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ORIGINAL STUDIES

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Impact of stent length and diameter on 10-year mortality in the SYNTAXES trial

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Abstract

Objectives: We investigated the impact of total stent length (TSL) and average nominal stent diameter (ASD) on 10-year mortality after percutaneous coronary intervention (PCI) in the SYNTAXES trial.

Background: TSL and ASD in patients treated with PCI are associated with major adverse cardiovascular events. However, the treatment effect of PCI with extensive and/or small stenting as compared with coronary artery bypass grafting (CABG) for complex coronary artery disease has not been fully evaluated.

Methods: Impacts on mortality of extensive stenting defined as TSL >100 mm and small stenting as ASD <3 mm were analyzed in 893 PCI patients and were compared to 865 CABG patients.

Results: TSL as a continuous variable was significantly associated with 10-year mortality (adjusted hazard ratio [HR], 1.05 [1.01–1.09] per 10 mm increase). PCI patients with extensive stenting had a higher 10 year mortality than CABG patients (adjusted HR, 1.97 [1.41–2.74]) or not- extensive stenting PCI (adjusted HR, 1.94 [1.36–2.77]). Although ASD did not have a significant association with 10 year mortality (adjusted HR, 0.97 [0.85–1.11] per 0.25 mm increase), PCI with small stents was associated

with a higher 10 year mortality, compared to CABG (adjusted HR, 1.66 [1.23–2.26]) and PCI performed with large stents (adjusted HR, 1.74 [1.19–2.53]). Patients treated with not-extensive and large stents had similar mortality rates (24.0 versus 23.8%) as those treated with CABG.

Conclusions: Extensive and small stenting were associated with higher 10 year mortality, compared with CABG. When patients have to be treated with extensive or small stenting, revascularization with CABG should be preferred.

KEYWORDS
coronary bypass grafts, percutaneous coronary intervention, stent, drug eluting.

1 | INTRODUCTION

In the era of bare-metal stents (BMS), stent length and stent diameter in patients treated with percutaneous coronary intervention (PCI) were associated with an increased risk of restenosis.[1,2] Drug-eluting stents (DES) significantly reduced neointimal hyperplasia and improved clinical outcomes compared to BMS. However, stent length still has been associated with major adverse cardiovascular events, and the rate of restenosis has also been higher in small vessels than in large vessels, although thresholds for stent length and small vessels associated with detrimental results varied among studies.[3-9] PCI with longer and smaller stents are intrinsically related with advanced and extensive atherosclerotic disease manifest in complex anatomic features that can be semiquantified by the anatomical SYNTAX score[10] and coronary artery bypass grafting surgery (CABG) may remain the gold standard of revascularization in these instances. The SYNTAXES trial[11] of patients with three-vessel disease (3VD) or left main coronary artery disease (LMCA) randomized to undergo either CABG or PCI allows assessment of (i) the impact of total stent length (TSL) and average nominal stent diameter (ASD) on 10 year all-cause mortality and 5 year cardiovascular mortality after PCI, (ii) the relationship between 10 year all-cause mortality or 5 year cardiovascular mortality and revascularization strategy (extensive and/or small stenting PCI vs. CABG), and (iii) the relationship between the anatomical SYNTAX score and the procedural use of extensive and small stents per patient.

2 | MATERIALS AND METHODS

2.1 | Study design and participants

The design and results up to 5 years of the SYNTAX trial (NCT00114972) have been reported previously.[12-14] The vital status up to 10 years has been reported in the SYNTAXES study (NCT03417050).[11] In brief, the SYNTAX trial was a prospective, multicenter, international randomized controlled trial. Patients with de novo 3VD and/or LMCAD, who were anticipated to achieve a clinical equipoise between CABG and PCI based on clinical assessment and the consensus of a Heart Team, were enrolled and randomized in a 1:1 fashion either to receive PCI (n = 903) with TAXUS Express paclitaxel-drug eluting stents (Boston Scientific Corporation, Marlborough, MA) or CABG (n = 897) between March, 2005, and April, 2007. The ethics committee at each investigating center approved the trial and all participates provided their written informed consent prior to enrolment. Follow-up was performed in accordance with local law and regulations of each institution and complied with the Declaration of Helsinki.

2.2 | Endpoints and definitions

TSL is the sum of all stents implanted per patient and ASD is the average diameter of all stents implanted per patient. Analysis of "extensive stenting," defined as TSL >100 mm per patient was prespecified in the protocol and the design paper.[12] Conversely, patients with a TSL of less than or equal to 100 mm are refered as "not-extensive stenting." "Small stenting" characterized a patient having an ASD of less than 3 mm, since the median of ASD was 3 mm for the entire cohort. Conversely, large stenting refered to a patient with an ASD larger or equal to 3 mm.

Vital status was confirmed by contact with medical care personnel or using electronic healthcare record review and national death registries. Patients with missing vital status were included in the analysis and censored at the time of lost to follow-up. Patients in institutes that did not participate in the SYNTAXES study for 10 year extended follow-up (five patients in two institutes) were censored at 5 years. The causes of death (cardiovascular or non-cardiovascular) were adjudicated by a central and independent CEC up to 5 years.

2.3 | Statistical analysis

All the analyses were performed according to the as-treated principle. The cumulative incidence of death was calculated using the Kaplan–Meier method. Kaplan–Meier survival curves were analyzed using the log-rank test. To adjust for baseline differences, propensity score matching analysis was performed. The propensity score was estimated by using a multivariable logistic regression model that included the following baseline variables: age, sex, body mass index, medically treated diabetes, hypertension, dyslipidemia, current smokers, previous MI, previous cerebrovascular disease, peripheral vascular disease (PVD), chronic obstructive pulmonary

disease, chronic kidney disease (defined as creatinine clearance <60 ml/min), left ventricular ejection fraction (LVEF), clinical presentation (silent ischemia, stable angina or unstable angina), disease type (LMCAD or 3VD), and anatomical SYNTAX score. Patients in each group were matched on the logit of the propensity score with a caliper distance of 0.1 times the standard deviation of the logit of the propensity score.

Hazard ratios (HRs) with 95% confidence intervals (CIs) for mortality was determined on the basis of Cox proportional hazards regression, and the same baseline variables for propensity score matching were applied for adjustment. Continuous relationships between death and TSL or ASD were depicted using restricted cubic spline function from the adjusted Cox regression model. Continuous variables were expressed as mean ± *SD*, and were compared using Student's *t*-test, Mann–Whitney *U* test, or Welch's ANOVA as appropriate. Categorical variables were reported as numbers and percentages, and were compared using chi square or Fisher's exact test as appropriate. A two-sided *p*-value < .05 was considered statistically significant. Analyses were performed using JMP Pro14 (SAS Institute, Cary, NC), Stata 15 (StataCorp, College Station, TX) and R version 3.6.0 (R Foundation for Statistical Computing, Vienna, Austria).

3 | RESULTS

3.1 | Study population

Out of 1800 patients, 34 patients who did not receive PCI or CABG were excluded, and 901 and 865 patients actually received PCI and CABG, respectively (Figure 1a). Details of procedure were not available in eight patients out of 901 patients treated with PCI. Out of 893 patients, 191, 117, 234, and 351 patients were treated with "extensive and small stents," "not-extensive and small stents," "extensive and large stents," and "not-extensive and large stents," respectively. The distribution of TSL and ASD per patient are shown in Figure 1b,c. Compared with patients treated with not-extensive stenting PCI and those treated with CABG, patients treated with extensive stenting PCI had a higher prevalence rate of hypertension and a lower prevalence of PVD

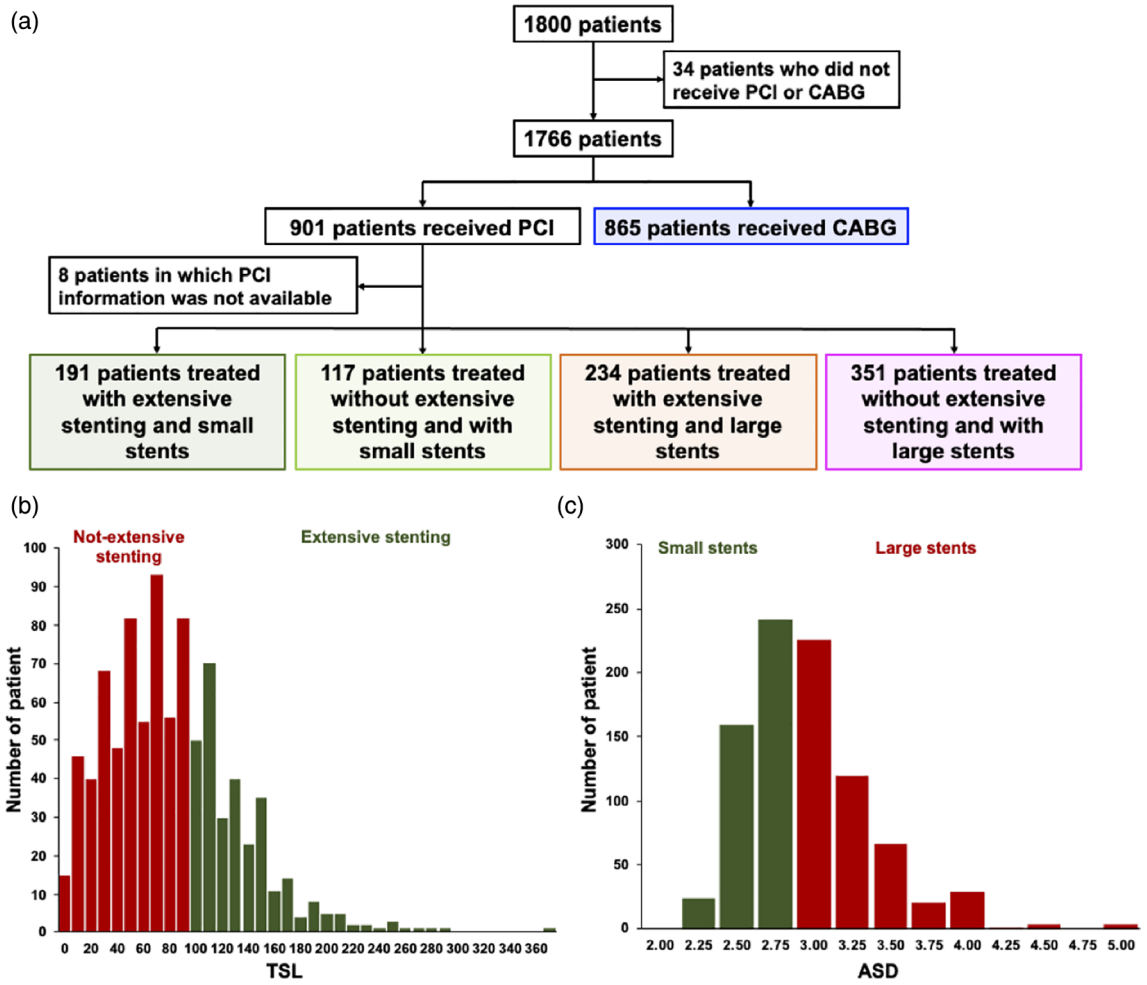


FIGURE 1 Study population flow chart. (a) Study population flow chart. (b) Distribution of total stent length (TSL) in patients treated with percutaneous coronary intervention (PCI). (c) Distribution of average nominal stent diameter (ASD). CABG, coronary artery bypass grafting surgery

(Table S1). By angiographic core laboratory analysis, patients treated with extensive stenting PCI had higher rates of 3VD, lesion length of >20 mm, bifurcation lesions and higher SYNTAX score (Table S1). Patients treated with small stents were more frequently female, and had higher rates of diabetes and previous cerebrovascular disease than patients treated with large stents or CABG (Table S2). In addition, patients treated with small stents had higher rates of 3VD, lesion length of >20 mm, bifurcation lesion, and had more numerous lesions.

When TSL and ASD were analyzed according to disease type, LMCAD were associated with short and large stenting (Table S3). In patients with LMCAD categorized as small stenting, ASDs were smaller both in LM and non-LM lesions compared with those categorized as large stenting (Table S4).

3.2 | TSL, ASD, and the SYNTAX score

The low-SYNTAX (<22) score has the shortest TSL, the lowest percentage of extensive stenting, the largest ASD and the lowest percentage of small stenting (Table S3). Conversely the high-SYNTAX (>33) score shows the longest TSL as well as the highest percentage of extensive stenting. Compared with patients with low-SYNTAX score, those with intermediate and high-SYNTAX scores had a higher percentage of small stenting (41.4 vs. 51.8%, $p = .034$, and 41.4 vs. 49.1%, $p = .201$, respectively) and their absolute diameters were smaller (3.13 ± 0.47 vs. 2.99 ± 0.33, $p = .003$, and 3.13 ± 0.47 vs. 3.01 ± 0.33, $p = .035$, respectively). However, individual correlations between the SYNTAX score, TSL, and ASD were poor (Figure S1).

3.3 | Mortality rates according to revascularization strategy (PCI vs. CABG)

PCI with extensive stenting (TSL >100 mm) was associated with a higher rate of all-cause mortality at 10 years compared with PCI with not-extensive stenting or CABG (32.3, 26.2, and 23.8%, respectively; Log-rank $p = .020$, Figure 2a). When the count of stent was dichotomized, rates of 10 year all-cause mortality were 31.4 and 26.7% in patients with >5 stents (n = 300) and ≤ 5 stents (n = 593), respectively, and the total implanted stents count was also associated to a poorer outcome (Figure S2).

In patients with 3VD, all-cause mortality rates in patients treated with extensive stenting PCI, not-extensive stenting PCI and CABG were significantly different (33.0, 25.9, and 20.5%, respectively; Log-rank

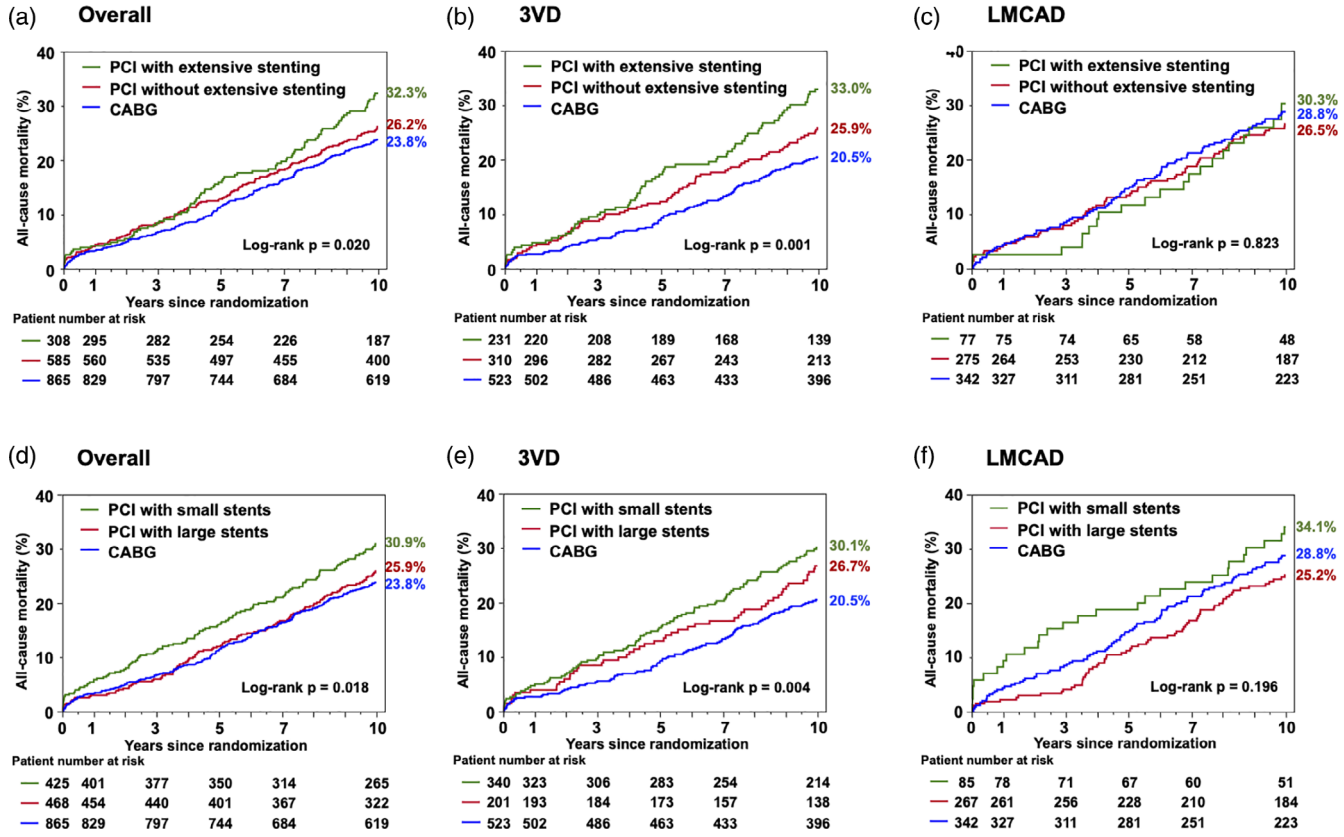


FIGURE 2 Kaplan–Meier curves for all-cause mortality at 10 years. (a–c) Mortality rates in patients with extensive stenting PCI, not-extensive stenting PCI and CABG. (a) The overall cohort. (b) Three-vessel disease (3VD) cohort. (c) Left main coronary artery disease (LMCAD) cohort. (d–f) Mortality rates in patients with small stenting PCI, large stenting PCI and CABG. (d) The overall cohort. (e) 3VD cohort. (f) LMCAD cohort. CABG, coronary artery bypass grafting surgery; PCI, percutaneous coronary intervention

$p = .001$, Figure 2b), whereas those were similar in patients with LMCAD (30.3, 26.5, and 28.8%, respectively; Log-rank $p = .823$, Figure 2c).

In the whole cohort, PCI with small stents (ASD <3 mm) was associated with a higher rate of all-cause mortality at 10 years compared with PCI with large stents or CABG (30.9, 25.9, and 23.8%, respectively; Log-rank $p = .018$, Figure 2d).

In 3VD cohort, all-cause mortality rates in patients treated with small stents, large stents and CABG were significantly different (30.1, 26.7, and 20.5%, respectively; Log-rank $p = .004$, Figure 2e).

In patients with LMCAD, mortality rates in patients with small stents and large stents and CABG were 34.1, 25.2, and 28.8% (Log-rank $p = .196$), respectively (Figure 2f). Of note, in the whole cohort, patients treated with CABG (n = 865) and those treated with not-extensive and large stenting PCI (n = 351) had similar mortality rates (24.0 vs. 23.8%, Figure 3).

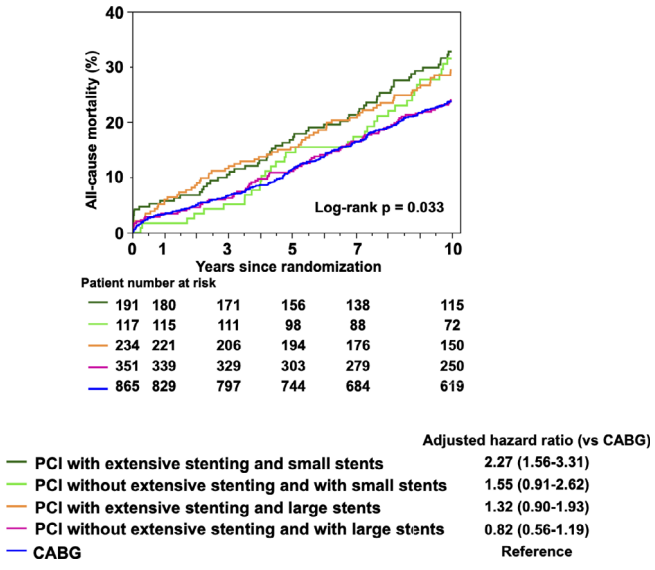


FIGURE 3 Mortality rates and adjusted hazard ratio according to revascularization strategy

In 1058 patients who were completely revascularized, extensive stenting or small stenting were still associated with worse survival, compared to CABG (Figure S3).

In the propensity score matched population, anatomical complexity based on the anatomical SYNTAX score was matched in addition to clinical comorbidities (Table S1, 2), and the Kaplan–Meier curves for all-cause mortality remained similar to those in the overall population (Figure S4).

3.4 | Impact of extensive or small stenting PCI on all-cause mortality

TSL treated as continuous variable was significantly associated with all-cause mortality at 10 years after adjusting for confounding variables (adjusted HR, 1.05 per 10 mm increase; 95% CI, 1.01–1.09; $p = .015$), whereas ASD did not have a significant association with 10 year mortality (adjusted HR, 0.97 per 0.25 mm increase; 95% CI, 0.85–1.11; $p = .655$, Figure 4).

When TSL was divided into "extensive" (>100 mm) and "not-extensive" (≤100 mm) based on the prespecified length of 100 mm, extensive-stenting PCI was significantly associated with all-cause mortality at 10 years, compared either with PCI without extensive stenting (adjusted HR, 1.94; 95% CI, 1.36–2.77; $p < .001$) or CABG (adjusted HR, 1.97; 95% CI, 1.41–2.74; $p < .001$, Figure 5a). On the other hand, the mortality outcome of PCI without extensive stenting was similar to that of CABG (adjusted HR, 1.01; 95% CI, 0.75–1.36; $p = .932$).

Although treatment effects were not significantly different between 3VD and LMCAD, in patients with 3VD, extensive stenting PCI was significantly associated with a higher mortality rate at 10 years, compared either with PCI without extensive stenting (adjusted HR, 2.12; 95% CI, 1.34–3.35; $p = .001$) or CABG (adjusted HR, 2.52; 95% CI, 1.66–3.82; $p < .001$) (Figure 5a).

When stent size was divided into "small" and "large" according to the threshold of 3 mm, the mortality risk in patients with small stents was significantly higher than in patients with large stents or those treated

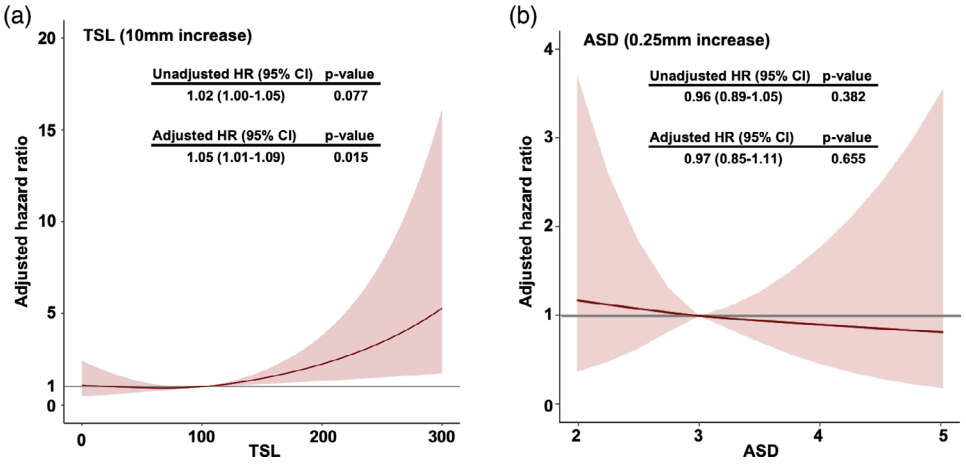
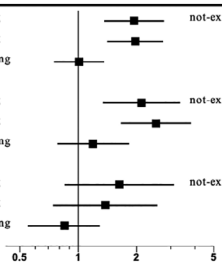


FIGURE 4 Impact of TSL and ASD on 10 year mortality. Red curve with light red area indicates adjusted hazard ratio (HR) with 95% CI for 10 year mortality according to (a) TSL with reference of 100 mm and (b) ASD with reference of 3 mm. The number of knots for the cubic spline curve was three. ASD, average nominal stent diameter; CI, confidence interval; TSL, total stent length

(a)

				Unadjusted HR (95% CI)	p-value	Adjusted HR (95% CI)	Better	Better	p-value	p-value for interaction
Overall	not-extensive stenting	vs	extensive stenting	1.26 (0.97-1.63)	0.079	1.94 (1.36-2.77)	extensive stenting	not-extensive stenting	< 0.001	
	CABG	vs	extensive stenting	1.42 (1.11-1.81)	0.005	1.97 (1.41-2.74)	extensive stenting	CABG	< 0.001	
	CABG	vs	not-extensive stenting	1.12 (0.91-1.39)	0.278	1.01 (0.75-1.36)	not-extensive stenting	CABG	0.932	
3VD	not-extensive stenting	vs	extensive stenting	1.33 (0.97-1.83)	0.081	2.12 (1.34-3.35)	extensive stenting	not-extensive stenting	0.001	0.451
	CABG	vs	extensive stenting	1.74 (1.29-2.35)	< 0.001	2.52 (1.66-3.82)	extensive stenting	CABG	< 0.001	0.142
	CABG	vs	not-extensive stenting	1.31 (0.98-1.76)	0.070	1.19 (0.78-1.83)	not-extensive stenting	CABG	0.423	0.417
LMCAD	not-extensive stenting	vs	extensive stenting	1.11 (0.69-1.79)	0.677	1.63 (0.85-3.12)	extensive stenting	not-extensive stenting	0.138	
	CABG	vs	extensive stenting	1.01 (0.63-1.61)	0.968	1.38 (0.74-2.56)	extensive stenting	CABG	0.306	
	CABG	vs	not-extensive stenting	0.91 (0.67-1.24)	0.558	0.85 (0.55-1.29)	not-extensive stenting	CABG	0.438	



(b)

				Unadjusted HR (95% CI)	p-value	Adjusted HR (95% CI)	Better	Better	p-value	p-value for interaction
Overall	large stents	vs	small stents	1.26 (0.98-1.62)	0.072	1.74 (1.19-2.53)	small stents	large stents	0.004	
	CABG	vs	small stents	1.37 (1.10-1.72)	0.005	1.66 (1.23-2.26)	small stents	CABG	0.001	
	CABG	vs	large stents	1.09 (0.87-1.37)	0.451	0.96 (0.69-1.33)	large stents	CABG	0.797	
3VD	large stents	vs	small stents	1.17 (0.83-1.63)	0.367	1.11 (0.66-1.85)	small stents	large stents	0.693	0.035
	CABG	vs	small stents	1.58 (1.20-2.07)	0.001	1.72 (1.17-2.51)	small stents	CABG	0.005	0.578
	CABG	vs	large stents	1.35 (0.97-1.88)	0.077	1.55 (0.93-2.59)	large stents	CABG	0.094	0.060
LMCAD	large stents	vs	small stents	1.49 (0.96-2.32)	0.078	2.90 (1.58-5.32)	small stents	large stents	<0.001	
	CABG	vs	small stents	1.25 (0.82-1.91)	0.295	2.07 (1.18-3.61)	small stents	CABG	0.011	
	CABG	vs	large stents	0.84 (0.61-1.15)	0.283	0.71 (0.46-1.11)	large stents	CABG	0.132	

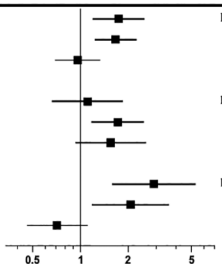


FIGURE 5 Treatment effect on 10 year mortality. HRs are (a) not-extensive stenting PCI versus extensive stenting PCI, CABG versus extensive stenting PCI, and CABG versus not-extensive stenting PCI and (b) not-extensive stenting PCI versus extensive stenting PCI, CABG versus extensive stenting PCI, and CABG versus not-extensive stenting PCI. CABG, coronary artery bypass grafting surgery; HR, hazard ratio; PCI, percutaneous coronary intervention

with CABG (adjusted HR, 1.74; 95% CI, 1.19–2.53; $p = .004$, and adjusted HR, 1.66; 95% CI, 1.23–2.26; $p = .001$, respectively, Figure 5b).

In patients with LMCAD, PCI with small stents resulted in worse outcomes, compared to PCI with large stents, (adjusted HR, 2.90; 95% CI, 1.58–5.32; $p < .001$), but that observation was not made in patients with 3VD (adjusted HR, 1.11; 95% CI, 0.66–1.85; $p = .693$, P for interaction = 0.035, Figure 5b).

3.5 | Impact of extensive or small stenting PCI on cardiovascular mortality

PCI with extensive stenting was associated with a higher rate of cardiovascular mortality at 5 years compared with PCI with not-extensive stenting or CABG (10.2, 8.1, and 5.0%, respectively; Log-rank $p = .005$, Figure S5A). Cardiovascular mortality rates in 3VD patients treated with extensive stenting PCI, not-extensive stenting PCI and CABG were significantly different (10.5, 7.6, and 3.9%, respectively; Log-rank $p = .003$, Figure S5B), whereas cardiovascular mortality rates were not significantly different in patients with LMCAD (9.2, 8.6, and 6.7%, respectively; Log-rank $p = .561$, Figure S5C).

In the whole cohort, PCI with small stents was associated with a higher 5-year cardiovascular mortality compared with PCI with large stents or CABG (10.4, 7.3, and 5.0%, respectively; Log-rank $p = .001$, Figure S5D). In 3VD cohort, cardiovascular mortality rates in patients treated with small stents, large stents and CABG were significantly different (9.8, 7.3, and 3.9%, respectively; Log-rank $p = .003$, Figure S5E). Mortality rates in LMCAD patients with small stents and large stents and CABG were 13.2, 7.3, and 6.7% (Log-rank $p = .091$), respectively (Figure S5F). The impact of not-extensive and large stenting PCI on 5 year cardiovascular mortality was similar to that of CABG (Figure S6).

Although TSL and ASD were not significantly associated with cardiovascular mortality at 5 years (adjusted HR for TSL [10 mm increase]: 1.07 [1.00–1.14], $p = .056$; adjusted HR for ASD [0.25 mm increase]: 0.79 [0.60–1.03], $p = .081$) (Figure S7), extensive/small stenting PCI were significantly associated with cardiovascular mortality at 5 years, compared either with not-extensive/large stenting PCI or CABG (Figure 6).

4 | DISCUSSION

The main findings of the present study are as follows:

(i) TSL treated as a continuous variable was significantly associated with all-cause mortality at 10 years, but ASD treated as a continuous variable was not significantly associated with all-cause mortality at 10 years.

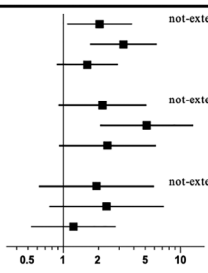
(ii) In patients with 3VD, extensive stenting PCI (TSL >100) was associated with a higher 10 year mortality, compared to CABG and not-extensive stenting PCI (TSL ≤100).

(iii) Patients who underwent either CABG, or PCI with not-extensive stenting (TSL ≤100) and large stents (ASD ≥3 mm) had similar all-cause mortality at 10 years.

(iv) The low-SYNTAX score stratum was associated with "large" and "not-extensive" stents, whereas the high-SYNTAX score stratum presaged the use of "extensive" and "small" stents.

(a)

				Unadjusted HR (95% CI)	p-value	Adjusted HR (95% CI)	Better	Better	p-value	p-value for interaction
Overall	not-extensive stenting	vs	extensive stenting	1.24 (0.78-1.96)	0.363	2.04 (1.08-3.86)	extensive stenting	not-extensive stenting	0.029	
	CABG	vs	extensive stenting	2.08 (1.29-3.33)	0.003	3.26 (1.69-6.28)	extensive stenting	CABG	< 0.001	
	CABG	vs	not-extensive stenting	1.68 (1.10-2.56)	0.017	1.60 (0.88-2.92)	not-extensive stenting	CABG	0.126	
3VD	not-extensive stenting	vs	extensive stenting	1.35 (0.75-2.40)	0.315	2.16 (0.91-5.12)	extensive stenting	not-extensive stenting	0.080	0.843
	CABG	vs	extensive stenting	2.72 (1.48-5.00)	0.001	5.15 (2.06-12.84)	extensive stenting	CABG	< 0.001	0.458
	CABG	vs	not-extensive stenting	2.02 (1.10-3.72)	0.023	2.38 (0.92-6.17)	not-extensive stenting	CABG	0.074	0.541
LMCAD	not-extensive stenting	vs	extensive stenting	1.07 (0.46-2.49)	0.876	1.92 (0.62-5.95)	extensive stenting	not-extensive stenting	0.259	
	CABG	vs	extensive stenting	1.42 (0.61-3.35)	0.419	2.34 (0.76-7.21)	extensive stenting	CABG	0.140	
	CABG	vs	not-extensive stenting	1.33 (0.74-2.41)	0.344	1.22 (0.53-2.80)	not-extensive stenting	CABG	0.644	



(b)

				Unadjusted HR (95% CI)	p-value	Adjusted HR (95% CI)	Better	Better	p-value	p-value for interaction
Overall	large stents	vs	small stents	1.47 (0.94-2.32)	0.093	2.41 (1.18-4.93)	small stents	large stents	0.016	
	CABG	vs	small stents	2.19 (1.42-3.37)	< 0.001	3.08 (1.67-5.69)	small stents	CABG	< 0.001	
	CABG	vs	large stents	1.48 (0.94-2.35)	0.094	1.28 (0.64-2.53)	large stents	CABG	0.485	
3VD	large stents	vs	small stents	1.37 (0.73-2.56)	0.332	1.35 (0.47-3.86)	small stents	large stents	0.576	0.207
	CABG	vs	small stents	2.58 (1.46-4.55)	0.001	3.68 (1.57-8.61)	small stents	CABG	0.003	0.726
	CABG	vs	large stents	1.89 (0.95-3.77)	0.071	2.73 (0.84-8.81)	large stents	CABG	0.094	0.337
LMCAD	large stents	vs	small stents	1.94 (0.93-4.09)	0.079	3.94 (1.37-11.30)	small stents	large stents	0.011	
	CABG	vs	small stents	2.16 (1.04-4.48)	0.039	3.85 (1.36-10.91)	small stents	CABG	0.011	
	CABG	vs	large stents	1.11 (0.60-2.07)	0.741	0.98 (0.41-2.34)	large stents	CABG	0.961	

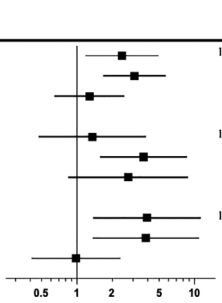


FIGURE 6 Treatment effect on 5 year cardiovascular mortality. HRs are (a) not-extensive stenting PCI versus extensive stenting PCI, CABG versus extensive stenting PCI, and CABG versus not-extensive stenting PCI and (b) not-extensive stenting PCI versus extensive stenting PCI, CABG versus extensive stenting PCI, and CABG versus not-extensive stenting PCI. CABG, coronary artery bypass grafting surgery; HR, hazard ratio; PCI, percutaneous coronary intervention

4.1 | Extensive stenting and 10-year all-cause death

Previous studies have demonstrated that TSL is associated not only with major adverse cardiovascular events but also with all-cause death.[4-6] In the j-Cipher registry (n = 10,773), TSL (≥55 mm) of the first generation sirolimus-eluting stents was associated with 3-year all-cause mortality, although extensive stenting was not significantly associated with all-cause mortality after adjustment for baseline characteristics.[4] In a pooled analysis of women undergoing PCI with new-generation DES (n = 5,232), TSL (≥36 mm) was also associated with 3-year all-cause mortality, but extensive stenting was not an independent predictor of all-cause mortality after adjustment.[5] In a larger GLOBAL LEADERS trial (n = 15,450), the fourth quartile group (TSL ≥46 mm) had a significantly higher adjusted risk of 2 year all-cause death, compared to first quartile group (TSL ≤16 mm) when patients were divided into quartiles according to TSL.[6] A risk model incorporating clinical, angiographic, and physiological parameters demonstrate that TSL (≥30 mm) is the most important predictor.[7] These results are derived from patients treated with PCI, but comparative treatment effect of CABG versus PCI with respect to TSL in patients with 3VD and/or LMCAD has not been fully evaluated. In the present study, extensive stenting PCI (TSL >100 mm) was associated with complex anatomic features. Although patients with extensive stenting achieved complete revascularization more frequently than patients with not-extensive stenting (Table S1), patients with extensive stenting showed a higher 5 year cardiovascular mortality and 10 year mortality (Figure S5, Figure 2a). This fact suggests that the patients who need extensive stenting could present a worse outcome. Even after adjustment for baseline characteristics, extensive stenting PCI was still a predictor of 5 year cardiovascular mortality and 10 year mortality, compared to CABG and not-extensive stenting PCI (Figures 5a and 6a). In addition, in patients who were completely revascularized, extensive stenting or small stenting were also associated with a higher 10 year mortality, compared to CABG and not-extensive stenting or large stenting (Figure S3). This sub-analysis confirms the results in the overall population.

Number of stents could also be associated with a mortality prediction, but the mortality rate (31.4%) in patients with >5 stents was similar and not higher, compared to the mortality rate (32.3%) in extensive stenting patients.

4.2 | PCI with small stents and 10-year all-cause death

It has been known that females have small epicardial vessel diameter than males.[15] In addition, diabetes is accompanied by impaired compensatory remodeling of the coronary arterial wall.[16] Therefore, patients with diabetes have smaller lumen diameter of coronary artery than those without diabetes. In accordance with these facts, patients treated with small stents were more frequently females and had a higher prevalence rate of diabetes in the SYNTAX trial.

PCI with DES in small vessels results more frequently in restenosis, compared to PCI in large vessels, although thresholds for small vessels varied among researches (from 2 to 3 mm).[8,9,17] In addition, CABG for small vessels has also been associated with higher perioperative mortality.[18] Although revascularization of small vessels is associated with poor prognosis regardless of the revascularization mode (PCI or CABG), comparative treatment effect of CABG versus PCI in patients with complex CAD considering stent diameter has not been investigated.

The present study demonstrated that PCI with small stents was associated with higher 5 year cardiovascular mortality and 10 year all-cause mortality, compared to either CABG or PCI with large stents, even after adjustment for baseline characteristics (Figures 5b and 6b). In addition, the benefit of larger stents, compared to smaller stents, was evident in patients with LMCAD.

4.3 | Treatment effects of CABG versus PCI considering procedure plan

In the SYNTAX trial, the use of IVUS was only 12.7% (113 patients). Post-procedural minimal stent area is associated with cardiovascular adverse events and the benefit of intravascular ultrasound (IVUS)-guided PCI has been demonstrated in the ULTIMATE and IVUS-XPL trials.[19,20] In the SYNTAX II trial, the contemporary state-of-the-art PCI, including use of current-generation DES (98.4%), physiology-guided treatment (96.4%) and IVUS optimization of stent deployment (84.1%), were applied. The contemporary state-of-the-art PCI in the SYNTAX II trial definitely improved the clinical outcomes, compared with an historical control such as the original SYNTAX trial, although TSLs in the propensity matched population of SYNTAX I (n = 308) and SYNTAX II (n = 440) were not significantly different (97.7 ± 43.7 mm and 92.3 ± 52.8 mm, $p = .13$).[21] Similarly, contemporary CABG as executed in the EXCEL trial offered superior outcomes when compared in a propensity analysis with the outcome of the SYNTAX trial.[22] Considering the technical improvement of PCI and CABG, the definition of extensive stenting and small stenting should be further evaluated following contemporary procedures as recommended in the SYNTAX II trial. However, when patients need extensive stenting or small stents for PCI revascularization as presaged by the SYNTAX strata, revascularization with CABG could be safer and beneficial.

The Interactive Planner (HeartFlow, Redwood City, CA) offers the possibility to anticipate the physiological benefit virtually obtainable by stenting and to predict the residual fractional flow reserve by computed tomography (FFRCT) as a function of the length and diameter stent used.[23] This planning program let presage the use of extensive and small stents needed to normalize as much as possible the conductance of the major epicardial vessel prior to the actual procedure. PCI planning with virtual stenting might become part of the heart team discussion at the time of the decision-making on the most appropriate mode of revascularization.

5 | LIMITATION

First, this is a post hoc analysis and all the presented findings must be interpreted as hypothesis generating due to the inherent limitations of post hoc analysis including multiple testing. Second, lesion characteristics data by quantitative coronary angiography (QCA, lesion length and reference vessel diameter of target lesions) are not available, therefore, we could not evaluate the quantitative impact on mortality of incomplete lesion coverage, overlapping, underexpansion or stent size mismatch. Third, the first generation TAXUS DES and an out dated PCI strategy was used in the SYNTAX trial since patients were enrolled between March, 2005, and April, 2007. The TAXUS stent is no longer commercially available and newer generation DES improved clinical outcomes. When the SYNTAX trial started in 2005, IVUS had not yet been introduced in the guidelines. The ACC/AHA/SCAI guideline published in 2006 recommended the clinical use of IVUS for lesion assessment as class IIa for the first time, and the rate of IVUS usage in the SYNTAX trial was low.[24] It is, however, unavoidable that the findings from long-term follow-up data are based on partially outdated technology and strategy of treatment while the evidence for contemporary technology can be derived only from short-term follow-up studies. Fourth, the endpoint in the SYNTAXES study was only all-cause death only and the results for cardiovascular death were available up to 5 years. However, the SYNTAXES study is a randomized data that was meticulously conducted and achieved a high follow-up rate of 93.8% for 10 year vital status (1,689 out of 1,800 enrolled patients).[11]

6 | CONCLUSION

Extensive and small stenting are associated with high 10 year mortality, compared with CABG. When patients with 3VD and/or LMCAD need extensive or small stenting for PCI revascularization, revascularization with CABG should be considered.

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CONFLICT OF INTERESTS

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DATA AVAILABILITY STATEMENT

The SYNTAX Extended Survival study declares that no data will be made available to others.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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