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Outcomes of stent optimisation in intravascular ultrasound-guided intervention for long or chronic totally occluded coronary lesions

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Abstract

Aims: We sought to investigate the incidence, predictors, and clinical outcomes of stent optimisation on intravascular ultrasound (IVUS) in long coronary lesions treated with new-generation drug-eluting stents (DESs).

Methods and Results: From four randomised trials comparing IVUS and angiography guidance in long (≥26 mm) or chronic total occlusion coronary lesions, a total of 1,396 patients who underwent IVUS-guided intervention were classified into two groups (Stent-optimisation and Non-optimisation) according to optimisation criteria [minimal stent area (MSA) ≥5.5 mm^2 or 80% of mean reference lumen area (MLA)]. Major adverse cardiac event (MACE) occurrence, defined as a composite of cardiac death, myocardial infarction, stent thrombosis, or target-vessel revascularisation, was compared. Stent optimisation was not met in 578 (41%) patients. Predictors of non-optimisation were older age, longer lesion length, and smaller stent diameter. MACE rate was significantly higher in the Non-optimisation vs. the Stent-optimisation group (4.8% vs. 1.9%, log-rank P=0.002; adjusted hazard ratio=2.95, 95% confidence interval=1.43–6.06). Among possible combinations of absolute and relative expansion criteria, the combination best predicting MACE was MSA ≥5.4 mm^2 or 80% of MLA (Youden index=0.264).

Conclusions: Achieving stent optimisation on IVUS evaluation was associated with favourable outcomes in IVUS-guided, new-generation DES implantation for long coronary lesions including CTO.

Classifications: diffuse disease; drug-eluting stent; intravascular ultrasound

Condensed Abstract

This study investigated the incidence, predictors, and clinical outcomes of stent optimisation on IVUS in long or chronic total occlusion lesions treated with new-generation DESs. Under IVUS guidance, 41.4% of patients did not meet the stent optimisation criteria. Predictors of non-optimisation were older age, longer lesion length, and smaller stent diameter. Compared to the Stent-optimisation group, the Non-optimisation group showed significantly higher rates of major adverse cardiac events including cardiac death, myocardial infarction, stent thrombosis, or target-vessel revascularisation. Stent optimisation by IVUS improves the likelihood of favourable outcomes in new-generation DES implantation for long coronary lesions

Abbreviations

AUC: area under curve

CI: confidence interval

CTO: chronic total occlusion

DES: drug-eluting stent(s)

HR: hazard ratio

IVUS: intravascular ultrasound

MACE: major adverse cardiac event(s)

MI: myocardial infarction

MLA: mean reference lumen area

MSA: minimal stent area

PCI: percutaneous coronary intervention

ROC: receiver operating characteristic

ST: stent thrombosis

TVR: target-vessel revascularisation

INTRODUCTION

In the era of drug-eluting stents (DESs), there is growing evidence from randomised controlled trials and meta-analyses that intravascular ultrasound (IVUS)-guided percutaneous coronary intervention (PCI) compared to conventional angiography guidance could improve clinical outcomes.[1-8] For IVUS-guided PCI, authors' own criteria of stent optimisation were mainly based on the various degrees of stent expansion.[4,5,8–11] However, in previous studies achieving favourable clinical outcomes with IVUS guidance, considerable number of patients did not meet the predefined stent optimisation targets. In addition, clinical implications of non-optimization have not been fully elucidated in long lesions.[12]

Therefore, we conducted a comprehensive analysis of individual patient-level randomised trials targeting long or chronic total occlusion (CTO) lesions to evaluate the incidence, predictors, and clinical outcomes of stent optimisation following new-generation DES implantation. We also investigated the association between the absolute and relative stent expansion and determined the optimal combination criteria of absolute and relative expansion predicting adverse outcomes.

METHODS

Study design and population

This study included four randomised controlled trials comparing IVUS and angiography guidance for long or CTO lesions treated by new-generation DESs, with available patient-level data for pooled analysis: RESET IVUS (Real safety and efficacy of 3-month dual antiplatelet therapy following endeavor zotarolimus-eluting stent implantation), CTO-IVUS (chronic total occlusion intervention with drug-eluting stents guided by intravascular ultrasound), IVUS-XPL (impact of intravascular ultrasound guidance on outcomes of Xience Prime stents in long lesions), and ULTRA-ZET (intravascular ultrasound guided vs. conventional angiography guided strategy to deploy zotarolimus and everolimus eluting third generation stents in long coronary artery lesions) (Figure 1). Detailed explanations of these studies are provided in Online Table 1.[2,4,5] Briefly, we included the studies which enrolled the patients with long lesions requiring stent length ≥26 mm or CTO. The statisticians from each trial extracted patient-level data by direct access to the study databases. Data on baseline patient characteristics,

procedure information, and clinical events were collected. These patient data were pooled and analyzed in a single dataset.

IVUS exam and analyses

IVUS exams were performed with commercially available imaging systems (40 MHz IVUS catheter, Boston Scientific Corp, Natick, MA, USA; 20 MHz IVUS catheter, Volcano Corp, Rancho Cordova, CA, USA). All images were analyzed at the Cardiovascular Research Center core laboratory (Seoul, Korea) by analysts blinded to patient and procedural information. Detailed explanations regarding imaging acquisition were provided in previous studies.[2,4,5] Using planimetry software (Echoplaque version 3.0, INDEC Systems, Santa Clara, California), cross-sectional lumen, stent, and vessel areas were measured at proximal and distal references (within 10 mm of the proximal or distal stent edge) and the minimal stent area (MSA) site according to current guidelines.[13]

Stent expansion was classified as absolute expansion, defined as MSA with an absolute measure,[14-16] and relative expansion, defined as the percent ratio of MSA to mean reference lumen area (MLA).[4,5,9,10] In this study, the main criteria of stent optimisation was defined as MSA $\geq$5.5 mm^2 or 80% of MLA according to the most recent expert consensus document.[12] Depending on if the stent optimisation criteria were met or not, all enrolled patients were classified into either a Stent-optimisation or Non-optimisation group.

Endpoints, definitions, and follow-up

The primary endpoint in this study was the occurrence of major adverse cardiac event (MACE), defined as a composite of cardiac death, myocardial infarction (MI), stent thrombosis (ST), or target-vessel revascularisation (TVR). The secondary endpoints were: 1) individual components of the primary endpoint; 2) incidence of stent optimisation; 3) major predictors for non-optimisation; and 4) the optimal combination criteria of the absolute and relative expansion for predicting MACE. Detailed definitions of clinical endpoints are presented in Online Appedix. Clinical follow-up and assessment were performed in the hospital after 1, 3, 6, and 12 months either by clinic visit or telephone interview.

Statistical analyses

Continuous variables are presented as mean±standard deviation, and categorical variables are presented

as numbers (percentages). Continuous and categorical variable data were analyzed using Student's t-tests and chi-square tests. Cumulative incidence values were calculated using the Kaplan-Meier method and compared using log-rank tests. Logistic regression analysis was performed to identify predictors of non-optimisation. Any variables with P <0.1 on univariate analysis were included in the multivariate logistic regression analysis. To estimate the effect of stent optimisation on clinical outcomes, hazard ratios (HRs) were calculated using the Cox proportional hazards model. In multivariate Cox regression analysis, HRs were adjusted for age, sex, hypertension, diabetes mellitus, current smoking status, prior MI, prior PCI, prior coronary artery bypass graft surgery, clinical presentation, ejection fracture, treated vessels, CTO, DES types, stented length, number of stents per lesion, maximum stent diameter, high-pressure post-dilation, and pre-procedural QCA parameters including reference lumen diameter and minimal lumen diameter. The analysis was performed using per-protocol analysis. The subgroup analysis was performed according to baseline characteristics. Receiver operating characteristic (ROC) analysis was performed to determine the best cut-off values for predictors of non-optimisation and expansion criteria predicting MACE. Simple linear regression analysis was performed to evaluate the association between the absolute (MSA) and the relative stent expansion (the ratio of MSA-to-MLA). To compare the performance of optimisation criteria to predict MACE occurrence, the Youden index (sensitivity+specificity-1) was calculated. Two-sided P-values were used, and P <0.05 was considered statistically significant. All analyses were performed using R version 3.5.2 (The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

In four randomised trials targeting long or CTO lesions, a total of 1,396 patients underwent IVUS-guided new-generation DES implantation (Figure 1). Of these cases, stent optimisation criteria were met in 818 (58.6%) patients (Stent-optimisation group) and not met in 578 (41.4%) (Non-optimisation group). The baseline characteristics of both groups are presented in Table 1. Compared to patients of the Stent-optimisation group, patients of the Non-optimisation group were more likely to be older in age, have different types of DESs implanted with more CTO lesions, smaller stent diameters, longer

stent-lengths, overlapping stents, multiple stents per lesion, and smaller balloon sizes used. Quantitative coronary analyses revealed that the Non-optimisation group had a longer lesion length, smaller reference vessel diameter, pre- and post-procedural minimal lumen diameter or diameter stenosis, and acute gain compared to the Stent-optimisation group.

In IVUS analyses, vessel or lumen areas at proximal and distal reference segments were smaller in the Non-optimisation group. MSA was significantly smaller in the Non-optimisation group than in the Stent-optimisation group (Table 1).

Predictors of non-optimisation for IVUS criteria

By multivariate logistic regression analysis, older age, longer lesion length, and smaller maximum stent diameter were independently associated with non-optimisation (Online Table 2). The best cut-off values predicting non-optimisation after DES implantation were age ≥72 years, lesion length ≥39 mm, and maximum stent diameter <3.0 mm (Figure 2A–C). When analyzing the incidences of non-optimisation based on these cut-off values, the rates were significantly different among various subgroups (Figure 2D).

Clinical outcomes with fulfillment of IVUS optimisation criteria

The analyses regarding clinical outcomes of both groups are presented in Figure 3 and Table 2. MACEs occurred in 27 (4.8%) patients in the Non-optimisation group and 15 (1.9%) patients in the Stent-optimisation group (log-rank P=0.002; unadjusted HR=2.58, 95% confidence interval [CI]=1.37–4.84; Figure 3A). The Non-optimisation group also had significantly higher rates of a fatal composite event including cardiac death, MI, and ST (P=0.017, Figure 3B); ST (P=0.039, Figure 3E); and TVR (P=0.006, Figure 3F). In multivariate Cox regression, non-optimisation was associated with increased risks of MACE (adjusted HR=2.95, 95% CI=1.43–6.06), the fatal composite event, and TVR (Table 2). No significant interactions were observed in the post-hoc subgroup analysis; the effects of non-stent-optimisation on the occurrence of MACE were consistent across various subgroups (Online Figure 1).

When comparing the cumulative incidences of MACE among the groups according to whether meeting each individual absolute (MSA ≥5.5 mm^2) and relative expansion (MSA ≥80% of MLA) criteria, MACE rate was significantly higher in the patients who met neither absolute nor relative

expansion criteria (MSA <5.5 mm^2 and <80% of MLA) than in those meeting at least one of absolute or relative expansion criteria (all log-rank P<0.05), without significant differences among the patients meeting only one or both (Figure 4).

Association between the absolute and relative expansion and the best predictive combination criteria

The absolute value of MSA was significantly correlated with the ratio of MSA-to-MLA (P<0.001, Figure 5A). The correlation was stronger in those with longer lesion length (≥34.5 mm, the median lesion length) than in those with lesion length <34.5 mm (R^2=0.226 vs. 0.134, P=0.012; Online Figure 2). The ROC curves of absolute and relative expansion for predicting MACE are presented in Figure 5B. There was no significant difference of area under curve (AUC) between absolute and relative expansion (DeLong test P=0.531): AUCs of absolute MSA and MSA-to-MLA ratio were 0.605 (95% CI 0.501-0.710) and 0.642 (95% CI 0.540-0.745). The optimal cut-off values predicting MACE were 5.6 mm^2 for MSA and 70% for the MSA-to-MLA ratio, respectively. When using the combined criteria using these optimal cut-offs, MACE rate was significantly higher in the Non-optimisation group than the Stent-optimisation group (log-rank P=0.003; adjusted HR=2.45, 95% CI=1.34–4.50) (Figure 5C).

The comparison of Youden indexes for determining the optimal combination of absolute and relative expansion criteria predicting the occurrence of MACE is presented in Figure 6. Among the possible combinations, the combination of MSA ≥5.4 mm^2 or 80% of MLA was best predictive with the greatest Youden index of 0.264 (sensitivity=64.5% and specificity=61.9%). When using this combination, the Non-optimisation group showed a significantly higher MACE rate compared to the Stent-optimisation group (4.8% vs. 2.0%, log-rank P=0.003; adjusted HR=2.65, 95% CI=1.29–5.44).

DISCUSSION

There were four principle findings from our comprehensive analyses of individual patient-level data from four randomised trials targeting long or CTO lesions: 1) Under IVUS guidance, 41.4% did not meet IVUS criteria for stent optimisation following new-generation DES implantation; 2) Predictors of non-optimisation were older age (≥72 years), longer lesion length (≥39 mm), and smaller stent diameter

(<3.0 mm); 3) The Non-optimisation group showed significantly higher rates of MACE or fatal events including cardiac death, MI, or ST. Especially, compared to the patients fulfilling either absolute or relative expansion, the patients who met neither of them had the worst clinical outcomes; 4) Absolute and relative stent expansion showed a statistically significant correlation and both could predict the occurrence of MACE. The best predictive combination criteria were MSA ≥5.4 mm^2 or 80% of MLA, nearly identical to those in the recent expert consensus document.

A considerable portion of patients with IVUS guidance did not meet the IVUS criteria for stent optimisation; implications of incidence, predictors, and outcomes had not been fully analyzed for this group. In this study targeting long or CTO lesions following new-generation DES implantation, over one-third of patients did not meet the IVUS criteria for stent optimization. Although caution is needed in interpreting our results due to a heterogeneity of optimisation criteria across the four included studies, the following factors significantly affected stent optimisation; age, lesion length, and stent diameter. Older age is independently associated with coronary artery calcification, which could have a negative effect on stent expansion.[17,18] Longer lesion length and smaller stent diameter are well-known independent risk factors for stent failure including restenosis, which may be associated with stent underexpansion.[14,19,20] The incidence of non-optimisation in patients with triple predictors of non-optimisation (age ≥72 years, lesion length ≥39 mm, or stent diameter <3.0 mm) was about 90% (89.7%) in this study. More careful IVUS assessment and strategy are necessary for such patients with multiple predictors for non-optimisation after DES implantation. Studies of how to achieve stent optimisation and specific optimisation criteria for these high-risk patients and lesions are needed.

Regarding clinical outcomes, the patients who did not meet the criteria for stent optimisation showed significantly worse clinical outcomes than those who did meet the IVUS criteria in long coronary lesions, even with IVUS guidance using new-generation DES implantation. In each included study, the between-group difference in MACE was not statistically different due to the relatively low event rate, even though all four trials showed a trend in favour of stent optimisation (Online Figure 1). In this pooled analysis, both the hard-clinical endpoints, including the composite of cardiac death, MI, or ST, and the efficacy endpoints, like TVR, were significantly higher in the patients that did not meet

the optimisation criteria. These clinical benefits could be attributable to the increased power according to the use of the individual-level data from 1396 patients. Improving clinical outcomes and maximising the impact of IVUS guidance will require meticulous IVUS evaluations and assessments before and after stenting; these would require going beyond simply performing IVUS catheter crossing and achieving visual confirmation.

As stent underexpansion is a major predictor of stent failure,[14] its evaluation is the most important component of the IVUS criteria for stent optimisation. With respect to absolute expansion, achieving a greater MSA has been associated with better stent patency and a lower risk of TVR, especially after DES introduction.[14-16] Sonoda et al. reported that the optimal MSA threshold predicting long-term stent patency was <5.0 mm^2 for sirolimus-eluting stents.[15] Hong et al. suggested a MSA of 5.5 mm^2 as the cut-off best discriminating subsequent events in IVUS-guided sirolimus-eluting stent implantation for non-left main lesions.[14] In addition, other DES studies using different stent types reported similar definite values as significant factors for predicting stent failure.[16] Thus, previous studies proposed various IVUS criteria for stent optimisation with respect to either absolute expansion (MSA ≥5 or 5.5 mm^2) or relative expansion (MSA ≥80 or 90% of MLA),[4,5,9-11,14-16] and several different criteria based on these findings have been employed in different clinical studies evaluating the effect of IVUS on clinical outcomes.[4,5,9,11] However, optimisation criteria based on absolute cut-off values might be vary depending on vessel size and result in relative stent under- and over-sizing in large and small vessels, respectively.[12] Particularly, in small vessels, the attainment of MSA ≥5 or 5.5 mm^2 might not be easy and could cause complications, such as perforation or edge dissection, by the vigorous post-dilation. Therefore, the criteria for optimal stent expansion for small and long lesions can be different from the larger vessels. In the present study, the relative expansion significantly correlated with the absolute expansion (as the lesion was longer, the correlation got stronger) and was a statistically significant predictor for the occurrence of MACE. When analyzing the risk of MACE according to whether meeting absolute or relative expansion criteria, meeting either absolute or relative expansion criteria showed low MACE rates, comparable to that of meeting both the two, whereas meeting neither absolute nor relative expansion had the worst outcomes. In the decision of IVUS-optimised criteria for

long coronary artery stenoses treated by new-generation DES, relative stent expansion was useful for determining of stent optimisation, and the evaluation of stent optimisation by using the combination of absolute and relative expansion criteria (meeting either relative or absolute criteria) would be more suitable, practical, and predictive. The best predictive combination in this study was MSA ≥5.4 mm^2 or 80% of MLA, which was almost same with MSA ≥5.5 mm^2 or 80% of MLA, suggested in the most recent expert consensus document and mainly analyzed in this study.[12]

Limitations

The limitations of this study are as follows. First, although we evaluated optimisation criteria for long coronary lesions, including CTO, the criteria of the four enrolled studies were not identical. In addition, CTO are usually long lesion but sometimes could offer non-diffuse long features. Thus, general extension of our results to entire long lesions might require attention. Second, analyses of qualitative IVUS assessment, including calcification, were not performed. Volumetric assessment was also not performed. Third, optimisation criteria usually include the status of stent apposition and post-stenting edge dissection, but these were not assessed in this study. Finally, a 1-year follow-up period may not be sufficient for assessing long-term clinical outcomes.

CONCLUSIONS

Achieving stent optimisation on IVUS evaluation was associated with favourable outcomes in IVUS-guided, new-generation DES implantation for long coronary lesions including CTO. This study confirmed that the combination of absolute and relative stent expansion criteria was useful and the optimisation criteria (MSA ≥5.5 mm^2 or 80% of MLA) according to the recent expert consensus document was predictive for the occurrence of MACE in long coronary lesions.

Impact on daily practice

In previous studies achieving favourable clinical outcomes with IVUS guidance, a considerable number of patients did not meet the predefined stent optimisation targets, reflecting the difficulty in sufficiently meeting IVUS criteria for stent optimisation, particularly for long coronary lesions even with the use of

IVUS during procedures. In our comprehensive analysis of individual patient-level randomised trials targeting long or chronic total occlusion lesions, achieving stent optimisation on IVUS evaluation was strongly associated with favourable outcomes. More careful IVUS assessment and strategy are necessary for patients with multiple predictors for non-optimisation (old age, longer lesion, and small stent diameter).

Conflicts of interest: The authors declare no conflicts of interest.

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Figure Legends

Figure 1. Study flow.

IVUS, intravascular ultrasound; PCI, percutaneous coronary intervention.

Figure 2. (A-C) Receiver operating characteristic curves of predictors for non-optimisation showing the capacities and optimal cut-off values. (D) Non-optimisation incidences by subgroup according to the predictors.

*P <0.001 compared to the patients without any non-optimisation predictors.

AUC, area under curve.

Figure 3. Kaplan-Meier estimates of clinical outcomes for the Stent-optimisation and Non-optimisation groups.

MACE, major adverse cardiac event.

Figure 4. Kaplan-Meier estimates of major adverse cardiac events according to whether meeting either absolute or relative expansion criteria.

*Comparison among 4 groups by the log rank test.

#Comparison between 2 groups by the log rank test.

MACE, major adverse cardiac event; MLA, mean reference lumen area; MSA, minimal stent area.

Figure 5. (A) Association between absolute and relative stent expansion. (B) Receiver operating characteristic curves of absolute and relative expansion showing the capacities and optimal thresholds for predicting major adverse cardiac event. (C) Kaplan-Meier estimates of major adverse cardiac events for the Stent-optimisation and Non-optimisation groups by applying the optimal cut-off values of absolute and relative expansion.

AUC, area under curve; MACE, major adverse cardiac event; MLA, mean reference lumen area; MSA, minimal stent area.

Figure 6. Comparison of predictive abilities for the occurrence of major adverse cardiac events among possible combinations of absolute and relative expansion criteria.

To compare the performance to predict MACE occurrence, the Youden index (sensitivity + specificity – 1, Z-axis) was calculated for each combination of absolute (MSA ≥2-8 mm, X-axis) and relative expansion (MSA/MLA ratio ≥50-140%, Y-axis) criteria.

CI, confidence interval; HR, hazard ratio; MLA, mean reference lumen area; MSA, minimal stent area.

Table 1. Baseline characteristics

	Stent-optimisation group (n=818)	Non-optimisation group (n=578)	P value
Age, years	62.3±9.8	64.3±9.6	<0.001
Male	594 (72.6)	399 (69.0)	0.163
Hypertension	522 (63.8)	365 (63.1)	0.843
Diabetes mellitus	274 (33.5)	223 (38.6)	0.058
Current smoking	194 (23.7)	150 (26.0)	0.373
Prior myocardial infarction	39 (4.8)	28 (4.8)	0.947
Prior percutaneous coronary intervention	100 (12.2)	66 (11.4)	0.708
Prior bypass surgery	14 (1.7)	11 (1.9)	0.951
Clinical presentation			0.311
Stable angina	479 (58.6)	360 (62.3)	
Unstable angina	247 (30.2)	164 (28.4)	
Acute myocardial infarction	92 (11.2)	54 (9.3)	
Ejection fraction, %	60.8±11.5	59.9±12.1	0.366
Dual-antiplatelet therapy ≥6 months	720 (88.0)	500 (86.5)	0.401
Left anterior descending artery treated	462 (56.5)	344 (59.5)	0.258
Chronic total occlusion	128 (15.6)	131 (22.7)	0.001
Stent elution			<0.001
Everolimus	579 (70.8)	350 (60.6)	
Biolimus	55 (6.7)	65 (11.2)	
Zotarolimus	184 (22.5)	163 (28.2)	
Maximum stent diameter, mm	3.2±0.4	2.9±0.3	<0.001
Total stented length, mm	37.0±14.4	42.9±18.9	<0.001
Number of stents per lesion	1.3±0.5	1.6±0.7	<0.001
Overlapping stents	260 (31.8)	275 (47.6)	<0.001
High-pressure post-dilation	330 (40.3)	255 (44.1)	0.176
Final balloon size, mm	3.2±0.5	3.1±0.6	<0.001
Maximum inflation pressure, atm	15.3±4.0	14.9±4.0	0.116
Pre-procedure quantitative coronary analyses			
Lesion length, mm	33.5±12.4	38.1±14.9	<0.001
Reference vessel diameter, mm	3.0±0.5	2.7±0.4	<0.001
Minimal lumen diameter, mm	0.8±0.5	0.6±0.5	<0.001
Diameter stenosis, %	73.8± 17.3	77.4±16.8	<0.001
Post-procedure quantitative coronary analyses			
Minimal lumen diameter, mm	2.8±0.4	2.5±0.3	<0.001
Diameter stenosis, %	11.9±8.2	13.7±8.5	<0.001

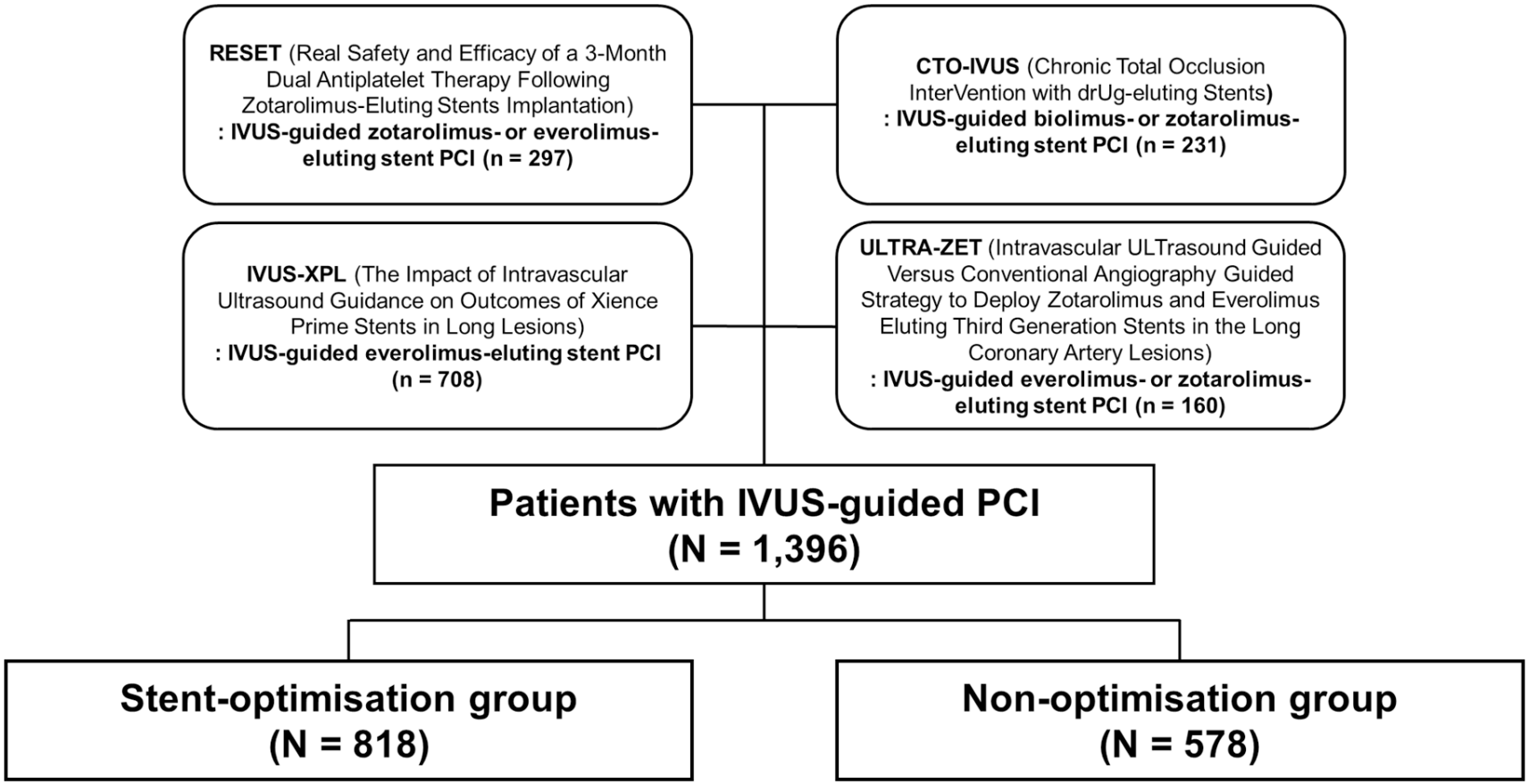
Acute gain, mm	2.0±0.7	1.9±0.6	0.002
Stent-to-artery ratio	1.0±0.1	1.0±0.1	0.863
Post-procedure IVUS analyses			
Proximal reference			
Vessel area, mm^2	17.7±5.3	16.8±4.8	0.010
Lumen area, mm^2	9.1±3.5	8.7±2.7	0.037
MSA site			
Vessel area, mm^2	13.6± 4.2	9.7±2.9	<0.001
Stent area, mm^2	6.5±1.6	4.3±0.8	<0.001
Distal reference			
Vessel area, mm^2	11.2±4.5	8.1±2.9	<0.001
Lumen area, mm^2	6.6±2.2	5.2±1.5	<0.001

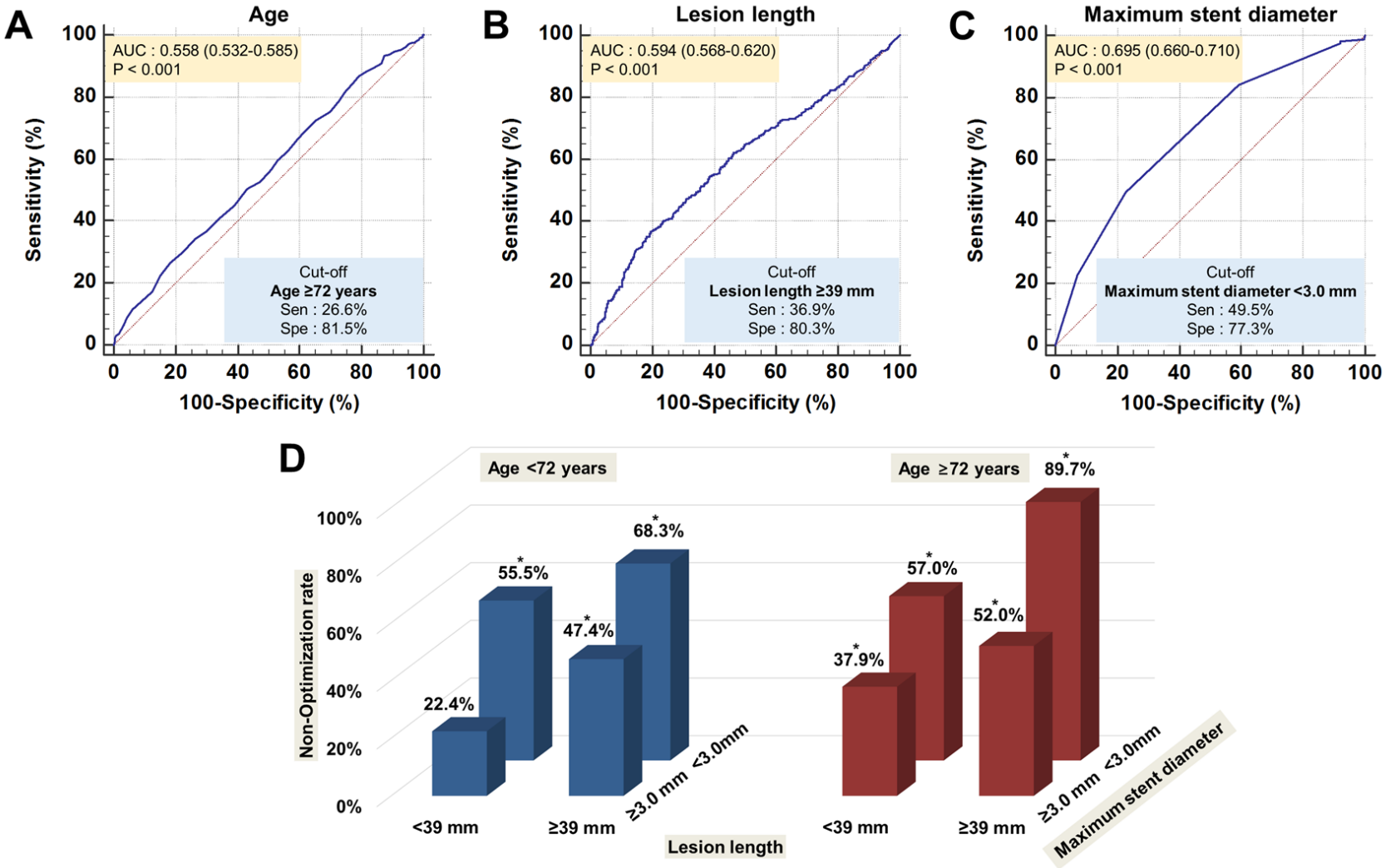
Values are mean ± SD or n (%). IVUS, intravascular ultrasound; MSA, minimal stent area.

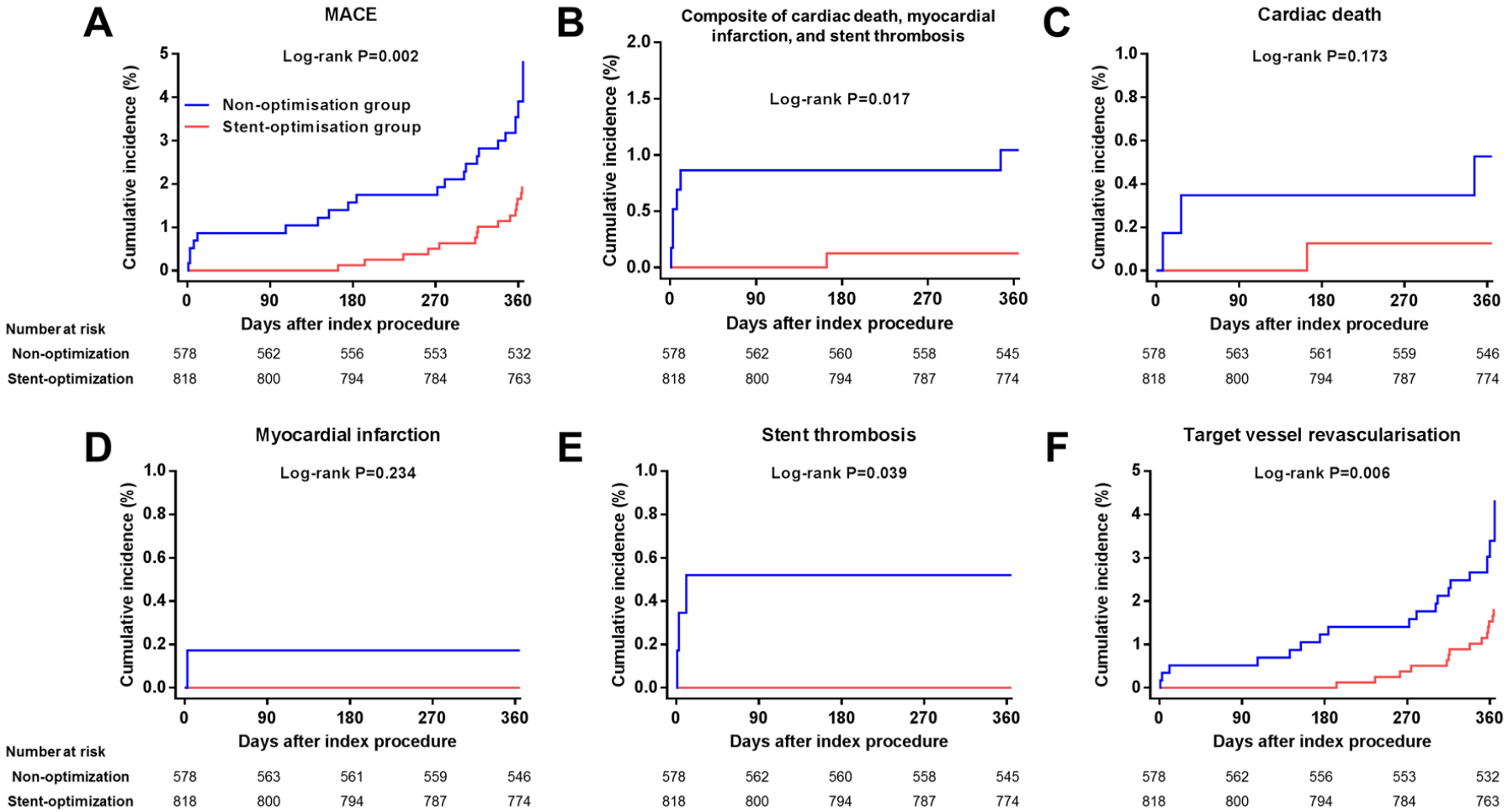
Table 2. Clinical outcomes in patients meeting or not meeting the IVUS criteria for stent optimisation

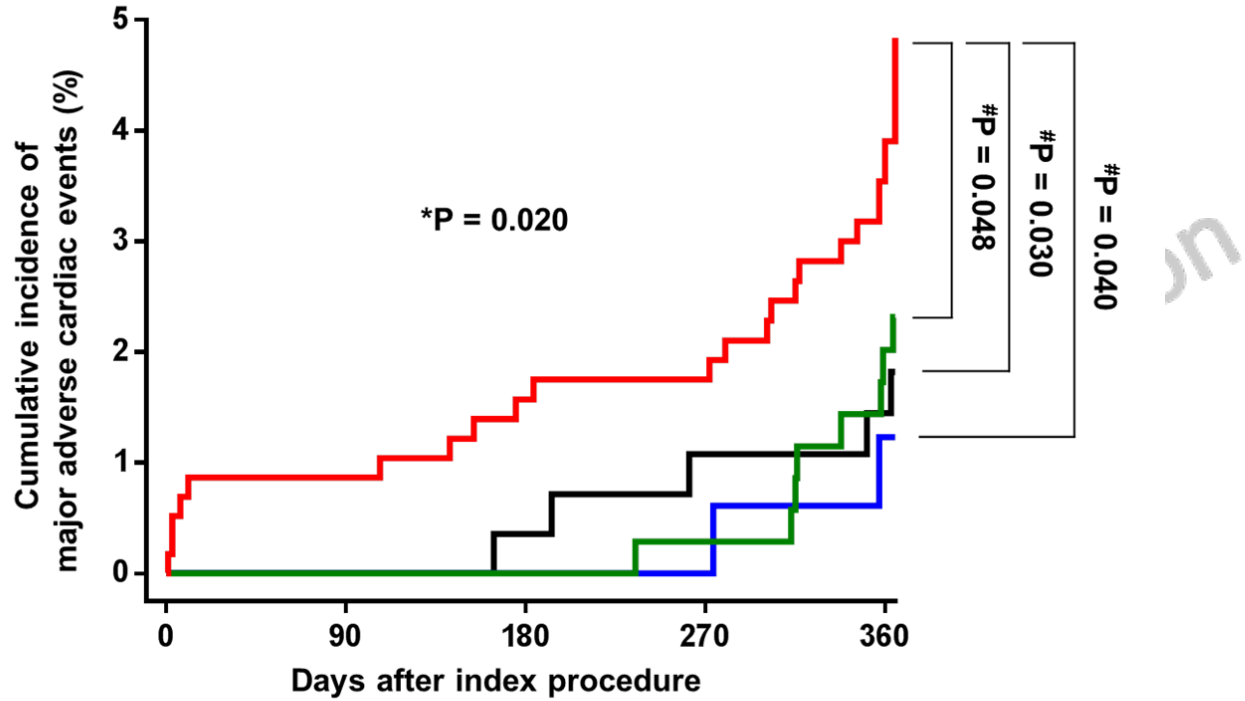
	Non-optimisation n=578	Stent-optimisation n=818	Univariable analysis		Multivariable analysis	
			HR (95% CI)	P value	HR (95% CI)	P value
MACE	27 (4.8)	15 (1.9)	2.58 (1.37–4.84)	0.003	2.95 (1.43–6.06)	0.003
Composite of cardiac death, myocardial infarction, and stent thrombosis	6 (1.0)	1 (0.1)	8.51 (1.02–70.65)	0.048	2.66 (3.17–222.87)	0.002
Cardiac death	3 (0.5)	1 (0.1)	4.24 (0.44–40.77)	0.211	4.90 (0.50–48.03)	0.172
Myocardial infarction	1 (0.2)	0 (0.0)	-	0.999	-	0.999
Stent thrombosis	3 (0.5)	0 (0.0)	-	0.999	-	0.823
Target vessel revascularisation	24 (4.3)	14 (1.8)	2.45 (1.27–4.75)	0.008	2.64 (1.25–5.58)	0.011

Values are number of events (% of the cumulative incidence). CI, confidence interval; HR, hazard ratio; MACE, major adverse cardiac event.



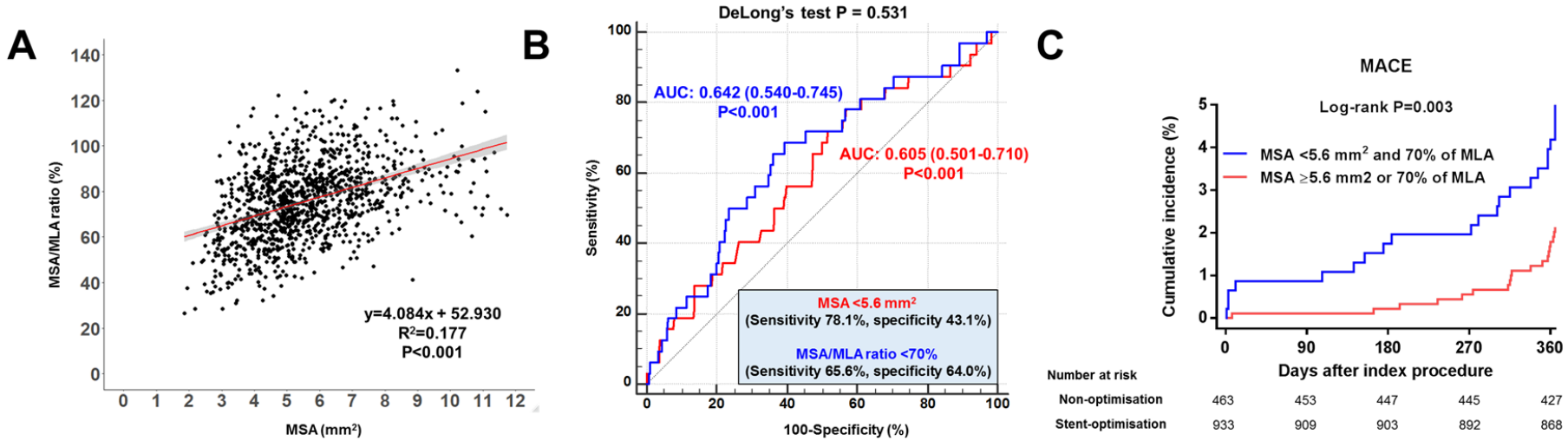


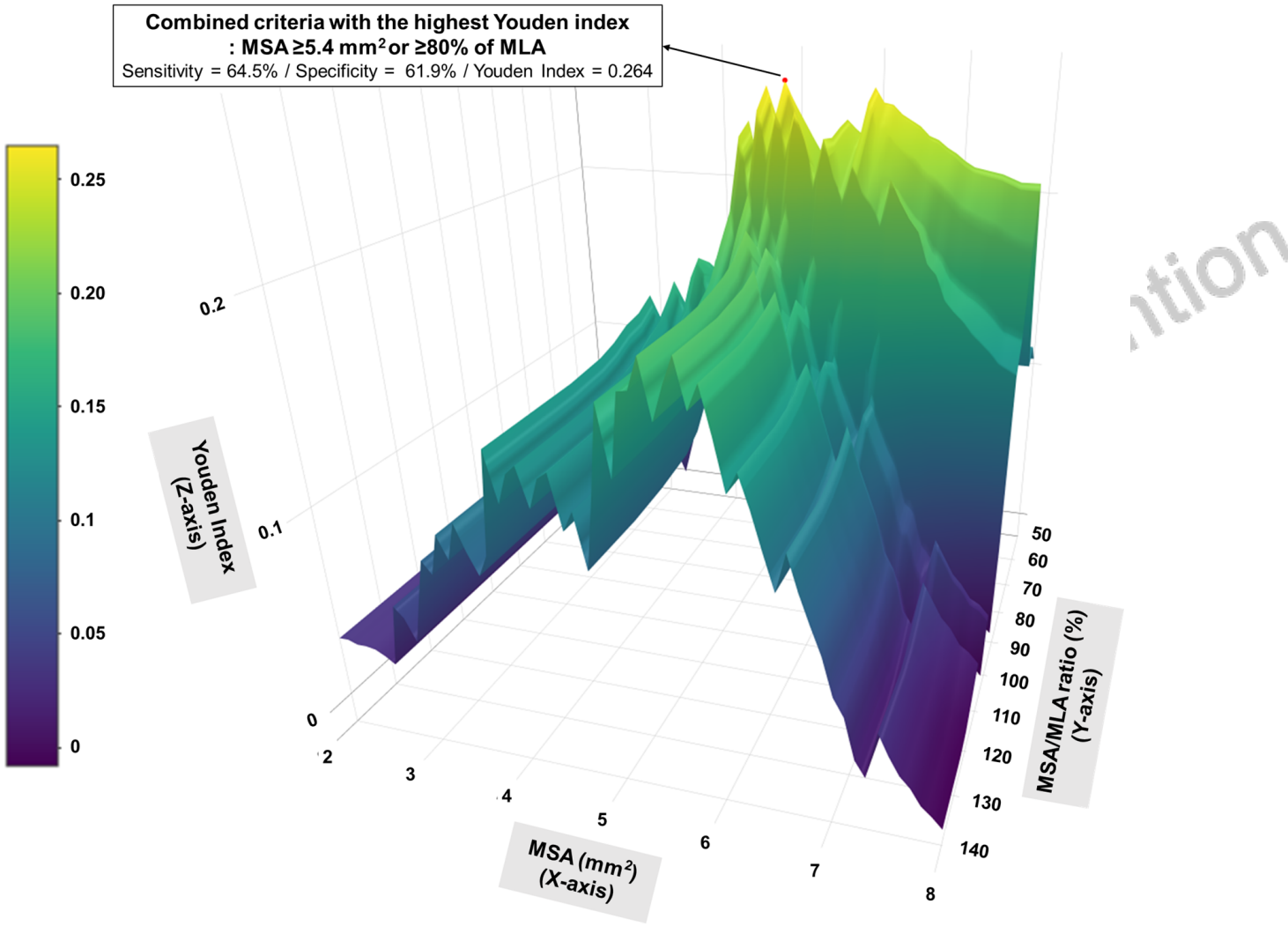




Number at risk

MSA <5.5 mm^2 and <80% of MLA	578	562	556	553	532
MSA ≥5.5 mm^2 and <80% of MLA	355	350	350	348	337
MSA <5.5 mm^2 and ≥80% of MLA	175	168	166	163	160
MSA ≥5.5 mm^2 and ≥80% of MLA	288	282	278	273	266





Online Data Supplement

Online Appendix

Definitions of endpoints

Academic Research Consortium (ARC) criteria were used to define clinical events. Specific endpoint definitions applied in each trial were also incorporated into the study. All deaths were considered cardiac deaths unless a definite non-cardiac cause was established. Myocardial infarction (MI) after hospital discharge was defined as the presence of clinical symptoms, electrocardiographic changes, or abnormal imaging findings that indicated MI, combined with an increase in the creatine kinase myocardial band fraction above the upper normal limit or an increase in troponin T or I levels greater than the 99th percentile of the upper normal limit, regardless of interventional procedures. Stent thrombosis (ST) was defined as definite or probable ST according to the ARC definition. Target-vessel revascularisation (TVR) was defined as repeat percutaneous coronary intervention or bypass surgery of the target vessel with either of the following (according to each study): 1) ischaemic symptoms or positive stress test results and angiographic diameter stenosis ≥50% measured by quantitative coronary analysis (QCA) or 2) angiographic diameter stenosis ≥70% measured by quantitative coronary analysis without ischaemic symptoms or positive stress test results. High-pressure dilation was defined as ≥15 atmospheric pressure.

Online Table 1. Summary of analysed studies.

Enrolled Study	Patient N with IVUS-guided PCI*	Inclusion criteria	Exclusion criteria	Lesion characteristics	Stent type	IVUS Optimisation criteria	Primary endpoint	Follow-up
RESET	297	Patients who were aged 20 years or older with typical chest pain or evidence of myocardial ischaemia	1) LM disease, CTO, ISR, bifurcation lesion with 2-stent technique 2) STEMI within 48 h 3) LVEF <40 %	Long lesions (implanted stent ≥28 mm)	EES (Xience V) and ZES (Endeavor Sprint)	-	MACEs	12 months
CTO-IVUS	231	Patients with CTO who were aged 20-80 years with typical symptomatic angina or positive test results for functional evaluation of ischaemia	1) Unprotected LM disease or ISR 2) Acute coronary syndrome 3) LVEF <30 %	CTO lesions	BES (Nobori) and ZES (Resolute Integrity®)	1) MSA ≥DLA 2) Stent area at CTO segment ≥5 mm^2 as far as vessel area permits 3) Complete stent apposition	Cardiac death	12 months
IVUS-XPL	708	Patients who were aged 20-80 years with typical chest pain or evidence of myocardial ischaemia	1) LM disease, CTO, ISR, bifurcation lesion with 2-stent technique 2) STEMI within 48 h 3) LVEF <40 %	Long lesions (implanted stent ≥28 mm)	EES (Xience Prime)	MSA ≥DLA	MACEs	12 months
ULTRA-ZET	160	Patients who were aged 19 years or older	1) Restenosis lesion or presence of previous implanted DES within 3 months 2) STEMI	Long lesions (implanted stent ≥26 mm)	EES (Promus Element™) and ZES (Resolute integrity®)	-	MACEs	12 months

*The number for per-protocol analyses. The ULTRA-ZET was terminated early due to delayed enrollment and launching of update versions of DESs.

BES, biolimus-eluting stent; CTO, chronic total occlusion; CTO-IVUS, Chronic Total Occlusion InterVention with drug-eluting Stents; DES, drug eluting stent; DLA, distal reference lumen area; EES, everolimus-eluting stent; ISR, in-stent restenosis; IVUS, intravascular ultrasound; IVUS-XPL, the Impact of Intravascular Ultrasound Guidance on Outcomes of Xience Prime Stents in long lesions; LM, left main; LVEF, left ventricle ejection fraction; MACE, major adverse cardiac event(s); MSA, minimal stent area; RESET, Real Safety and Efficacy of a 3-Month Dual Antiplatelet Therapy Following Zotarolimus-Eluting Stents Implantation; STEMI, ST-segment elevation myocardial infarction; ULTRA-ZET, Intravascular ULTrasound Guided Versus Conventional Angiography Guided Strategy to Deploy Zotarolimus and Everolimus Eluting Third Generation Stents in the Long Coronary Artery Lesions; ZES, zotarolimus-eluting stent.

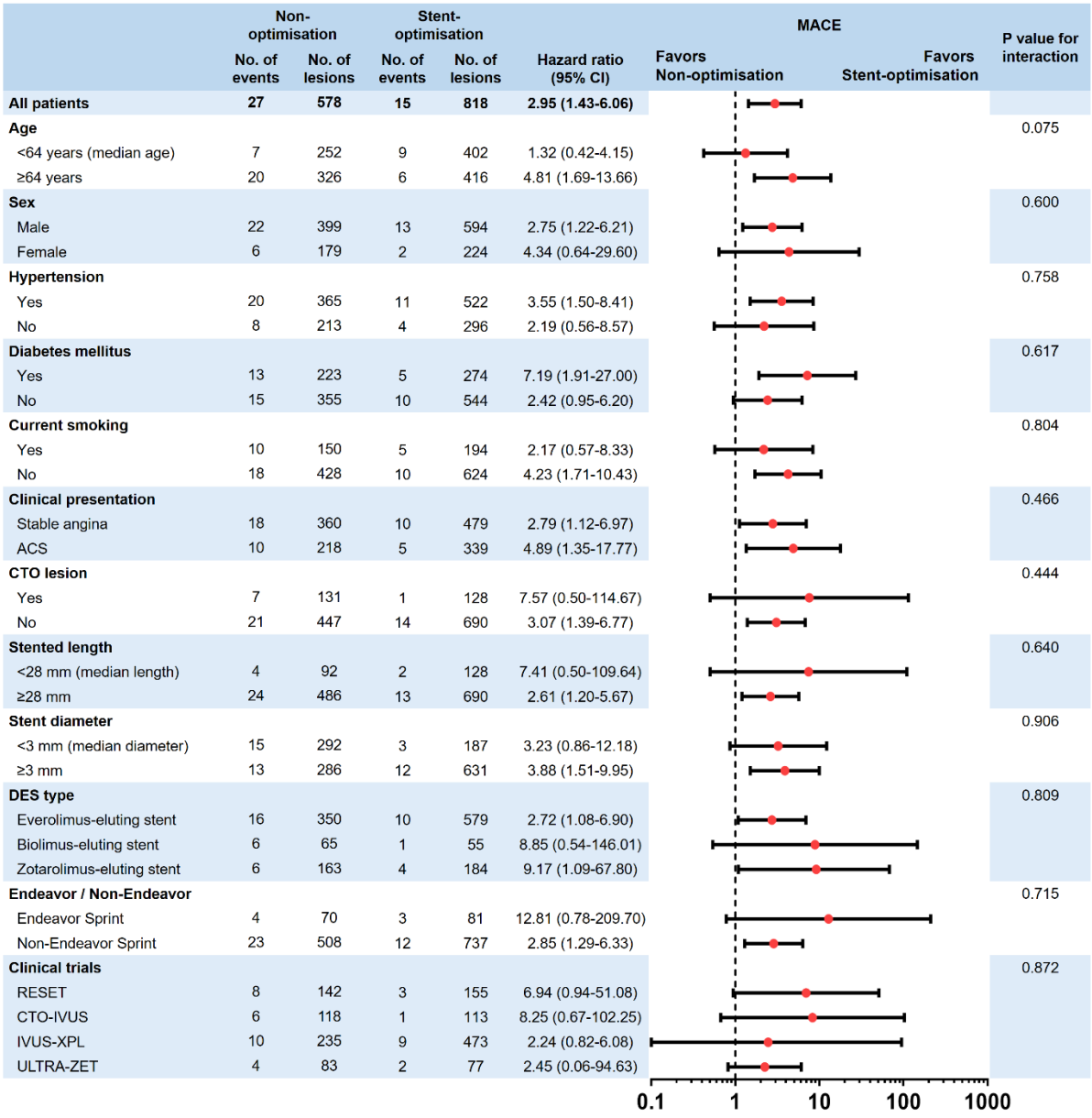
Online Table 2. Predictors of non-optimisation on IVUS

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Older age (per 1-year increase)	1.02 (1.01-1.03)	<0.001	1.02 (1.01-1.04)	<0.001
Female sex	1.19 (0.94-1.50)	0.146		
Hypertension	0.97 (0.78-1.21)	0.799		
Diabetes mellitus	1.25 (1.00-1.56)	0.051	1.03 (0.81-1.32)	0.794
Current smoking	1.13 (0.88-1.44)	0.340		
Prior myocardial infarction	1.02 (0.62-1.67)	0.947		
Prior percutaneous coronary intervention	0.93 (0.67-1.29)	0.647		
Prior bypass surgery	1.11 (0.50-2.47)	0.790		
Acute coronary syndrome	0.86 (0.69-1.06)	0.162		
Chronic total occlusion	1.58 (1.21-2.07)	0.001	0.78 (0.55-1.12)	0.182
Left anterior descending artery treated	0.88 (0.71-1.10)	0.258		
Stent elution				
Everolimus	1 (reference)	-	1 (reference)	-
Biolimus	1.96 (1.33-2.87)	0.001	1.66 (0.61-4.55)	0.323
Zotarolimus	1.47 (1.14-1.88)	0.003	1.34 (0.82-2.18)	0.240
Longer lesion length	1.03 (1.02-1.03)	<0.001	1.03 (1.02-1.04)	<0.001

(per 1-mm increase)				
Maximum stent diameter				
	7.46 (5.35-10.42)	<0.001	8.00 (5.62-11.36)	<0.001
(per 1-mm decrease)				
High-pressure post-dilation	1.17 (0.94-1.45)	0.159		

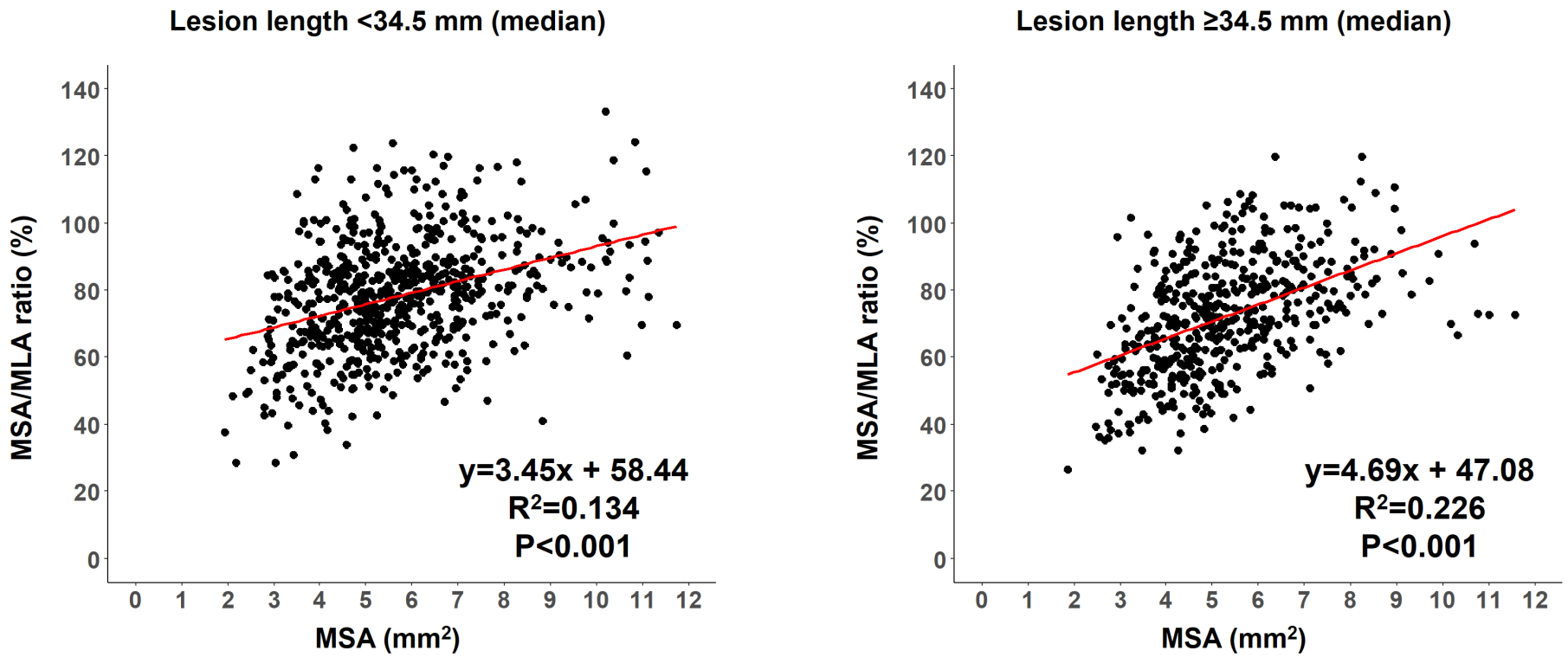
CI, confidence interval; OR, odds ratio.

Online Figure 1. Subgroup analyses of the occurrence of major adverse cardiac events in the Stent-optimisation and the Non-optimisation groups



ACS, acute coronary syndrome; CI, confidence interval; CTO, chronic total occlusion; MACE, major adverse cardiac event.

Online Figure 2. Association between minimal stent area and the ratio of minimal stent area-to-mean reference lumen area in subgroups according to lesion length.



MLA, mean reference lumen area; MSA, minimal stent area.