 (3.8)	31 (7.9)	24 (5.1)		10 (2.0)	16 (2.8)	14 (3.2)	
Lesion location				<0.001				0.28
Ostial or shaft	139 (53.5)	154 (39.1)	155 (33.0)		147 (29.9)	164 (29.0)	111 (25.4)	
Bifurcation	121 (46.5)	240 (60.9)	315 (67.0)		345 (70.1)	401 (71.0)	326 (74.6)	
Disease extent				<0.001				<0.001
Left main only	102 (39.2)	63 (16.0)	38 (8.1)		34 (6.9)	13 (2.3)	11 (2.5)	
Left main plus 1 VD	75 (28.8)	86 (21.8)	107 (22.8)		51 (10.4)	42 (7.4)	28 (6.4)	
Left main plus 2 VD	55 (21.2)	113 (28.7)	184 (39.1)		122 (24.8)	100 (17.7)	77 (17.6)	
Left main plus 3 VD	28 (10.8)	132 (33.5)	141 (30.0)		285 (57.9)	410 (72.6)	321 (73.5)	
Ejection fraction, %	64 (59–67)	62 (58–66)	61 (56–64)	<0.001	61 (52–66)	59 (50–64)	59 (53–64)	<0.001

NSTEMI indicates non-ST-segment elevation myocardial infarction; STEMI, ST-segment-elevation myocardial infarction; and VD, vessel disease.

*Data are median (interquartile range) or number (%).

†Waves were classified according to the implanted type of stents; wave 1, between 1995 and 2002 (bare metal stent era); wave 2, between 2003 and 2006 (early drug-eluting stent era); wave 3, between 2007 and 2010 (late drug-eluting stent era).

Results

Patient Characteristics

A total of 2618 patients with significant ULMCA stenosis were enrolled in the ASAN MAIN registry between January 1995 and December 2010. In the overall population, 1124 patients underwent PCI and 1494 patients underwent CABG. CABG was less frequently performed over time (Figure 1). In wave 3, ≈52% of patients with significant ULMCA were treated by PCI.

Baseline characteristics of patients are shown in Table 1. The mean age of all patients with ULMCA stenosis receiving revascularization increased over the study period from 62 (54–69) to 66 (58–72) years, and the proportions of patients with hypertension, diabetes mellitus, hyperlipidemia, and history of stroke also increased. The vascular extent and complexity

of ULMCA stenosis increased over time, and mean ejection fraction decreased.

Revascularization Strategies

In patients receiving PCI, DES almost completely replaced BMS as the default stent platform over the period studied. The use of intravascular IVUS during PCI significantly increased. In wave 1, stents were mostly implanted in left main ostial or shaft lesions. More recently, bifurcation lesions were more frequently treated with a simple cross over technique than with 2-stent techniques. The number of stents per left main coronary artery and per patient also increased. In patients receiving CABG, the use of off-pump CABG increased. The total number of grafts decreased, but the use of the left internal mammary artery increased from 87% in wave 1 to 97% in wave 3 (Tables 2 and 3). Medications prescribed at discharge also

Table 2. Procedural Characteristics: Percutaneous Coronary Intervention

	Wave 1* (n=260)	Wave 2 (n=394)	Wave 3 (n=470)	P Value
Use of intravascular ultrasound	207 (79.9)	341 (86.8)	406 (86.6)	0.028
Stent technique				<0.001
Left main stent only	169 (65.0)	110 (28.0)	68 (14.5)	
Simple cross over technique	54 (20.8)	168 (42.7)	283 (60.3)	
2-Stent technique	37 (14.2)	115 (29.3)	108 (25.1)	
Total stent number per patient	1 (1–2)	2 (1–2)	2 (2–3)	<0.001
Total stent length per patient	17 (9–31)	46 (20–74)	60 (33–84)	<0.001
Stent type				<0.001
Bare metal stent	260 (100)	27 (6.9)	12 (2.6)	
Sirolimus-eluting stent	0	346 (87.8)	207 (44.0)	
Paclitaxel-eluting stent	0	19 (4.8)	10 (2.1)	
Zotarolimus-eluting stent	0	2 (0.6)	51 (10.9)	
Everolimus-eluting stent	0	0	189 (40.2)	

*Data are median (interquartile range) or number (%).

changed over time, with most medications more frequently prescribed in recent years (Table 4).

Outcomes

Unadjusted clinical outcomes are shown in Figure 2. In patients receiving PCI, the incidence rates of death, the composite of death, MI, or stroke, repeat revascularization, and MACCE significantly decreased over the study period. However, in patients receiving CABG, the incidence rates of all clinical outcomes were unchanged, with the exception of the rate of repeat revascularization, which decreased over time.

Table 5 shows risk-adjusted incidence rates (per 100 person-years). Similarly, in patients receiving PCI, the risk-adjusted incidence rates of death, the composite of death, MI, or stroke, repeat revascularization, and MACCE significantly decreased. In patients receiving CABG, the risk-adjusted incidence rates of death, the composite of death, MI, or stroke, and MACCE did not change, but the risk-adjusted incidence rate of repeat revascularization was significantly decreased.

The adjusted hazard ratio for MACCE of PCI compared with CABG significantly decreased over the period studied (Figure 3). In wave 3, the adjusted hazard ratio for MACCE of PCI was not significantly different to that of CABG.

Discussion

This large study of patients with ULMCA stenosis demonstrates that during the past 16 years, clinical outcomes of

patients receiving PCI for significant ULMCA stenosis have improved with respect to the safety and efficacy of the procedure although patient comorbidities and ULMCA stenosis complexity have worsened over time. Therefore, the gap in treatment effect between PCI and CABG has decreased and more patient received PCI for the treatment for ULMCA stenosis in recent years.

Until recently, PCI for ULMCA stenosis was performed to a limited extent in poor candidates for CABG.¹⁰ In addition, data on elective PCI in the BMS or early DES eras are sparse. Therefore, systematic evaluations of changes or improvements to ULMCA revascularization strategies were not properly evaluated.

During the period studied here, substantial changes in patients' risk profiles were observed. Particularly, PCI and CABG were performed in significantly older patients in recent years. In addition, the proportion of patients with diabetes mellitus and hypertension has significantly increased. About the complexity of coronary artery disease, distal left main bifurcation involvement has become more frequent, and the extent of extra-LMCA disease has become more severe.

Despite the worsening of patient risk profiles and lesion complexity, a progressive decline in mortality, and other clinical adverse events, was observed over time in patients receiving PCI for significant ULMCA. These improved outcomes could be explained by the synergistic effects of the introduction of DES, a progressive increase in the use of IVUS during

Table 3. Procedural Characteristics: Coronary Artery Bypass Grafting

	Wave 1* (n=492)	Wave 2 (n=565)	Wave 3 (n=437)	P Value
Off-pump surgery	73 (14.8)	204 (36.1)	292 (66.8)	<0.001
Use of left internal mammary artery	425 (86.4)	542 (95.9)	422 (96.6)	<0.001
Total conduit	4 (3–5)	3 (3–4)	3 (2–3)	<0.001
Artery graft	1 (1–3)	2 (2–3)	2 (1–2)	<0.001
Vein graft	2 (0–3)	1 (1–1)	1 (0–2)	<0.001

*Data are median (interquartile range) or number (%).

Table 4. Medication at Discharge*

	Percutaneous Coronary Intervention			P Value	Coronary Artery Bypass Grafting			P Value
	Wave 1 † (n=260)	Wave 2 (n=394)	Wave 3 (n=470)		Wave 1 † (n=260)	Wave 2 (n=394)	Wave 3 (n=470)	
Aspirin	230 (88.5)	375 (95.2)	464 (98.7)	<0.001	461 (93.7)	544 (96.3)	420 (96.1)	0.094
Thienopyridine	187 (71.9)	382 (97.0)	463 (98.5)	<0.001	195 (39.6)	477 (84.4)	409 (93.6)	<0.001
β-Blocker	204 (78.5)	313 (79.4)	365 (77.7)	0.82	201 (40.9)	260 (46.0)	241 (55.1)	<0.001
ACEi or ARB	31 (11.9)	80 (20.3)	122 (26.0)	<0.001	92 (18.7)	123 (21.8)	103 (23.6)	0.18
Calcium channel blocker	223 (85.8)	331 (84.0)	404 (86.0)	0.70	316 (64.2)	459 (81.2)	266 (60.9)	<0.001
Statin	47 (18.1)	254 (64.5)	431 (91.7)	<0.001	51 (10.4)	145 (25.7)	141 (32.3)	<0.001

ACEi indicates angiotensin-converting enzyme inhibitor; and ARB, angiotensin II receptor blocker.

*Data are number (%).

†Waves were classified according to the implanted type of stents; wave 1, between 1995 and 2002 (bare metal stent era); wave 2, between 2003 and 2006 (early drug-eluting stent era); wave 3, between 2007 and 2010 (late drug-eluting stent era).

PCI, simplified stenting techniques for distal ULMCA disease, and optimized antiplatelet treatment and adjuvant pharmacological treatment, as well as the accumulation of experience.

The introduction of DES could be a major contributing factor to the improvement of PCI outcomes. Although the LMCA itself seems to be relatively resistant to repeat stenosis because of its large caliber, PCI with BMS, particularly for distal left main bifurcation lesion or for the associated extra-LMCA disease shows a high event rate.^{11,12} In addition, in the critical left main position, a small or moderate degree of repeat

stenosis could theoretically precipitate critical ischemia. A meta-analysis of observational studies and randomized controlled trials involving 10 342 patients with ULMCA stenosis demonstrated significantly lower crude mortality and adverse event rates in DES implanted patients than in BMS recipients, which is in accordance with the current study’s observations.¹² In addition, the development and widespread use of second-generation DES, which is safer and more effective than first generation DES, could have further reduced adverse event rates in recent years.^{13,14}

The increasing use of IVUS is another important factor. Angiographic evaluation of ULMCA stenosis has inherent limitations, but IVUS provides accurate information for stent sizing and helps to detect suboptimal stent deployment or stent-related complications, thereby making ULMCA PCI more effective and safer. In 1 clinical study, IVUS during ULMCA PCI reduced mortality, particularly in patients receiving DES, and some IVUS-defined parameters for left main stents was associated with a higher rate of mortality.¹⁵

PCI strategy could determine prognosis, particularly for distal left main disease. In recent years, more patients with distal left main bifurcation stenosis received the single-stent crossover technique. In general, the single-stent crossover technique shows more favorable long-term clinical outcomes compared with the 2-stent technique, even in true bifurcation stenosis.^{16,17} The selection of a single- or 2-stent technique should be based on disease involvement and the supplying territory of the left circumflex ostium. IVUS provides accurate information for both main and side branch disease status and affects treatment strategy. Therefore, more frequent selection of the single-stent technique guided by the IVUS could further reduce adverse event rates over time.

The ASAN MAIN registry also shows that significant changes have occurred over time in revascularization strategies. The proportion of patients receiving PCI has progressively increased, and in recent years about half of patients with ULMCA stenosis received PCI. This trend has already been reported for patients with ULMCA stenosis presenting with acute coronary syndrome.¹⁸ These findings extend it into the elective ULMCA PCI setting. These trends might be accelerating because of supportive data and updated practical guidelines.

In contrast to PCI, CABG did not show any decline in clinical events except repeat revascularization. This is not

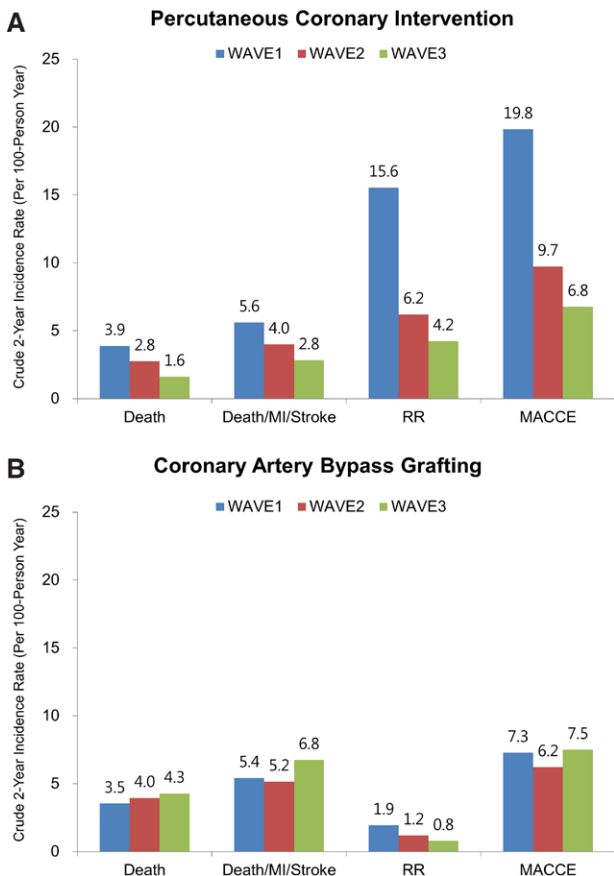


Figure 2. Unadjusted incidence rate (per 100 person-years). MACCE indicates major adverse cardiac or cerebral events; and RR, repeat revascularization.

Table 5. Risk-Adjusted Incidence Rate (per 100 Person-Years) of Outcomes

Risk-Adjusted Incidence Rate	Wave 1*	Wave 2	Wave 3	Adjusted HR (95% CI)†	P for Trend
Percutaneous coronary intervention					
Death	4.51	2.13	1.62	0.60 (0.41–0.87)	0.008
Death, MI, or stroke	6.71	3.61	2.83	0.65 (0.48–0.89)	<0.001
Repeat revascularization	14.03	5.99	4.24	0.54 (0.43–0.67)	<0.001
MACCE	20.18	9.28	6.77	0.57 (0.47–0.70)	<0.001
Coronary artery bypass grafting					
Death	4.35	3.77	4.28	0.99 (0.77–1.29)	0.97
Death, MI, or stroke	6.09	5.07	6.75	1.06 (0.85–1.31)	0.60
Repeat revascularization	2.14	1.24	0.79	0.60 (0.38–0.95)	0.028
MACCE	7.63	6.03	7.50	0.99 (0.82–1.20)	0.92

CI indicates confidence intervals; HR, hazard ratios; MACCE; major adverse cardiac or cerebral events; MI, myocardial infarction; and RR, repeat revascularization.

*Waves were classified according to the implanted type of stents; wave 1, between 1995 and 2002 (bare metal stent era); wave 2, between 2003 and 2006 (early drug-eluting stent era); wave 3, between 2007 and 2010 (late drug-eluting stent ear).

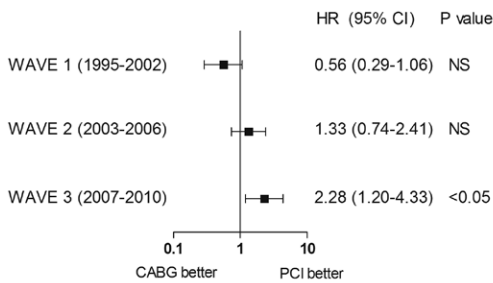
†Adjusted HR and P values for trend were determined with a model evaluating waves as a continuous variable.

easily explained; however, the effects of recent developments, including off-pump CABG and total arterial grafts, on clinical outcomes are subject to debate.^{19,20} In addition, the outcomes of CABG are likely to be more sensitive to surgeons' technique than PCI. Comorbidities in patients receiving CABG have also worsened in recent years, which may be neutralizing the effects of the accumulation of experience and the improvement of operative or perioperative performance over time.

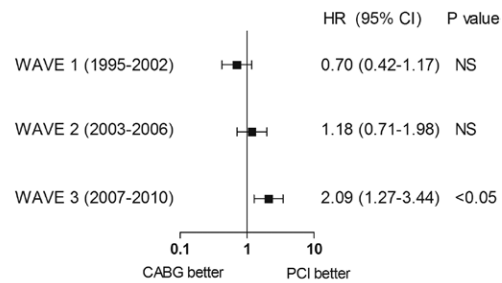
We conducted the evaluation of the comparative effectiveness between PCI and CABG according to the periods and

showed the trend of the progressive decline in the gap of the treatment effect between 2 strategies over time, which was primarily because of the improved outcome of PCI. The lower mortality of patients receiving PCI than CABG in population of wave 3 was unexpected and was not easily explained. The difference in patient's characteristics and some medication including the lower prescription rate of statin and β-blocker in CABG group may affect the current results. However, this analysis was not random-comparison and thereby was not free from the selection bias of the observational study despite of

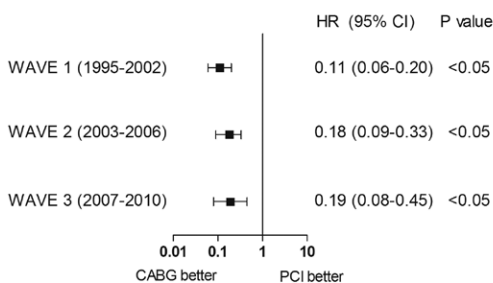
A Death from any causes



B Death, MI or Stroke



C Repeat Revascularization



D MACCE

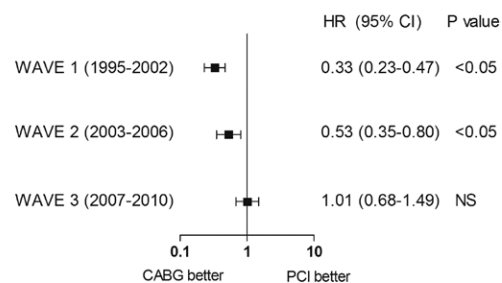


Figure 3. Risk-adjusted hazard ratios of outcomes between coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI). Waves were classified according to the implanted type of stents: wave 1, between 1995 and 2002 (bare metal stent era); wave 2, between 2003 and 2006 (early drug-eluting stent era); wave 3, between 2007 and 2010 (late drug-eluting stent ear). Adjusted hazard ratios were for CABG as compared with PCI. MACCE indicates major adverse cardiac or cerebral events; and RR, repeat revascularization.

the appropriate statistical adjustment. Therefore, these findings should be considered as the hypothesis generating and should be confirmed in large randomized controlled study.

This study has the inherent limitations of single-center study. However, the ASAN MAIN registry has several advantages: its start date is January 1996, an early period for left main PCI, and it includes all consecutive patients receiving PCI, mostly in the elective setting. The population size and event numbers were statistically analyzable in each period. In addition, all ULMCA PCI procedures were performed by experienced operators. New techniques or technologies were adopted in a timely manner, and homogeneously applied through consensus among operators. Therefore, the registry provides a valuable opportunity to evaluate trends in the practice and outcomes of ULMCA revascularization. In addition, high rate of IVUS use could be limited in the generalization of our findings.

In conclusion, the outcomes of LMCA PCI have significantly improved over time. In addition, more patients received PCI for LMCA stenosis in recent years.

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Disclosures

None.

References

- Giannoglou GD, Antoniadis AP, Chatzizisis YS, Damvopoulou E, Parcharidis GE, Louridas GE. Prevalence of narrowing $\geq 50\%$ of the left main coronary artery among 17,300 patients having coronary angiography. *Am J Cardiol.* 2006;98:1202–1205. doi: 10.1016/j.amjcard.2006.05.052.
- 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. doi: 10.1056/NEJMoa0801441.
- Park SJ, Kim YH, Park DW, Yun SC, Ahn JM, Song HG, Lee JY, Kim WJ, Kang SJ, Lee SW, Lee CW, Park SW, Chung CH, Lee JW, Lim DS, Rha SW, Lee SG, Gwon HC, Kim HS, Chae IH, Jang Y, Jeong MH, Tahk SJ, Seung KB. Randomized trial of stents versus bypass surgery for left main coronary artery disease. *N Engl J Med.* 2011;364:1718–1727. doi: 10.1056/NEJMoa1100452.
- Morice MC, Serruys PW, Kappetein AP, Feldman TE, Stähle E, Colombo A, Mack MJ, Holmes DR, Torracca L, van Es GA, Leadley K, Dawkins KD, Mohr F. Outcomes in patients with de novo left main disease treated with either percutaneous coronary intervention using paclitaxel-eluting stents or coronary artery bypass graft treatment in the Synergy Between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery (SYNTAX) trial. *Circulation.* 2010;121:2645–2653. doi: 10.1161/CIRCULATIONAHA.109.899211.
- Fihn SD, Gardin JM, Abrams J, Berra K, Blankenship JC, Dallas AP, Douglas PS, Foody JM, Gerber TC, Hinderliter AL, King SB III, Kliffeld PD, Krumholz HM, Kwong RY, Lim MJ, Linderbaum JA, Mack MJ, Munger MA, Prager RL, Sabik JF, Shaw LJ, Sikkema JD, Smith CR Jr, Smith SC Jr, Spertus JA, Williams SV, Anderson JL; American College of Cardiology Foundation/American Heart Association Task Force. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *Circulation.* 2012;126:e354–e471. doi: 10.1161/CIR.0b013e318277d6a0.
- Task Force on Myocardial Revascularization of the European Society of C, the European Association for Cardio-Thoracic S, European Association for Percutaneous Cardiovascular I, Wijns W, Kolh P, Danchin N, Di Mario C, Falk V, Folliquet T, Garg S, Huber K, James S, Knuuti J, Lopez-Sendon J, Marco J, Menicanti L, Ostojic M, Piepoli MF, Pirlot C, Pomar JL, Reifart N, Ribichini FL, Schalij MJ, Sergeant P, Serruys PW, Silber S, Sousa Uva M, Taggart D. Guidelines on myocardial revascularization. *Eur Heart J.* 2010;31:2501–2555.
- Park DW, Kim YH, Yun SC, Lee JY, Kim WJ, Kang SJ, Lee SW, Lee CW, Kim JJ, Choo SJ, Chung CH, Lee JW, Park SW, Park SJ. Long-term outcomes after stenting versus coronary artery bypass grafting for unprotected left main coronary artery disease: 10-year results of bare-metal stents and 5-year results of drug-eluting stents from the ASAN-MAIN (ASAN Medical Center-Left MAIN Revascularization) Registry. *J Am Coll Cardiol.* 2010;56:1366–1375. doi: 10.1016/j.jacc.2010.03.097.
- Jung SH, Song H, Choo SJ, Je HG, Chung CH, Kang JW, Lee JW. Comparison of radial artery patency according to proximal anastomosis site: direct aorta to radial artery anastomosis is superior to radial artery composite grafting. *J Thorac Cardiovasc Surg.* 2009;138:76–83. doi: 10.1016/j.jtcvs.2008.12.004.
- Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, Katus HA, Lindahl SB, Morrow DA, Clemmensen PM, Johanson P, Hod H, Underwood R, Bax JJ, Bonow RO, Pinto F, Gibbons RJ, Fox KA, Atar D, Newby LK, Galvani M, Hamm CW, Uretsky BF, Steg PG, Wijns W, Bassand JP, Menasché P, Ravkilde J, Ohman EM, Antman EM, Wallentin LC, Armstrong PW, Simoons ML, Januzzi JL, Nieminen MS, Gheorghade M, Filippatos G, Luepker RV, Fortmann SP, Rosamond WD, Levy D, Wood D, Smith SC, Hu D, Lopez-Sendon JL, Robertson RM, Weaver D, Tendera M, Bove AA, Parkhomenko AN, Vasilieva EJ, Mendis S; Joint ESC/ACCF/AHA/WHF Task Force for the Universal Definition of Myocardial Infarction. Third universal definition of myocardial infarction. *Circulation.* 2012;126:2020–2035. doi: 10.1161/CIR.0b013e31826e1058.
- Brennan JM, Dai D, Patel MR, Rao SV, Armstrong EJ, Messenger JC, Curtis JP, Shunk KA, Anstrom KJ, Eisenstein EL, Weintraub WS, Peterson ED, Douglas PS, Hillegeass WB. Characteristics and long-term outcomes of percutaneous revascularization of unprotected left main coronary artery stenosis in the United States: a report from the National Cardiovascular Data Registry, 2004 to 2008. *J Am Coll Cardiol.* 2012;59:648–654. doi: 10.1016/j.jacc.2011.10.883.
- Buszman PE, Buszman PP, Kiesz RS, Bochenek A, Trela B, Konkolewska M, Wallace-Bradley D, Wilczyński M, Banasiewicz-Szkróbka I, Peszek-Przybyła E, Krol M, Kondys M, Milewski K, Wiernek S, Debiński M, Zurakowski A, Martin JL, Tendera M. Early and long-term results of unprotected left main coronary artery stenting: the LE MANS (Left Main Coronary Artery Stenting) registry. *J Am Coll Cardiol.* 2009;54:1500–1511. doi: 10.1016/j.jacc.2009.07.007.
- Pandya SB, Kim YH, Meyers SN, Davidson CJ, Flaherty JD, Park DW, Mediratta A, Pieper K, Reyes E, Bonow RO, Park SJ, Beohar N. Drug-eluting versus bare-metal stents in unprotected left main coronary artery stenosis: a meta-analysis. *JACC Cardiovasc Interv.* 2010;3:602–611. doi: 10.1016/j.jcin.2010.03.019.
- Bangalore S, Kumar S, Fusaro M, Amoroso N, Attubato MJ, Feit F, Bhatt DL, Slater J. Short- and long-term outcomes with drug-eluting and bare-metal coronary stents: a mixed-treatment comparison analysis of 117 762 patient-years of follow-up from randomized trials. *Circulation.* 2012;125:2873–2891. doi: 10.1161/CIRCULATIONAHA.112.097014.
- Park KW, Lim WH, Ahn HS, Kang SH, Han JK, Lee SE, Cho JH, Gwon HC, Lee SY, Rhew JY, Kim W, Chae IH, Kim HS. Everolimus- versus sirolimus-eluting stents for the treatment of unprotected left main coronary artery stenosis (results from the EXCELLENT registry). *Int J Cardiol.* 2013;168:2738–2744. doi: 10.1016/j.ijcard.2013.03.086.
- Kang SJ, Ahn JM, Song H, Kim WJ, Lee JY, Park DW, Yun SC, Lee SW, Kim YH, Lee CW, Mintz GS, Park SW, Park SJ. Comprehensive intravascular ultrasound assessment of stent area and its impact on restenosis and adverse cardiac events in 403 patients with unprotected left main disease. *Circ Cardiovasc Interv.* 2011;4:562–569. doi: 10.1161/CIRCINTERVENTIONS.111.964643.
- 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, Falsini G, Benassi A, Palmieri C, Filippone V, Sangiorgi D, Barlocco F, De Servi S. Impact of bifurcation technique on 2-year clinical outcomes in 773 patients with distal unprotected left main coronary artery stenosis treated with drug-eluting stents. *Circ Cardiovasc Interv.* 2008;1:185–192. doi: 10.1161/CIRCINTERVENTIONS.108.800631.

17. Kim WJ, Kim YH, Park DW, Yun SC, Lee JY, Kang SJ, Lee SW, Lee CW, Park SW, Park SJ. Comparison of single- versus two-stent techniques in treatment of unprotected left main coronary bifurcation disease. *Catheter Cardiovasc Interv*. 2011;77:775–782. doi: 10.1002/ccd.22915.
18. Montalescot G, Brieger D, Eagle KA, Anderson FA Jr, FitzGerald G, Lee MS, Steg PG, Avezum A, Goodman SG, Gore JM; GRACE Investigators. Unprotected left main revascularization in patients with acute coronary syndromes. *Eur Heart J*. 2009;30:2308–2317. doi: 10.1093/eurheartj/ehp353.
19. Lamy A, Devereaux PJ, Prabhakaran D, Taggart DP, Hu S, Paolasso E, Straka Z, Piegas LS, Akar AR, Jain AR, Noiseux N, Padmanabhan C, Bahamondes JC, Novick RJ, Vajjyanath P, Reddy SK, Tao L, Olavegogeochea PA, Airan B, Sulling TA, Whitlock RP, Ou Y, Pogue J, Chrolavicius S, Yusuf S; CORONARY Investigators. Effects of off-pump and on-pump coronary-artery bypass grafting at 1 year. *N Engl J Med*. 2013;368:1179–1188. doi: 10.1056/NEJMoa1301228.
20. Goldman S, Sethi GK, Holman W, Thai H, McFalls E, Ward HB, Kelly RF, Rhenman B, Tobler GH, Bakaeen FG, Huh J, Soltero E, Moursi M, Haime M, Crittenden M, Kasirajan V, Ratliff M, Pett S, Irimpen A, Gunnar W, Thomas D, Femes S, Moritz T, Reda D, Harrison L, Wagner TH, Wang Y, Planting L, Miller M, Rodriguez Y, Juneman E, Morrison D, Pierce MK, Kreamer S, Shih MC, Lee K. Radial artery grafts vs saphenous vein grafts in coronary artery bypass surgery: a randomized trial. *JAMA*. 2011;305:167–174. doi: 10.1001/jama.2010.1976.