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ORIGINAL PAPER

Impact of left main coronary artery disease on long-term mortality in patients undergoing drug-eluting stent implantation

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Abstract

Background Limited data are available on long-term mortality according to the extent of coronary artery disease (CAD) in patients undergoing percutaneous coronary intervention (PCI) with drug-eluting stent (DES). We assessed long-term mortality DES implantation according to the extent of CAD and the impact of left main CAD alone on mortality among patients undergoing PCI with DES.

Methods and results A total of 18,716 patients were pooled from real-world PCI registries. The primary outcome was death from any cause. The median follow-up duration was 47.1 (interquartile range 32.8–57.9) months. The presence of left main CAD [adjusted hazard ratio (HR) 1.24, 95% confidence interval (CI) 1.05–1.46, $p = 0.012$] and the extent of diseased vessels (adjusted HR 1.17, 95% CI 1.08–1.27, $p < 0.001$) significantly increased the risk of all-cause mortality. Left main CAD alone was associated with a risk of all-cause mortality similar to one- and two-vessel CAD, whereas it was associated with a significantly lower risk of mortality compared with three-vessel CAD (adjusted HR 0.42, 95% CI 0.18–0.98, $p = 0.044$). Among patients with left main CAD, the risk of mortality tended to increase in proportion with the number of concomitant vessel CAD, but it did not achieve statistical significance.

Conclusions Among patients undergoing DES implantation, the risk of mortality increased in a stepwise manner according to the extent of coronary CAD. Left main CAD alone was associated with a risk of long-term mortality similar to one- and two-vessel CAD.

Keywords All-cause mortality · Drug-eluting stents · Left main coronary artery disease

Introduction

The prognosis of patients with coronary artery disease (CAD) depends on the extent and severity of CAD and the status of left ventricular function. The annual mortality rate was the highest in patients with significant left main CAD, followed by patients with three-vessel, two-vessel, and one-vessel disease before the introduction of revascularization therapies [1]. Coronary artery bypass graft surgery (CABG) has been the treatment of choice for left main CAD, because it offers better survival compared to medical therapy [2–4]. However, percutaneous coronary intervention (PCI) with drug-eluting stents (DESs) has remarkably progressed over the past decade, and a growing body of evidence supports the use of PCI with DES in the treatment of left main CAD [5–10]. PCI with DES seems to be associated with a risk of all-cause mortality similar to CABG in patients with left main CAD. In general, PCI compared with medical therapy does not reduce all-cause mortality in patients with non-acute CAD [11]. In real-world practice, however, PCI is increasingly used to treat a broad range of patients with significant CAD. Death from any cause may be the most definite outcome to guide clinical decision making for patients with significant CAD. However, there is little information about the long-term mortality according to the

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extent of CAD in patients undergoing PCI with DES. In the present study, we investigated long-term mortality after DES implantation according to the extent of CAD and the influence of left main CAD alone on long-term mortality in a broad range of patients with CAD undergoing PCI with DES.

Methods

Study population

We pooled data from two large-scale, independent, multicenter, observational studies of the Interventional Cardiology Research Incorporation Society Drug-Eluting Stents (IRIS-DES) registry (NCT01070420) and the Interventional Research Incorporation Society-Left MAIN Revascularization (IRIS-MAIN) registry (NCT01341327) and one single center, prospective observational study of the Asan Multivessel Registry (NCT02039752). Details of the design and organization of the IRIS-DES, IRIS-MAIN, and Asian Multivessel studies have been published elsewhere [12–14]. In brief, the IRIS-DES involves a prospective, multicenter recruitment of unrestricted patients undergoing PCI with DES in Korea and comprises several different DES arms of first- and second-generation devices. The current analysis includes patients treated with five different types of DES. In contrast, IRIS-MAIN is a prospective, multinational registry involving consecutive patients with unprotected left main CAD who were treated with PCI, bypass surgery, or medical therapy alone. The Asan Multivessel registry included consecutive patients with multivessel CAD who received PCI with DES or isolated CABG at the Asan Medical Center. The institutional review board approved the studies and all patients provided written informed consent. The study was conducted in accordance with the Declaration of Helsinki.

Patients were eligible for this study if they had significant CAD (diameter stenosis for epicardial coronary artery, ≥70 or 50–70% with objective evidence of myocardial ischemia; diameter stenosis for left main coronary artery, ≥50%) and DES implantation in at least one epicardial coronary artery or the left main coronary artery. Exclusion criteria included acute ST-elevation myocardial infarction, cardiogenic shock at the time of the index procedure, malignancy, and a history of CABG or concomitant valvular or aortic surgery. In all three registries, PCI was performed according to standard techniques at the discretion of the treating physician. All patients undergoing PCI received a loading dose of aspirin and adenosine diphosphate receptor antagonists before or during the intervention. After the procedure, aspirin was continued indefinitely and adenosine diphosphate receptor antagonists were prescribed for at least 6 months.

Definition and follow-up

The primary outcome of the current analysis was all-cause death. All clinical events were based on clinical diagnoses assigned by the treating physician and were centrally adjudicated according to the source documentation by an independent group of clinicians. All baseline characteristics and outcome data were collected using a dedicated electronic case report form by specialized personnel at each participating center. Clinical follow-up of the patients was performed according to per-protocol follow-up visits. The Internet-based system provides each center with immediate and continuous feedback on processes and quality of care measures. Monitoring and verification of registry data have been periodically performed in participating hospitals by members of the academic coordinating center (Clinical Research Center, Asan Medical Center, Seoul, Korea).

Statistical analysis

Continuous variables are presented as mean ± standard deviation (SD), whereas categorical variables are presented as counts or percentages. The prevalence of risk factors and patient characteristics between survivor and non-survivor were compared using the Kruskal–Wallis test for continuous variables and the Chi square test or Fisher's exact test for categorical variables, as appropriate. Cumulative event rates and incidence curves for clinical outcomes were generated using the Kaplan–Meier method and compared using the log-rank test.

Multivariable Cox proportional hazards regression modeling with stepwise backward elimination methods (retention threshold, $p < 0.05$) was used to examine the independent effect of the left main involvement and the extent of epicardial CAD. Previously published candidate variables (demographics, coexisting clinical conditions, risk factors, cardiovascular history, clinical presentations, CAD extent, and left main CAD), which are listed in Tables 1 and 2, were introduced into a multivariable model. Most variables were >99% complete. However, left ventricular ejection fraction was missing for 21.4% of the patients. Missing values for left ventricular ejection fraction were imputed using multiple imputations. Given that results with and without imputation were not meaningfully different, we present the former. The proportional hazards assumption was tested by examining log–log survival curves and partial Schoenfeld residuals, with no significant violations being found. Statistical analyses were performed using SPSS software version 21.0 (SPSS, Inc., Chicago, IL, USA). All p values were two sided and those <0.05 were considered to be statistically significant.

Table 1 Baseline clinical characteristics

	Total ($N = 18,716$)	Survivor ($N = 17,433$)	Non-survivor ($N = 1283$)	p
Age (years)	63.8 ± 10.5	63.5 ± 10.4	67.5 ± 11.2	<0.001
Sex (male)	12,910 (69.0%)	12,035 (69.1%)	875 (68.2%)	0.543
BMI (kg/m^2)	24.8 ± 3.1	24.9 ± 3.1	23.7 ± 3.4	<0.001
Hypertension	11,835 (63.2%)	10,944 (62.8%)	891 (69.4%)	<0.001
Diabetes mellitus	6426 (34.3%)	5797 (33.3%)	629 (49.0%)	<0.001
Requiring insulin	906 (19.7%)	745 (18.3%)	161 (29.4%)	<0.001
Ever smoker	8830 (47.2%)	8263 (47.4%)	567 (44.2%)	0.028
Dyslipidemia	7528 (40.2%)	7152 (41.0%)	376 (29.3%)	<0.001
Acute coronary syndrome	9487 (50.7%)	8808 (50.5%)	679 (52.9%)	0.103
Previous myocardial infarction	1049 (5.6%)	943 (5.4%)	106 (8.3%)	<0.001
Previous PCI	2603 (13.9%)	2373 (13.6%)	230 (17.9%)	<0.001
Family history of CAD	1152 (6.2%)	1102 (6.3%)	50 (3.9%)	0.001
Previous heart failure	405 (2.2%)	295 (1.7%)	110 (8.6%)	<0.001
Previous stroke	1422 (7.6%)	1243 (7.1%)	179 (14.0%)	<0.001
Peripheral vascular disease	407 (2.2%)	337 (1.9%)	70 (5.5%)	<0.001
Chronic renal failure	650 (3.5%)	465 (2.7%)	185 (14.4%)	<0.001
Chronic lung disease	427 (2.3%)	339 (1.9%)	88 (6.9%)	<0.001
Left ventricular ejection fraction				
Mean (%)	59.9 ± 9.8	60.4 ± 9.3	54.1 ± 13.0	<0.001
Data missing	4010 (21.4%)	3790 (21.7%)	220 (17.1%)	
Discharge medication				
Aspirin	18411 (98.4%)	17202 (98.7%)	1209 (94.2%)	<0.001
Clopidogrel	18,236 (97.4%)	17,027 (97.7%)	1209 (94.2%)	<0.001
Beta blocker	10,438 (58.0%)	9913 (59.2%)	525 (42.3%)	<0.001
Calcium channel blocker	8017 (45.3%)	7626 (46.3%)	391 (32.0%)	<0.001
ACEi or ARB	8290 (47.6%)	7857 (48.4%)	433 (37.7%)	<0.001
Statin	13,611 (72.7%)	13,096 (75.1%)	515 (40.1%)	<0.001

ACEi angiotensin-converting enzyme inhibitor, *ARB* angiotensin II receptor blockers, *BMI* body mass index, *PCI* percutaneous coronary intervention

Results

Baseline characteristics

A total of 18,716 patients with significant CAD undergoing DES implantation were eligible for the current analysis. The baseline characteristics of patients are summarized according to survival status Tables 1, 2). The mean age of the patients was 63.8 ± 10.5 years; 69.0% were men and 10.4% had left the main CAD. Compared with survivors, non-surviving patients were significantly older and had a higher prevalence of risk factors or comorbidities (i.e., hypertension, diabetes, previous stroke, previous heart failure, previous PCI, and lower ejection fraction) (Table 1). In addition, non-surviving patients had a higher prevalence of left main and multivessel CAD (57.1 vs. 72.1%, $p < 0.001$), lower rates of complete revascularization, higher rates of hemodynamic supporting device, and higher rates of first-generation stent implantation (29.1 vs. 42.5%, $p < 0.001$) compared with surviving patients (Table 2).

Extent of CAD and mortality

During a median follow-up time of 47.1 months (interquartile range 32.8–57.9 months), there were 1283 deaths. The risk of all-cause deaths significantly increased according to the presence of left main CAD and the extent of diseased vessels (Table 2). In unadjusted analysis, the risk of all-cause mortality increased with the presence of the left main CAD [hazard ratio (HR) 1.44, 95% confidence interval (CI) 1.24–1.68, $p < 0.001$]. Adjusted analysis also revealed that the left main involvement was significantly associated with a higher risk of all-cause mortality (adjusted HR 1.24, 95% CI 1.05–1.46, $p = 0.012$). Similarly, adjusted analysis showed that all-cause mortality increased with the number of diseased vessels (adjusted HR 1.17, 95% CI 1.08–1.27, $p < 0.001$). In addition,

Table 2 Angiographic and procedural characteristics

	Total ($N = 18,716$)	Survivor ($N = 17,433$)	Non-survivor ($N = 1283$)	p
Extent of CAD				
LM alone	159 (0.8%)	153 (0.9%)	6 (0.5%)	0.123
1VD	7680 (41.0%)	7328 (42.0%)	352 (27.4%)	<0.001
2VD	6876 (36.7%)	6377 (36.6%)	499 (38.9%)	
3VD	4001 (21.4%)	3575 (20.5%)	426 (33.2%)	
Diseased artery				
LM involvement	1948 (10.4%)	1752 (10.0%)	196 (15.3%)	<0.001
LAD	14,582 (77.9%)	13,534 (77.6%)	1048 (81.7%)	0.001
LCX	9233 (49.3%)	8468 (48.6%)	765 (59.6%)	<0.001
RCA	9620 (51.4%)	8805 (50.5%)	815 (63.5%)	<0.001
Number of stents	1.8 ± 1.1	1.8 ± 1.1	2.0 ± 1.1	<0.001
Complete revascularization	12,175 (65.1%)	11,470 (65.8%)	705 (54.9%)	<0.001
Hemodynamic support	235 (1.3%)	201 (1.2%)	34 (2.7%)	<0.001
Types of DES				<0.001
SES	5080 (27.1%)	4609 (26.4%)	471 (36.7%)	
PES	542 (2.9%)	467 (2.7%)	75 (5.8%)	
ZES	3265 (17.4%)	3113 (17.9%)	152 (11.8%)	
EES	7476 (39.9%)	7003 (40.2%)	473 (36.9%)	
BES	2311 (12.3%)	2203 (12.6%)	108 (8.4%)	
Others	42 (0.2%)	38 (0.2%)	4 (0.3%)	

BES biolimus-eluting stent, *DES* drug-eluting stents, *EES* everolimus-eluting stent, *LAD* left anterior descending artery, *LCX* left circumflex artery, *LM* left main disease, *PES* paclitaxel-eluting stents, *RCA* right coronary artery, *SES* sirolimus-eluting stent, *VD* vessel disease, *ZES* zotarolimus-eluting stent

the risk of all-cause mortality was significantly lower in patients with complete revascularization than in those with incomplete revascularization (adjusted HR 0.87, 95% CI 0.77–0.98, $p = 0.020$). Among the subgroup of patients with left main plus three-vessel CAD or three-vessel CAD, the risk of mortality tended to be lower with complete versus incomplete revascularization (adjusted HR 0.85, 95% CI 0.68–1.06, $p = 0.143$).

Left main CAD alone and mortality

The influences of left main CAD alone on long-term mortality are summarized in Table 3 and Fig. 1. Among patients with non-left main disease, there was an increase in the risk of all-cause mortality proportional to the number of diseased vessels (Table 3; Fig. 1a). Patients with left main disease alone had a risk of mortality similar to those with non-left

Table 3 Risk of all-cause mortality according to the extent of coronary disease

	Unadjusted HR (95% CI)	p value	Adjusted HR (95% CI)	p value
LM alone	Reference	–	Reference	–
1VD	1.357 (0.604–3.046)	0.460	1.722 (0.736–4.029)	0.210
2VD	1.755 (0.783–3.932)	0.172	1.939 (0.831–4.525)	0.126
3VD	2.414 (1.075–5.420)	0.033	2.403 (1.025–5.634)	0.044
LM alone	Reference	–	Reference	–
LM + 1VD	1.927 (0.797–4.657)	0.145	1.549 (0.633–3.790)	0.338
LM + 2VD	2.111 (0.913–4.881)	0.081	1.734 (0.738–4.078)	0.207
LM + 3VD	3.310 (1.448–7.565)	0.005	2.165 (0.926–5.064)	0.075

Adjusted hazard ratios are adjusted for age, left ventricular ejection fraction <35%, acute coronary syndrome, hypertension, diabetes, previous MI, previous PCI, history of heart failure, family history of coronary artery disease, stroke, peripheral arterial disease, chronic renal failure, history of chronic lung disease, use of hemodynamic support, complete revascularization, and stent generation

LM left main, *V* vessel

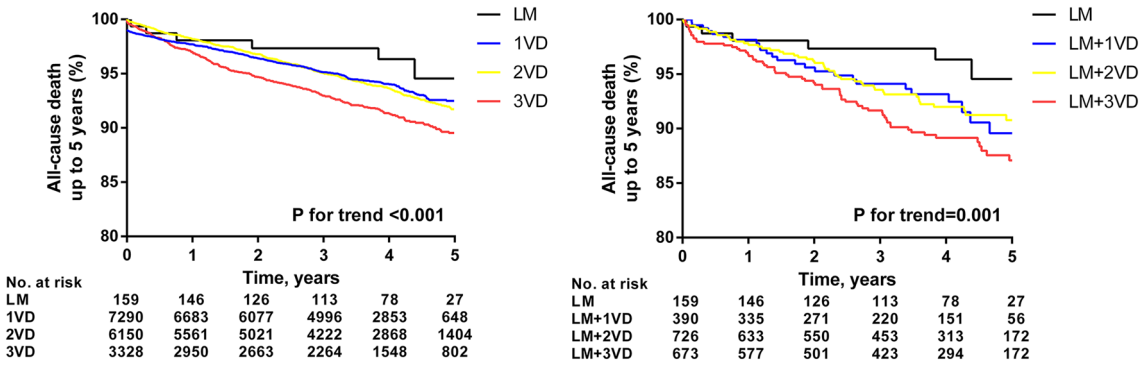

Fig. 1 All-cause mortality according to the extent of coronary artery disease. The cumulative incidences of all-cause mortality according to the extent of coronary artery stenting are shown, with left main CAD alone as reference (**a** non-left main disease; **b** left main disease with concomitant vessel disease). *LM* left main, *VD* vessel disease

main one- or two-vessel disease. However, left main CAD alone was associated with a significantly lower risk of mortality compared with three-vessel CAD (adjusted HR 0.42, 95% CI 0.18–0.98, $p = 0.044$). Among patients with left main CAD, there was a trend toward increased risk of mortality in accordance with the number of concomitant vessel CAD (Table 3; Fig. 1b). In addition, the risk of all-cause mortality tended to be lower in patients with left main CAD alone when compared with that in subgroups of completely revascularized patients with left main plus three-vessel CAD (adjusted HR 0.55, 95% CI 0.23–1.32, $p = 0.100$) or three-vessel CAD (adjusted HR 0.46, 95% CI 0.19–1.16, $p = 0.181$).

Discussion

In this large patient-level pooled analysis of real-world PCI registries, we found that left main CAD alone resulted in a risk of all-cause mortality similar to one- and two-vessel CAD among patients undergoing DES implantation. In addition, there was a stepwise increase in the risk of all-cause mortality proportional to the extent of CAD, showing the highest mortality in patients with three-vessel CAD. These findings support that PCI with DES could be a safe method of revascularization in patients with left main CAD alone and could be reserved for those with three-vessel CAD who are not suitable for CABG.

Age and major organ failure are key determinants of all-cause mortality in patients with CAD undergoing PCI [11, 15–17]. In our study, there were significant differences in age, chronic lung disease, chronic kidney disease, left ventricular function, and previous stroke between survivors and non-survivors, highlighting the critical importance of major organ dysfunction in predicting the long-term mortality of patients undergoing PCI with DES. These variables are incorporated as key factors for predicting outcomes in well-known risk models, including EuroSCORE [18] and clinical SYNTAX SCORE [19, 20]. PCI with DES is anticipated to increase in patients with high-risk features because life expectancy increases globally. In fact, since the introduction of DES, the use of PCI has been expanded to high-risk populations, including those with left main and three-vessel CAD. However, there is no evidence that PCI improves survival or prevents myocardial infarction in patients with non-acute CAD [11].

The left main coronary artery typically supplies more than 70% of the left ventricle, and acute left main coronary artery occlusion carries the highest risk of mortality because of a large ischemic burden. Medical therapy of patients with left main CAD is associated with a poor prognosis [1]. Early studies established the superiority of CABG over medical therapy with respect to survival in the treatment of significant left main CAD, and CABG was considered as the standard of care for nearly four decades [2–4]. However, PCI continued to evolve with the concomitant improvement of medical therapy, and the use of PCI for these patients significantly increased in real-world practice [21]. Several randomized trials have compared CABG to PCI with DES for the treatment of left main CAD [5–9]. The composite outcome of death, myocardial infarction, or stroke was generally comparable between PCI and CABG, but repeat revascularization was significantly higher after PCI. All-cause mortality was the same in both groups, although these studies were limited by inadequate power regarding mortality. In the present analysis, patients with left main CAD were associated with poor survival than those with other vessel CAD. However, all-cause mortality was similar between patients with left main CAD alone and those with one- and two-vessel CAD, suggesting that left main stenting may improve prognosis in patients with left main CAD alone. Therefore, PCI with DES might be considered a safe and effective alternative to CABG for those individuals with limited left main CAD who do not require simultaneous multivessel stenting.

CABG leads to lower rates of major adverse cardiac events than PCI with DES in patients with multivessel CAD [22–24]. The survival benefit of CABG over PCI with DES was found in such patients, although each trial was underpowered for all-cause mortality [22–24]. Long-term mortality was significantly lower with CABG than that with PCI in both diabetic and non-diabetic patients with multivessel CAD. The largest observational ACCF and STS Database Collaboration on the Comparative Effectiveness of Revascularization Strategies (ASCERT) study also showed that mortality at 4 years was substantially lower after CABG than that after PCI with DES irrespective of baseline variables [25]. The CABG benefit was the same across all patient subgroups, including those with and without diabetes. In addition, complete revascularization seems to be associated with lower long-term mortality irrespective of revascularization modality, which is more common following a CABG than PCI for patients with multivessel CAD [26]. In our present analysis, complete revascularization was also an independent predictor of lower mortality. The rate of complete revascularization was significantly lower in patients with three-vessel CAD, with or without concomitant left main CAD, than that in those with non-three-vessel CAD (27.9 vs. 75.2%, $p < 0.001$). These findings support that CABG could be the preferred approach in patients with three-vessel CAD, whereas PCI with DES could be reserved for those who are unsuitable for CABG or at high surgical risk.

Limitations

There were several potential limitations in our study. First, this was an observational study with inherent methodological limitations. Second, the lack of a control group treated with bypass surgery or medical therapy precluded the determination of the role of treatment differences on clinical outcomes. Third, the choice of DES was left to the physician, leading to possible selection bias. Finally, given that most of the patients in our registry were Asian, it remains uncertain whether these findings can be generalized to other ethnic or social groups with different patient and procedural characteristics.

Conclusions

The risk of all-cause mortality increased in a stepwise manner according to the extent of CAD in patients with CAD undergoing PCI with DES implantation. The left main CAD alone was associated with a long-term mortality risk similar to one- and two-vessel CAD, but a lower risk of mortality than three-vessel CAD.

Compliance with ethical standards

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Conflict of interest The authors declare that they have no conflict of interest.

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