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Intravascular ultrasound-guided versus angiography-guided percutaneous coronary intervention with drug-eluting stents: five-year outcomes from the CREDO-Kyoto PCI/CABG registry

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KEYWORDS

- drug-eluting stent
- intravascular ultrasound
- stable angina

Abstract

Aims: We sought to investigate the clinical impact of intravascular ultrasound (IVUS) use in first-generation drug-eluting stent (DES) implantation as compared with angiography guidance only.

Methods and results: From the CREDO-Kyoto registry cohort-2, the current study population consisted of 4,768 patients treated with first-generation DES only without acute myocardial infarction (AMI) at enrolment. As a retrospective cohort study, we compared clinical outcomes between the two groups of patients with or without IVUS use during the procedure (IVUS group: N=2,768, angiography group: N=2,000). The outcome measures were target vessel revascularisation (TVR), target lesion revascularisation (TLR), all-cause death, myocardial infarction, stent thrombosis, and major adverse cardiovascular events. There was no significant difference between the groups in the cumulative incidence of TVR (21.5% vs. 22.2%, p=0.57). Even after adjusting the confounders, the risk of IVUS use relative to angiography guidance for TVR remained neutral (HR: 1.09, 95% CI: 0.90-1.32, p=0.37).

Conclusions: IVUS-guided PCI as compared with angiography-guided PCI was not associated with a lower risk of TVR in non-AMI patients treated with first-generation DES.

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Abbreviations

AMI	acute myocardial infarction
BMS	bare metal stent
CABG	coronary artery bypass grafting
CI	confidence interval
DES	drug-eluting stent
HR	hazard ratio
IVUS	intravascular ultrasound
MI	myocardial infarction
PCI	percutaneous coronary intervention
RCT	randomised controlled trial
STEMI	ST-elevation myocardial infarction
TVR	target vessel revascularisation

Introduction

Intravascular ultrasound (IVUS) has been utilised in percutaneous coronary intervention (PCI) not only for obtaining more accurate information about the coronary anatomy and the implanted stents, but also for earlier detection of procedure-related complications and suboptimal stent expansion[1-3]. Accordingly, previous observational and randomised studies have demonstrated the clinical efficacy of IVUS-guided PCI in the bare metal stent (BMS) era[1,4]. However, with the advent of drug-eluting stents (DES), several recent studies have reported inconsistent results regarding the advantage of IVUS guidance in PCI[5-8]. Therefore, we aimed to investigate the long-term clinical outcomes of IVUS-guided PCI as compared with angiography-guided PCI using DES in a large Japanese observational database of patients undergoing first coronary revascularisation.

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Methods

STUDY POPULATION

The Coronary REvascularization Demonstrating Outcome Study in Kyoto (CREDO-Kyoto) PCI/CABG registry cohort-2 is a physician-initiated, non-company sponsored, multicentre registry which enrolled consecutive patients who underwent first coronary revascularisation in 26 centres in Japan between January 2005 and December 2007 **(Supplementary Appendix 1)**. The relevant review boards or ethics committees in all participating centres approved the research protocol. Because of retrospective enrolment, written informed consent from the patients was waived; however, we excluded those patients who refused to participate in the study when contacted at follow-up. This strategy is in accordance with the guidelines for epidemiological studies issued by the Ministry of Health, Labor and Welfare of Japan.

Among 15,939 patients enrolled in this registry, the current study population included 4,768 patients without acute myocardial infarction (AMI) at enrolment, who underwent PCI using DES only, after excluding 86 patients who refused study participation, 2,795 patients who underwent coronary artery bypass grafting (CABG), 4,721 AMI patients, 601 patients who had both DES and BMS implantation, 2,502 patients who received BMS only, and 466 patients who had no stent implantation **(Figure 1)**. The

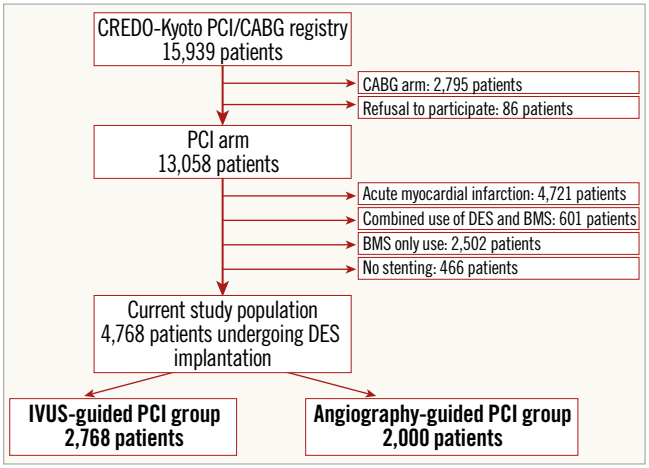


Figure 1 *Study flow chart. CABG: coronary artery bypass grafting; CREDO-Kyoto registry: Coronary REvascularization Demonstrating Outcome Study in Kyoto registry; DES: drug-eluting stent; IVUS: intravascular ultrasound; PCI: percutaneous coronary intervention*

study patients were classified into two groups according to the use of IVUS during the procedure: 2,768 patients (58.1%) who underwent IVUS-guided DES implantation (IVUS group) and 2,000 patients (41.9%) who underwent angiography-guided DES implantation without the use of IVUS (angiography group).

DEFINITIONS AND ENDPOINTS

Definitions of baseline clinical characteristics have been described in detail previously[9]. IVUS-guided PCI was defined as PCI with the use of IVUS regardless of the type of IVUS catheter(s) or the timing of IVUS examination (pre- or post-stent deployment or both). Angiography-guided PCI was defined as PCI performed without IVUS use.

The outcome measures for the current analysis were target vessel revascularisation (TVR), clinically driven TVR, target lesion revascularisation (TLR), clinically driven TLR, all-cause death, myocardial infarction (MI), definite stent thrombosis (ST), and major adverse cardiac events (MACE), defined as a composite of all-cause death, MI, or TVR. TVR was defined as any repeat revascularisation for the coronary vessels stented at the index PCI procedure. TLR was defined as either repeat percutaneous or surgical revascularisation for a lesion anywhere within the stent or the 5 mm borders proximal or distal to the stent. Death was regarded as cardiac in origin unless obvious non-cardiac causes could be identified. MI was defined according to the definition in the Arterial Revascularization Therapy Study[10]. Definite ST was defined as thrombosis at the target lesion, confirmed by angiography or autopsy in accordance with the criteria of the Academic Research Consortium[11].

DATA COLLECTION FOR BASELINE CHARACTERISTICS AND FOLLOW-UP EVENTS

Demographic, angiographic, and procedural data were collected from hospital charts or hospital databases according to

the pre-specified definitions by experienced clinical research co-ordinators from the study management centre (Research Institute for Production Development, Kyoto, Japan) **(Supplementary Appendix 2)**. In this retrospective cohort study, data collection for follow-up events was performed in 2010 and 2012. Collection of follow-up information was mainly conducted through review of the in-patient and out-patient hospital charts by the clinical research co-ordinators, and additional follow-up information was collected through contact with patients, relatives and/or referring physicians by sending mails with questions regarding vital status, subsequent hospitalisations, and status of antiplatelet therapy. Death, MI, ST, and stroke were adjudicated by the clinical events committee **(Supplementary Appendix 3)**. Median follow-up duration was 1,864 (interquartile range [IQR]: 1,589-2,143) days.

STATISTICAL ANALYSIS

We expressed categorical variables as numbers and percentages, and continuous variables as the mean±standard deviation. We compared categorical variables with the χ^2 test when suitable. Otherwise, we used Fisher's exact test. We compared continuous variables with the Student's t-test or the Wilcoxon rank-sum test based on their distributions. We used the Kaplan-Meier method to estimate cumulative incidences of the clinical events and evaluated the difference with the log-rank test. Consistent with our previous reports, we used a multivariable Cox proportional hazards model stratified by participating centres to estimate the effects of PCI under IVUS use for the outcome measures by incorporating 37 clinically relevant risk-adjusting variables, as listed in **Table 1** and **Table 2**, together with IVUS use. Proportional hazard assumptions for the risk-adjusting variables were assessed on the plots of log (time) versus log (-log [survival]) stratified by the variable and it was confirmed that the assumptions were acceptable for all the variables. We calculated adjusted hazard ratios (HR) and their 95% confidence intervals (CI). We could not conduct multivariable adjustment for definite ST due to the small number of events. Furthermore, as observational studies inevitably involve the inherent limitations of measured and unmeasured confounders, a propensity score-matching analysis was additionally performed as a sensitivity analysis. A logistic regression model was used to compute the propensity score for the use of IVUS with 13 independent variables relevant to the use of IVUS **(Table 1, Table 2)**. Using the propensity score, patients in the IVUS group were matched to ones in the angio group. Clinical outcomes were compared between the IVUS and the angio groups in the propensity score-matched cohorts. Cumulative incidence was estimated by the Kaplan-Meier method and the difference was assessed with the log-rank test. As all the clinically relevant variables were not well matched, we conducted an adjusted comparison using Cox proportional hazard models with 10 clinically relevant adjusting variables **(Table 1, Table 2)**. As in our previous reports, we dichotomised continuous variables by using clinically relevant reference values or median values. We also evaluated the effect of IVUS use on TVR in several clinically relevant subgroups including diabetes

Table 1. Baseline patient characteristics.

Variables	IVUS group N=2,768	Angiography group N=2,000	*p*-value
Clinical characteristics			
Age	68.5±9.8	68.5±10.2	0.91
*>75 years	845 (30.5%)	602 (30.1%)	0.75
*Male gender	1,979 (71.5%)	1,433 (71.7%)	0.91
Body mass index	23.7±3.4	23.9±3.5	0.03
*<25.0 kg/m²	1,855 (67.0%)	1,308 (65.4%)	0.24
*Hypertension	2,347 (84.8%)	1,664 (83.2%)	0.14
Diabetes mellitus	1,148 (41.5%)	861 (43.1%)	0.28
*requiring insulin therapy	286 (10.3%)	241 (12.1%)	0.06
*Current smoking	672 (24.3%)	530 (26.5%)	0.08
*Heart failure (current and prior)	404 (14.6%)	310 (15.5%)	0.39
*Multivessel disease	1,669 (60.0%)	1,188 (59.4%)	0.53
*Mitral regurgitation 3-4/4	82 (3.0%)	88 (4.4%)	0.009
*Previous myocardial infarction	378 (13.7%)	348 (17.4%)	0.0004
*Previous stroke	342 (12.4%)	226 (11.3%)	0.27
*Peripheral vascular disease	236 (8.5%)	196 (9.8%)	0.13
Left ventricular ejection fraction	61.5±12.5 (2,556)	60.0±13.1 (1,658)	0.0003
≤40%	173/2,556 (6.8%)	154/1,658 (9.3%)	0.003
*eGFR <30, without haemodialysis	99 (3.6%)	80 (4.0%)	0.45
*Haemodialysis	139 (5.0%)	104 (5.2%)	0.78
*Atrial fibrillation	225 (8.1%)	160 (8.0%)	0.87
*Anaemia (haemoglobin <11.0 g/dl)	322 (11.6%)	246 (12.3%)	0.48
*Thrombocytopaenia (platelet <100*109/L)	37 (1.3%)	27 (1.4%)	0.97
*COPD	87 (3.1%)	83 (4.2%)	0.07
*Liver cirrhosis	64 (2.3%)	49 (2.5%)	0.76
*Malignancy	243 (8.8%)	186 (9.3%)	0.54
Medication at discharge			
Aspirin	2,732 (98.7%)	1,971 (98.6%)	0.66
Thienopyridine	2,759 (99.7%)	1,995 (99.8%)	0.63
*Cilostazole	264 (9.5%)	138 (6.9%)	0.001
*Statin	1,603 (57.9%)	961 (48.1%)	<0.0001
*ACE-I/ARB	1,474 (53.3%)	962 (48.1%)	0.0004
*β-blocker	720 (26.0%)	521 (26.1%)	0.98
*Calcium channel blocker	1,458 (52.7%)	1,005 (50.3%)	0.10
*Nitrate	940 (19.7%)	838 (17.6%)	<0.0001
*Nicorandil	656 (23.7%)	401 (20.1%)	0.003
*PPI	648 (23.4%)	365 (18.3%)	<0.0001
*H2 blocker	630 (22.8%)	390 (19.5%)	0.007
*Warfarin	217 (7.8%)	149 (7.5%)	0.62

Categorical variables are expressed as number (%) unless otherwise indicated. Continuous variables are shown as mean±SD. *Risk-adjusting variables selected for the multivariable analysis. ACE-I/ARB: angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; COPD: chronic obstructive pulmonary disease; eGFR: estimated glomerular filtration rate; IVUS: intravascular ultrasound; PPI: proton pump inhibitor

Table 2. Angiographic and procedural characteristics.

Variables	IVUS group N=2,768	Angiography group N=2,000	*p*-value
Target lesion			
*Unprotected LMCA	117 (4.2%)	62 (3.1%)	0.04
*Proximal LAD	1,827 (66.0%)	1,167 (58.4%)	<0.001
LAD	1,892 (68.4%)	1,218 (60.9%)	<0.001
LCX	799 (28.9%)	659 (33.0%)	0.003
RCA	993 (35.9%)	789 (39.5%)	0.01
*Bifurcated lesion	1,208 (43.6%)	770 (38.5%)	0.0004
*Chronic total occlusion	353 (12.8%)	383 (19.2%)	<0.0001
*Side branch stenting	142 (5.1%)	128 (6.4%)	0.06
Sirolimus-eluting stent use	2,537 (91.7%)	1,892 (94.6%)	<0.0001
Implanted stents	2 (1-2)	2 (1-2)	0.26
Total stent length (mm)	36 (23-56)	33 (18-56)	0.14
*>28 mm	1,570 (56.7%)	1,053 (52.7%)	0.005
Minimal stent diameter (mm)	2.75 (2.5-3.0)	2.5 (2.5-3.0)	0.004
*<3.0 mm	1,425 (51.5%)	1,082 (54.1%)	0.07
Final balloon pressure (atmosphere)	18.4±3.5 (3,752/3,984)	17.2±3.6 (2,631/2,830)	<0.0001

Categorical variables are expressed as number (%) unless otherwise indicated. Continuous variables are shown as mean±SD or median (interquartile range). *Risk-adjusting variables selected for the multivariable analysis. IVUS: intravascular ultrasound; LAD: left anterior descending coronary artery; LCX: left circumflex coronary artery; LMCA: left main coronary artery; RCA: right coronary artery

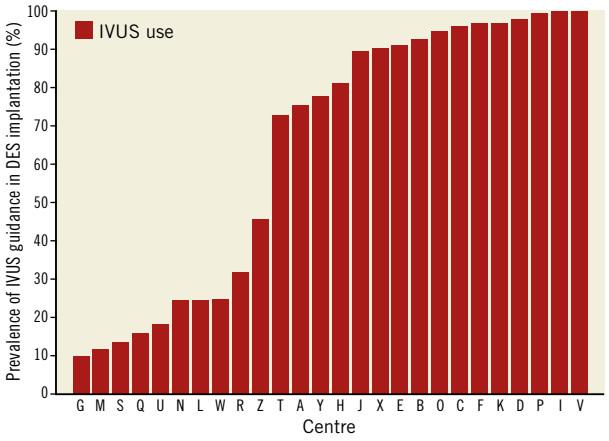


Figure 2. *Prevalence of IVUS use according to centre. DES: drug-eluting stent; IVUS: intravascular ultrasound*

mellitus, total stent length (≤28 mm and >28 mm), multivessel disease, minimum stent diameter (≥3 mm or <3 mm), and the frequency of IVUS use in each centre (>70% or ≤70%). Statistical analyses were performed by a physician (H. Watanabe) with JMP 10.0 (SAS Institute Inc., Cary, NC, USA) software and by a statistician (T. Morimoto) with SAS 9.4 (SAS Institute Inc.) software. All the statistical analyses were two-tailed. P-values <0.05 were considered statistically significant.

Results

BASELINE CHARACTERISTICS

Among the 4,768 study patients for the current analysis, 2,768 patients (58%) received DES implantation under IVUS use. There was a sharply bipolar division regarding the prevalence of IVUS use among the 26 participating centres with median of 79%: more than 70% of the total PCI procedures were performed under IVUS use in 16 centres (62%), while less than 30% of the total PCI procedures were performed under IVUS use in eight centres (31%) **(Figure 2)**. The baseline characteristics are not very different between the IVUS and the angiography groups, except for the higher prevalence of patients with greater body mass index, severe mitral regurgitation, previous myocardial infarction, and left ventricular ejection fraction ≤40% in the angiography group than in the IVUS group **(Table 1)**. As for the medications at discharge, cilostazole, statins, angiotensin-converting inhibitors/angiotensin receptor blockers, nitrate, nicorandil, proton pump inhibitors and H2 blockers were more often used in the IVUS group than in the angiography group **(Table 1)**. Regarding angiographic and procedural characteristics, patients in the IVUS group more often had the target lesions in an unprotected left main artery, and proximal left anterior descending artery, as well as bifurcation lesions, but less often had chronic total occlusion, and the target lesions in the left circumflex artery, and right coronary artery **(Table 2)**. The IVUS group had larger minimal stent diameter, higher final balloon pressure, and a greater prevalence of long (>28 mm) stent use than the angiography group **(Table 2)**.

LONG-TERM CLINICAL OUTCOMES

The cumulative five-year incidence of TVR was not significantly different between the IVUS and the angiography groups (21.5% versus 22.2%, log rank p=0.57) **(Table 3, Figure 2)**. Even after adjusting the confounders, the risk of IVUS guidance relative to angiography guidance for TVR remained neutral (HR: 1.09, 95% CI: 0.90-1.32, p=0.37) **(Table 3)**.

The adjusted risks of IVUS guidance relative to angiography guidance for all-cause death and MACE were also neutral (HR: 0.93, 95% CI: 0.87-1.17, p=0.65, HR: 0.82, 95% CI: 0.65-1.02, p=0.08, and HR: 0.96, 95% CI: 0.83-1.11, p=0.64, respectively), although the cumulative five-year incidences of all-cause death and MACE were significantly lower in the IVUS group than in the angiography group **(Table 3)**. There was no significant difference in the cumulative five-year incidences of clinically driven TVR, TLR, clinically driven TLR, MI and definite ST between the two groups **(Table 3)**.

The neutral adjusted risk for TVR between the IVUS and the angiography groups was observed consistently across the subgroups stratified by diabetes mellitus, total stent length, minimum stent diameter, the number of coronary lesions, and the frequency

Table 3. Crude and adjusted 5-year clinical outcomes: IVUS group versus angiography group.

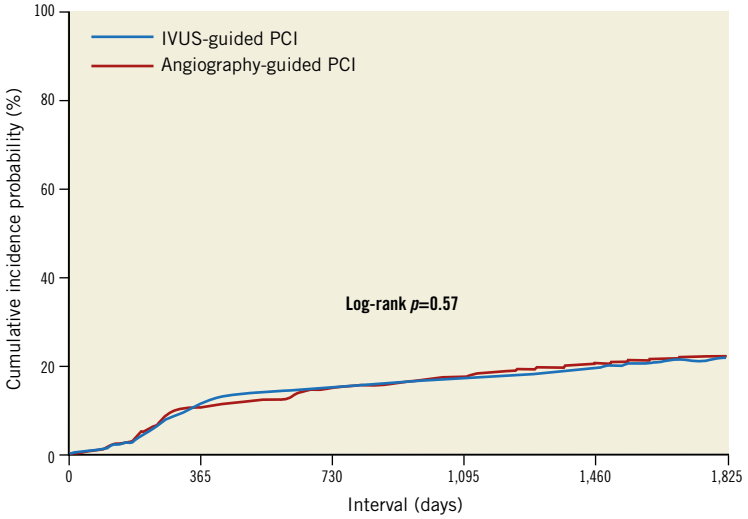
Variables	IVUS group Number of patients with events (cumulative 5-year incidence) N=2,768	Angio group Number of patients with events (cumulative 5-year incidence) N=2,000	Crude HR (95% CI)	*p*-value (log-rank)	Adjusted HR (95% CI)	*p*-value
TVR	556 (21.5%)	408 (22.2%)	0.97 (0.85-1.09)	0.57	1.09 (0.90-1.32)	0.37
Clinically driven TVR	281 (11.3%)	211 (11.8%)	0.94 (0.79-1.11)	0.44	1.01 (0.78-1.31)	0.93
TLR	413 (16.0%)	292 (15.9%)	1.01 (0.87-1.17)	0.93	1.04 (0.89-1.20)	0.65
Clinically driven TLR	192 (7.9%)	134 (7.7%)	1.00 (0.81-1.23)	0.97	1.00 (0.80-1.24)	0.99
All-cause death	368 (14.1%)	303 (16.0%)	0.85 (0.74-0.98)	0.02	0.82 (0.65-1.02)	0.08
Myocardial infarction	177 (6.8%)	143 (7.4%)	0.84 (0.68-1.04)	0.12	0.87 (0.62-1.22)	0.41
Stent thrombosis (definite)	31 (1.2%)	20 (1.1%)	1.14 (0.68-1.98)	0.62	–	–
MACE	905 (33.9%)	697 (36.2%)	0.90 (0.82-0.99)	0.02	0.96 (0.83-1.11)	0.64

Cumulative incidence was estimated by the Kaplan-Meier method. CI: confidence interval; HR: hazard ratio; IVUS: intravascular ultrasound; MACE: major adverse cardiac events; TLR: target lesion revascularisation; TVR: target vessel revascularisation

of IVUS in each centre **(Figure 3)**. There were no significant interactions between the subgroup factors and the effect of IVUS guidance relative to angiography guidance for TVR **(Figure 4)**.

SENSITIVITY ANALYSIS

We performed propensity score matching, which selected 1,932 patients in each group using 13 risk variables influencing the use of IVUS **(Supplementary Table 1-Supplementary Table 3)**. The result from the analysis for the primary outcome measure (TVR) was consistent with the result from the Cox model. We observed significant between-group differences in all-cause death as well as MI in the propensity score-matched analysis, which might be explained by the residual confounding related to the important between-group differences in the prevalence of previous MI, LVEF, and low LVEF after propensity score matching **(Supplementary Table 1)**.



Interval	0 day	1 year	3 years	5 years
IVUS-guided group				
No. of patients with at least one event		307	455	556
No. of patients at risk	2,768	2,375	2,051	1,198
Cumulative incidence probability		11.3%	17.0%	21.5%
Angio-guided group				
No. of patients with at least one event		205	334	408
No. of patients at risk	2,000	1,707	1,459	857
Cumulative incidence probability		10.6%	17.6%	22.2%

Figure 3. *Kaplan-Meier curve for the crude cumulative incidence of target vessel revascularisation in the IVUS group and the angio group.*

Variable	IVUS group No. of patients with TVR (Cumulative incidence) N=2,768	Angiography group No. of patients with TVR (Cumulative incidence) N=2,000	Crude HR (95% CI)	Log-rank *p*	Adjusted HR (95% CI)	*p*-value	Interaction *p*
Diabetes	291 (27.3%)	208 (26.7%)	1.04 (0.88-1.24)	0.65	0.92 (0.83-1.03)	0.14	0.35
Non-diabetes	265 (17.5%)	200 (18.9%)	0.90 (0.75-1.07)	0.23	0.91 (0.76-1.09)	0.31	
Total stent length							
>28 mm	406 (27.5%)	271 (27.9%)	0.99 (0.85-1.15)	0.88	1.04 (0.89-1.21)	0.66	0.14
≤28 mm	150 (13.7%)	137 (15.9%)	0.83 (0.67-1.04)	0.11	0.89 (0.71-1.12)	0.31	
Minimal stent diameter							
<3 mm	351 (26.3%)	273 (27.5%)	0.96 (0.53-1.12)	0.61	0.93 (0.80-1.10)	0.41	<0.0001
≥3 mm	205 (16.5%)	135 (16.1%)	1.01 (0.82-1.25)	0.93	1.07 (0.86-1.32)	0.55	
Multivessel disease	420 (27.0%)	291 (27.0%)	1.00 (0.87-1.16)	0.97	1.02 (0.88-1.19)	0.76	0.13
Single-vessel disease	136 (13.3%)	117 (15.4%)	0.85 (0.67-1.07)	0.169	0.84 (0.66-1.08)	0.18	
IVUS use per centres							
Frequent use (>70%)	470 (21.3%)	33 (16.8%)	1.23 (0.90-1.74)	0.22	1.15 (0.82-1.61)	0.42	0.36
Non-frequent use (≤70%)	86 (22.7%)	375 (22.8%)	1.02 (0.81-1.28)	0.84	1.03 (0.81-1.30)	0.81	

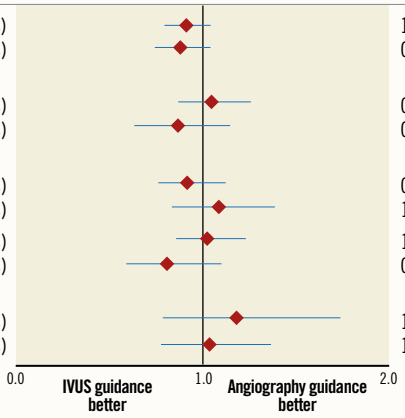


Figure 4. *Subgroup analyses and forest plots of hazard ratio for target vessel revascularisation (primary outcome measure). CI: confidence interval; HR: hazard ratio; TVR: target vessel revascularisation*

Discussion

The principal finding in the current analysis is that IVUS-guided PCI was not associated with a lower risk for TVR in non-AMI patients treated with first-generation DES.

No standardised criteria have been established for IVUS-guided PCI; however, our current IVUS guidance strategy is based on hypotheses extrapolated from previous IVUS studies[2,3]. In short, our current IVUS guidance strategy is to target the complete lesion coverage from "healthy" to "healthy" site and appropriate expansion of the stent matching the reference segment. However, this strategy was somewhat limited by the fact that the use of longer stents resulted in higher rates for stent thrombosis and restenosis[12,13]. It was sometimes difficult to find an optimal landing site with less plaque in severe atherosclerotic lesions as in diabetic patients, which might also weaken the efficacy of this strategy. Considering the balance between less plaque burden in the landing point and the shorter stent length, our arbitrary decision in IVUS-guided DES implantation might be unavoidable, which might influence the efficacy of the IVUS-guided DES implantation.

Concerning clinical data, available randomised and observational data are relatively scarce and the results are conflicting[5-8,14]. One of the recent trials indicating the advantage of IVUS use was the IVUS-XPL (Intravascular Ultrasound Guidance on Outcomes of XIENCE Prime Stents in Long Lesions) randomised trial, which was the largest one to date, randomising 1,400 study participants to IVUS-guided PCI versus angiography-guided PCI[8]. It demonstrated the usefulness of IVUS-guided DES implantation on long lesions. IVUS-guided everolimus-eluting stent (EES) implantation was associated with a lower rate of the composite of MACE at one year in comparison with angiography-guided EES implantation (2.9% vs. 5.8%, HR: 0.48, 95% CI: 0.28-0.83, p=0.007). The difference was mainly due to a lower risk of ischaemia-driven target lesion revascularisation (TLR) between the groups (2.5% vs. 5.0%, HR: 0.51, 95% CI: 0.28-0.91, p=0.02). Currently, this is the only adequately powered randomised trial to have evaluated the efficacy of IVUS guidance, but it may not be immune to some limitations, although "randomised" trials are generally regarded as providing the highest level of evidence. The open label trial design might introduce important biases particularly in this type of strategic trial. The final stent optimisation might not have been sufficient in the angiography-guided PCI group if the investigators had had the intention to get positive results for IVUS. The targeted procedural endpoint in the angiography-guided PCI group was less than 30% residual stenosis by visual estimation, and post-stent dilatation was not recommended if this procedural endpoint was satisfied. Actually, the prevalence of post-dilatation was lower in the angiography-guided PCI group than in the IVUS-guided PCI group (57% vs. 76%, p<0.001), resulting in greater residual diameter stenosis in the angiography-guided PCI group (13.74±8.05% vs. 12.79±8.66%, p=0.04). The use of TLR as an endpoint may not be without problems in this type of open label randomised trial, because the occurrence of TLR could be highly influenced by the physicians' decision.

As an observational study, ADAPT-DES (The Assessment of Dual Antiplatelet Therapy With Drug-Eluting Stents) is the largest study to date (enrolling 8,583 patients), which suggested the clinical efficacy of IVUS-guided DES implantation. IVUS guidance compared with angiography guidance was strongly associated with reduced one-year rates of definite/probable stent thrombosis (0.6% vs. 3.7%, adjusted HR: 0.40, 95% CI: 0.21-0.73, p=0.003), MI (2.5% vs. 3.7%, adjusted HR: 0.70, 95% CI: 0.55-0.88, p=0.004), and MACE, defined as a composite of cardiac death, MI, or stent thrombosis (3.1% vs. 4.7%, adjusted HR: 0.70, 95% CI: 0.55-0.88, p=0.004)[15]. However, we should note that the study population

was a mixture of AMI and non-AMI patients. The advantage of IVUS-guided PCI in patients with AMI also remains a subject of debate[16,17]. Furthermore, the median prevalence of IVUS use across the 11 enrolling sites was only 33% (ranging from 1% to 90%), which was much lower than that in the present study (79%). In the present study, there was a sharply bipolar division regarding the prevalence of IVUS use among the participating centres, indicating that both IVUS-guided and angiography-guided PCI procedures were largely performed in centres that are proficient in either strategy. These differences in the demographics and prevalence of IVUS use among different studies might lead to different results in the comparison of clinical outcomes between the IVUS-guided and angiography-guided PCI procedures.

In both randomised trials and observational studies, it would not be possible to draw a simple and generalised conclusion such as that IVUS-guided PCI is better than angiography-guided PCI, or vice versa. Achieving the optimal luminal outcome has been recognised as the most important determinant of stent-related clinical outcomes such as target lesion revascularisation and stent thrombosis, although DES are much more forgiving than BMS in terms of minimum requirement for the luminal outcome. Therefore, we should pursue achieving the optimal luminal outcome in both IVUS-guided and angiography-guided PCI procedures. IVUS guidance might be useful, for example, in detecting underexpansion of the stent that could not be easily recognised by angiography, while responding to those subtle IVUS findings such as malapposition and minor dissections may not improve clinical outcomes, but may result in just increasing the procedural time and cost. We might be able to compromise on the debate of IVUS-guided versus angiography-guided PCI by taking a balanced attitude towards using IVUS when something is in doubt by angiography.

Limitations

The current study has many limitations. First, this retrospective observational study could not exclude unmeasured confounders despite extensive multivariable adjustment. In particular, one of the major limitations is that we set no clear criteria for IVUS guidance, particularly about optimised stent implantation, in our analysis. The decision and timing of the IVUS examination (prior to and/or after stent deployment) and how to utilise the information from the IVUS images depended on the operator. Second, although our study targeted patients undergoing first-generation DES implantation, second-generation DES are currently being used for PCI in daily clinical practice. Third, no quantitative measurements in the IVUS or angiographic images were available and the effect of these parameters on clinical outcomes was not assessed in the current analysis. Furthermore, the angiograms of patients with TLR were not analysed by the independent angiographic core laboratory. Fourth, the degree of proficiency in IVUS examination in routine procedures differed from one hospital to another. Also, the procedural endpoint, practice patterns and clinical outcomes might have been different according to centre. Although our statistical adjustment included stratification by participating centre, a cautious attitude should be taken in generalising the results of this analysis to hospitals with limited experience of IVUS-guided PCI.

Conclusions

In this observational study, IVUS-guided PCI as compared with angiography-guided PCI was not associated with a lower risk for TVR in non-AMI patients treated with first-generation DES.

Impact on daily practice

As our study clearly suggested a neutral result as to IVUS use in non-AMI patients treated with first-generation DES, this topic requires further investigation. We should focus on stent optimisation guided by IVUS in the era of second- or third-generation DES.

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Conflict of interest statement

The authors have no conflicts of interest to declare.

References

1. Fitzgerald PJ, Oshima A, Hayase M, Metz JA, Bailey SR, Baim DS, Cleman MW, Deutsch E, Diver DJ, Leon MB, Moses JW, Oesterle SN, Overlie PA, Pepine CJ, Safian RD, Shani J, Simonton CA, Smalling RW, Teirstein PS, Zidar JP, Yeung AC, Kuntz RE, Yock PG. Final results of the Can Routine Ultrasound Influence Stent Expansion (CRUISE) study. *Circulation.* 2000;102:523-30.

2. Fujii K, Carlier SG, Mintz GS, Yang YM, Moussa I, Weisz G, Dangas G, Mehran R, Lansky AJ, Kreps EM, Collins M, Stone GW, Moses JW, Leon MB. Stent underexpansion and residual reference segment stenosis are related to stent thrombosis after sirolimus-eluting stent implantation: an intravascular ultrasound study. *J Am Coll Cardiol.* 2005;45:995-8.

3. Sakurai R, Ako J, Morino Y, Sonoda S, Kaneda H, Terashima M, Hassan AH, Leon MB, Moses JW, Popma JJ, Bonneau HN, Yock PG, Fitzgerald PJ, Honda Y; SIRIUS Trial Investigators. Predictors of edge stenosis following sirolimus-eluting stent deployment (a quantitative intravascular ultrasound analysis from the SIRIUS trial). *Am J Cardiol.* 2005;96:1251-3.

4. de Jaegere P, Mudra H, Figulla H, Almagor Y, Doucet S, Penn I, Colombo A, Hamm C, Bartorelli A, Rothman M, Nobuyoshi M, Yamaguchi T, Voudris V, DiMario C, Makovski S,

Hausmann D, Rowe S, Rabinovich S, Sunamura M, van Es GA. Intravascular ultrasound-guided optimized stent deployment. Immediate and 6 months clinical and angiographic results from the Multicenter Ultrasound Stenting in Coronaries study (MUSIC study). *Eur Heart J.* 1998;19:1214-23.

5. Jakabcin J, Spacek R, Bystron M, Kvasnak M, Jager J, Veselka J, Kala P, Cervinka P. Long-term health outcome and mortality evaluation after invasive coronary treatment using drug eluting stents with or without the IVUS guidance. Randomized control trial. HOME DES IVUS. *Catheter Cardiovasc Interv.* 2010;75:578-83.

6. Chieffo A, Latib A, Caussin C, Presbitero P, Galli S, Menozzi A, Varbella F, Mauri F, Valgimigli M, Arampatzis C, Sabate M, Erglis A, Reimers B, Airoldi F, Laine M, Palop RL, Mikhail G, Maccarthy P, Romeo F, Colombo A. A prospective, randomized trial of intravascular-ultrasound guided compared to angiography guided stent implantation in complex coronary lesions: the AVIO trial. *Am Heart J.* 2013;165:65-72.

7. Kim JS, Kang TS, Mintz GS, Park BE, Shin DH, Kim BK, Ko YG, Choi D, Jang Y, Hong MK. Randomized comparison of clinical outcomes between intravascular ultrasound and angiography-guided drug-eluting stent implantation for long coronary artery stenoses. *JACC Cardiovasc Interv.* 2013;6:369-76.

8. Hong SJ, Kim BK, Shin DH, Nam CM, Kim JS, Ko YG, Choi D, Kang TS, Kang WC, Her AY, Kim YH, Hur SH, Hong BK, Kwon H, Jang Y, Hong MK; IVUS-XPL Investigators. Effect of Intravascular Ultrasound-Guided vs Angiography-Guided Everolimus-Eluting Stent Implantation: The IVUS-XPL Randomized Clinical Trial. *JAMA.* 2015;314:2155-63.

9. Kimura T, Morimoto T, Furukawa Y, Nakagawa Y, Kadota K, Iwabuchi M, Shizuta S, Shiomi H, Tada T, Tazaki J, Kato Y, Hayano M, Abe M, Tamura T, Shirotani M, Miki S, Matsuda M, Takahashi M, Ishii K, Tanaka M, Aoyama T, Doi O, Hattori R, Tatami R, Suwa S, Takizawa A, Takatsu Y, Takahashi M, Kato H, Takeda T, Lee JD, Nohara R, Ogawa H, Tei C, Horie M, Kambara H, Fujiwara H, Mitsudo K, Nobuyoshi M, Kita T. Long-term safety and efficacy of sirolimus-eluting stents versus bare-metal stents in real world clinical practice in Japan. *Cardiovasc Interv Ther.* 2011;26:234-45.

10. Serruys PW, Ong AT, van Herwerden LA, Sousa JE, Jatene A, Bonnier JJ, Schönberger JP, Buller N, Bonser R, Disco C, Backx B, Hugenholtz PG, Firth BG, Unger F. Five-year outcomes after coronary stenting versus bypass surgery for the treatment of multivessel disease: the final analysis of the Arterial Revascularization Therapies Study (ARTS) randomized trial. *J Am Coll Cardiol.* 2005;46:575-81.

11. Mauri L, Hsieh WH, Massaro JM, Ho KK, D'Agostino R, Cutlip DE. Stent thrombosis in randomized clinical trials of drug-eluting stents. *N Engl J Med.* 2007;356:1020-9.

12. Hong MK, Mintz GS, Lee CW, Park DW, Lee SW, Kim YH, Jung IH, Kim SH, Cheong SS, Kim JJ, Park SW, Park SJ. Late target lesion revascularization after implantation of sirolimus-eluting stent. *Catheter Cardiovasc Interv.* 2008;71:299-303.

13. Miura K, Kadota K, Habara S, Miyawaki H, Shimada T, Ohya M, Amano H, Izawa Y, Hyodo Y, Otsuru S, Hasegawa D, Tada T, Tanaka H, Fuku Y, Goto T, Mitsudo K. Ten-year clinical outcomes after sirolimus-eluting stent implantation: Impact of an in-stent restenosis target lesion. *Am Heart J.* 2016;175:47-55.

14. Tian NL, Gami SK, Ye F, Zhang JJ, Liu ZZ, Lin S, Ge Z, Shan SJ, You W, Chen L, Zhang YJ, Mintz G, Chen SL. Angiographic and clinical comparisons of intravascular ultrasound- versus angiography-guided drug-eluting stent implantation for patients with chronic total occlusion lesions: two-year results from a randomised AIR-CTO study. *EuroIntervention.* 2015;10:1409-17.

15. Witzenbichler B, Maehara A, Weisz G, Neumann FJ, Rinaldi MJ, Metzger DC, Henry TD, Cox DA, Duffy PL, Brodie BR, Stuckey TD, Mazzaferri EL Jr, Xu K, Parise H, Mehran R, Mintz GS, Stone GW. Relationship between intravascular ultrasound guidance and clinical outcomes after drug-eluting stents: the assessment of dual antiplatelet therapy with drug-eluting stents (ADAPT-DES) study. *Circulation.* 2014;129:463-70.

16. Ahmed K, Jeong MH, Chakraborty R, Ahn Y, Sim DS, Park K, Hong YJ, Kim JH, Cho KH, Kim MC, Hachinohe D, Hwang SH, Lee MG, Cho MC, Kim CJ, Kim YJ, Park JC, Kang JC; Other Korea Acute Myocardial Infarction Registry Investigators. Role of intravascular ultrasound in patients with acute myocardial infarction undergoing percutaneous coronary intervention. *Am J Cardiol.* 2011;108:8-14.

17. Nakatsuma K, Shiomi H, Morimoto T, Ando K, Kadota K, Watanabe H, Taniguchi T, Yamamoto T, Furukawa Y, Nakagawa Y, Horie M, Kimura T; CREDO-Kyoto AMI investigators. Intravascular Ultrasound Guidance vs. Angiographic Guidance in Primary Percutaneous Coronary Intervention for ST-segment Elevation Myocardial Infarction - Long-Term Clinical Outcomes From the CREDO-Kyoto AMI Registry. *Circ J.* 2016;80:477-84.

Supplementary data

Supplementary Appendix 1. List of participating centres and investigators for the CREDO-Kyoto PCI/CABG registry cohort-2.

Supplementary Appendix 2. List of clinical research co-ordinators.

Supplementary Appendix 3. List of clinical events committee members.

Supplementary Table 1. Baseline patient characteristics in the propensity score-matched cohorts.

Supplementary Table 2. Angiographic and procedural characteristics in the propensity score-matched cohorts.

Supplementary Table 3. Clinical outcomes in the IVUS and the angio groups.

The supplementary data are published online at: www.asiaintervention.org