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Impact of *ad hoc* percutaneous coronary intervention with drug-eluting stents in angina patients

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KEYWORDS

- complex lesions
- coronary artery disease
- drug-eluting stent

Abstract

Aims: To evaluate the impact of *ad hoc* percutaneous coronary intervention (PCI) which combines coronary angioplasty and PCI in the same procedure in the era of drug-eluting stents (DES).

Methods and results: From the IRIS-DES registry, 4,738 angina patients treated using PCI with DES were enrolled. The 18-month outcomes were compared between *ad hoc* and non-*ad hoc* groups after adjustment using inverse-probability-of-treatment weighting. *Ad hoc* PCI was performed in 3,562 (75.2%) patients. The *ad hoc* PCI group had less extensive coronary disease and received fewer stents. The incidence of major adverse cardiac or cerebrovascular events, consisting of death, myocardial infarction (MI), stroke, and repeat revascularisation, did not differ between the *ad hoc* and the non-*ad hoc* groups (8.3% vs. 7.6%; adjusted hazard ratio [aHR] of *ad hoc* PCI, 1.22; 95% confidence interval [CI]: 0.91 to 1.63; p=0.18). The individual endpoints of death (2.0% vs. 1.9%; aHR, 1.57; 95% CI: 0.86- 2.88; p=0.14), MI (0.8% vs. 1.0%; aHR, 0.62; 95% CI: 0.29 - 1.33; p=0.22), stroke (1.0% vs. 0.9%; aHR, 1.25; 95% CI: 0.58-2.69; p=0.57), and repeat revascularisation (4.4% vs. 4.0%; aHR, 1.23; 95% CI: 0.86-1.77; p=0.25) also did not differ between the groups.

Conclusions: *Ad hoc* PCI using DES appears to be feasible for angina patients at a relatively low risk of procedure. This approach may reasonably be performed with evaluation of objective ischaemia using non-invasive or invasive tests.

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Introduction

Ad hoc percutaneous coronary intervention (PCI) combines angiography and PCI in the same procedure. In contrast, non-*ad hoc* PCI is a staged procedure performed during two different sessions. With the recent advancement in devices and techniques, *ad hoc* PCI has now been widely used in elective and urgent situations[1]. This strategy can reduce access problems, hospital stay, and contrast-induced nephropathy, which are potentially related to repeated procedures. However, this was also countered by the lack of a long enough pause for physicians to consider the appropriate treatment strategy thoughtfully[2]. The patient may not be provided with the full information about the course of disease and the benefit of alternative treatments. In addition, *ad hoc* PCI may cause potentially rushed doctors not to comply with standard recommendations due to the "oculo-stenotic" reflex[3]. Angiography-guided revascularisation may lead to overutilisation of devices and poor long-term prognosis[4,5].

Despite their importance and clinical implication, the acute and long-term outcomes of *ad hoc* PCI compared to non-*ad hoc* PCI have not been fully evaluated. In particular, there is a lack of data in the era of drug-eluting stents (DES). The benefit of DES, which have decreased the need for repeat revascularisation together with the cost of high incidence of stent thrombosis, may alter the impact of *ad hoc* PCI compared to PCI previously using bare metal stents. Therefore, our study aimed at comparing the long-term outcomes of *ad hoc* PCI with non-*ad hoc* PCI in a large multicentre registry which prospectively enrolled consecutive patients receiving DES.

Methods

PATIENTS

The study population was part of the IRIS-DES (Interventional Cardiology Research In-cooperation Society-Drug-Eluting Stents) registry and included 4,738 patients. The IRIS-DES registry was a prospective, multicentre recruitment of all consecutive consenting patients undergoing PCI with DES from 42 academic and community hospitals in Korea between April 1st, 2008, and June 30th, 2010, and for whom complete follow-up data were available for at least one year and up to three years[6]. During the enrolment period, a DES was the default device for PCI. Patients who were treated with everolimus-eluting stents (XIENCE V®; Abbott Vascular, Santa Clara, CA, USA) or sirolimus-eluting stents (Cypher Select; Cordis, Johnson & Johnson, Warren, NJ, USA) were included in this study. Exclusion criteria were minimal. Patients with cardiogenic shock, acute myocardial infarction (MI), malignant disease, or other comorbid conditions with life expectancy less than 12 months, those treated with a mixture of different types of DES, and those with planned surgery necessitating interruption of antiplatelet drugs within six months after the procedure were excluded from the study. After DES implantation, dual antiplatelet therapy with aspirin and clopidogrel was recommended for at least one year. The institutional review board of our hospitals approved the use of clinical data for this study, and all patients provided written informed consent for enrolment into our registry.

ENDPOINTS AND FOLLOW-UP

The primary endpoint of this study was the rate of major adverse cardiac and cerebrovascular events (MACCE), consisting of death, MI, stroke, and repeat revascularisation. Secondary endpoints included the individual endpoints of MACCE and the composite of death, MI, and stroke. Deaths were considered cardiac unless an unequivocal, non-cardiac cause was established. MI as a complication was defined as either at index admission (defined as new Q-wave after index treatment) or at follow-up (defined as any CK-MB or troponin increase above the upper range limit with or without the development of Q-waves), as described[7]. Repeat revascularisation included target vessel revascularisation, regardless of whether the procedure was clinically or angiographically driven, and non-target vessel revascularisation. Stroke, as indicated by neurologic deficits, was confirmed by a neurologist based on imaging modalities. Definite stent thrombosis was captured according to the Academic Research Consortium classification[8].

Clinical, angiographic, procedural and outcome data were prospectively recorded in a dedicated, electronic case report form by independent research personnel. Patients were clinically followed up at one, six, and 12 months, and then every six months thereafter, via office visit or telephone contact. Monitoring and verification of registry data have been periodically performed in participating hospitals by members of the academic coordinating centre. All outcomes of interest were confirmed by source documentation collected at each hospital and were centrally adjudicated by an independent clinical events committee.

STATISTICAL ANALYSIS

Differences in baseline clinical and angiographic characteristics and procedural findings were compared using the t-test for continuous variables and χ^2 or Fisher's exact tests for categorical variables, as appropriate. Survival curves were constructed using the Kaplan-Meier method and compared using the log-rank test. Patients were censored at 18 months (540 days) or when events occurred.

For the primary and secondary endpoints, differences between the *ad hoc* and non-*ad hoc* groups in unadjusted long-term rates of outcomes were assessed using Cox proportional hazards regression analysis. The proportional hazards assumption was confirmed by testing of partial (Schoenfeld) residuals[9], and no relevant violations were identified. In addition, we adjusted for differences in patient baseline characteristics by using weighted Cox proportional hazards regression models with inverse-probability-of-treatment weighting[10]. Adjustments were performed in all patients using the clinical covariates of age, sex, body mass index, diabetes mellitus, hypertension, current smoking, hyperlipidaemia, left ventricular ejection fraction, history of MI, cerebrovascular disease, chronic lung disease, peripheral vascular disease, congestive heart failure, prior coronary angioplasty, unstable angina, multivessel disease, and number of diseased lesions. Subgroups of patients based on various clinical and angiographic characteristics, including age ≥70 years old, stent type, sex, diabetes mellitus, renal failure, decreased EF of <50%, and multivessel disease, were analysed after adjustment using the multivariable

Cox model with clinical factors as covariates. The frailty Cox model was used to account for the effect of hospitals. Interactions between factors associated with *ad hoc* PCI and subgroups were tested by incorporation of formal interaction terms in the multivariable Cox model. All reported p-values are two-sided, and p-values less than 0.05 were considered statistically significant. SAS software, version 9.1 (SAS Institute Inc., Cary, NC, USA) and R programming language were used for statistical analyses.

Results

PATIENT CHARACTERISTICS

Investigating centres enrolled a median number of 82 patients (range, 12~1,529; interquartile range, 40~107) in this study. *Ad hoc* PCI was performed in 3,562 (75.2%) patients. From the total, 908 (77.2%) of patients receiving non-*ad hoc* PCI were treated in a hospital, in which 1,592 (32.3%) of all patients were enrolled. **Figure 1** shows the prevalence of *ad hoc* PCI in each hospital. From 42 centres, the mean prevalence of *ad hoc* PCI was 90±16% and more than 50% of the patients received *ad hoc* PCI in 40 (95%) centres. *Ad hoc* PCI patients were more likely to be female and have hypertension and cerebrovascular disease **(Table 1)**. However, a history of hyperlipidaemia and prior coronary angioplasty were more prevalent in non-*ad hoc* PCI patients. In addition, non-*ad hoc* PCI patients had lower left ventricular ejection fraction, more extensive coronary artery disease, and received more stents.

UNADJUSTED AND ADJUSTED OUTCOMES

Table 2 and **Figure 2** present the crude incidence of events over 18 months in the *ad hoc* and non-*ad hoc* PCI groups. The incidences of MACCE or individual endpoints did not differ between the two groups. When the outcomes were adjusted using inverse-probability-of-treatment weighting, the risks of any individual or composite endpoints were not associated with the use of *ad hoc* PCI. The significance of the p-value was not changed with the frailty Cox model.

Figure 3 shows the adjusted hazard ratios of *ad hoc* PCI for the primary endpoint of MACCE over 18 months in diverse subgroups. In most of the subgroups, *ad hoc* PCI was not associated with the risk of MACCE. However, in subgroups stratified by stent type, *ad hoc* PCI increased the risk of MACCE in the everolimus-eluting stent subgroup, but not the sirolimus-eluting stent subgroup without a significant interaction.

Table 1. Clinical and procedural characteristics.

Variable	*Ad hoc*	Non-*ad hoc*	*p*-value
Clinical characteristics	N=3,562	N=1,176	
Age, years	64.0±10.3	63.4±10.0	0.093
Male	2,245 (63.0)	846 (71.9)	<0.001
Body mass index, kg/m^2	24.8±3.1	25.0±3.0	0.096
Diabetes mellitus	1,295 (36.4)	413 (35.1)	0.44
Hypertension	2,334 (65.5)	733 (62.3)	0.047
Current smoker	859 (24.1)	256 (21.8)	0.10
Hyperlipidaemia	1,335 (37.5)	627 (53.3)	<0.001
Previous MI	220 (6.2)	70 (6.0)	0.78
Previous coronary angioplasty	635 (17.8)	259 (22.0)	0.001
Previous CABG	86 (2.4)	36 (3.1)	0.23
Previous congestive heart failure	81 (2.3)	20 (1.7)	0.24
Family history of coronary artery disease	153 (4.3)	62 (5.3)	0.16
Obstructive pulmonary disease	99 (2.8)	28 (2.4)	0.46
Cerebrovascular disease	291 (8.2)	68 (5.8)	0.007
Peripheral vascular disease	36 (1.0)	19 (1.6)	0.093
Renal failure	139 (3.9)	40 (3.4)	0.44
Left ventricular ejection fraction, %	61.2±9.6	59.8±7.4	<0.001
Clinical presentation			<0.001
Asymptomatic or stable angina	1,803 (50.6)	826 (70.2)	
Unstable angina	1,759 (49.4)	350 (29.8)	
Angiographic stenosis			
Left anterior descending artery	2,687 (75.4)	944 (80.3)	0.001
Left circumflex artery	1,425 (40.0)	548 (46.6)	<0.001
Right coronary artery	1,597 (44.8)	578 (49.1)	0.010
Left main	230 (6.5)	194 (16.5)	<0.001
Disease extent			<0.001
1-vessel disease	1,886 (52.9)	511 (43.5)	
2-vessel disease	1,060 (29.8)	390 (33.2)	
3-vessel disease	571 (16.0)	260 (22.1)	
Isolated left main disease	45 (1.3)	15 (1.3)	
Number of diseased lesions	1.9±1.1	2.0±1.0	0.013
Presence of total occlusion	309 (8.7)	117 (9.9)	0.19
Presence of restenotic lesion	221 (6.2)	128 (10.9)	<0.001
Number of treated lesions	1.4±0.7	1.5±0.7	0.013
Used stent			0.009
Sirolimus-eluting stent	1,794 (50.4)	541 (46.0)	
Everolimus-eluting stent	1,768 (49.6)	635 (54.0)	
Number of stents used per patient	1.7±1.0	2.3±1.3	<0.001
Total length of stents used per patient, mm	40.5±26.9	57.1±35.5	<0.001
Antiplatelet agents at 12 months			
Aspirin	3,392 (95.2)	1,124 (95.6)	0.62
Clopidogrel	3,129 (87.8)	1,053 (89.5)	0.12

CABG: coronary artery bypass graft; MI: myocardial infarction

Discussion

The major findings of our study were: (1) *ad hoc* PCI is frequently performed for patients with stable angina, but the utilisation rate is diverse according to physician preference, and (2) long-term outcomes of PCI with DES appear to be similar whether or not *ad hoc* PCI is performed. However, in patients receiving everolimus-eluting stents, the MACCE rate was higher after *ad hoc* PCI than after non-*ad hoc* PCI.

With the improvement of devices and medications, *ad hoc* PCI is frequently performed[1]. The prevalence of *ad hoc* PCI ranged from 40% to 80% in the literature and seems to be more widely used in current practices[1,11-13]. This procedure may reduce the cost and risk of complications related to the second procedure. In particular, it was preferred when patients had fewer comorbidities, such as renal failure, chronic lung disease, and extensive coronary disease[14].

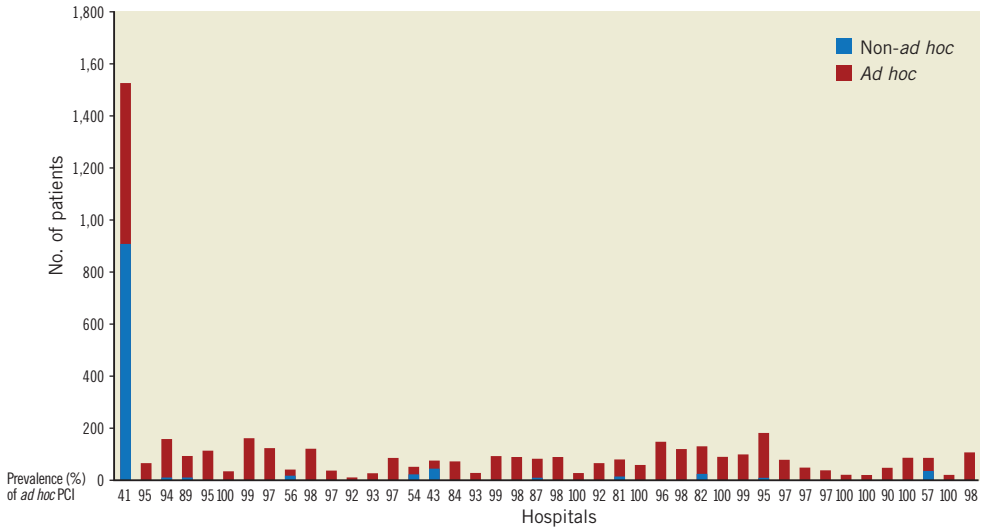

Figure 1. *Prevalence of ad hoc percutaneous coronary intervention (PCI) in investigating centres.*

In the New York State registry, which was a large registry evaluating hospital-level outcomes after cardiac surgery or PCI in New York State, the prevalence increased from 62% between 1995 and 1998[14] to 83% between 2003 and 2005[1]. In our study, *ad hoc* PCI was also commonly performed in three quarters of all PCIs using DES for angina patients. In spite of the variations in utilisation rates, most centres utilised *ad hoc* PCI in more than half of the patients.

A few studies reported the prevalence and long-term outcomes of *ad hoc* PCI compared with non-*ad hoc* PCI[1,11,14-16]. The investigators involved in the New York State registry reported a series of studies addressing the issue of *ad hoc* PCI. In the bare metal stent era, *ad hoc* PCI did not affect the rate of in-hospital mortality[14,15]. However, in the DES era DES, *ad hoc* PCI was reported to decrease the risk of three-year mortality, but to increase the risk of repeat revascularisation[1]. In spite of several limitations related to its non-randomised observational nature, this study has been used as supporting evidence for the rapid spread of *ad hoc* PCI in current practice. However, extensive use of *ad hoc* PCI was recently criticised by studies which showed no benefit of the prompt revascularisation strategy using PCI in stable angina patients[2,17,18]. Since *ad hoc* PCI provides less opportunity for thoughtful decision making when considering medical treatment versus revascularisation strategy or PCI versus coronary artery bypass graft, some authors recommended a "pause" after angiography to consider the risk and benefit of PCI[2,19].

Table 2. Unadjusted and adjusted risks of *ad hoc* PCI.

Variable	Kaplan-Meier incidences			Unadjusted Cox model		Adjustment with inverse-probability weighting	
	Ad hoc (n=3,562)*	Non-*ad hoc* (n=1,176)*	Log-rank *p*-value	Hazard ratio (95% CI)	*p*-value	Hazard ratio (95% CI)	*p*-value
Primary endpoint of MACCE	258 (8.3)	77 (7.6)	0.37	1.17 (0.91, 1.52)	0.22	1.22 (0.91, 1.63)	0.18
Composite of death, MI, or stroke	116 (3.6)	36 (3.2)	0.68	1.23 (0.84, 1.87)	0.30	1.15 (0.74, 1.77)	0.54
Death	63 (2.0)	20 (1.9)	0.78	1.59 (0.91, 2.78)	0.10	1.57 (0.86, 2.88)	0.14
Cardiac	35 (1.2)	9 (0.8)	0.45				
Non-cardiac	28 (0.8)	11 (1.1)	0.69				
MI	27 (0.8)	12 (1.0)	0.40	0.75 (0.38, 1.48)	0.051	0.62 (0.29, 1.33)	0.22
ST-elevation	13 (0.4)	4 (0.3)	0.89				
Non-ST-elevation	14 (0.4)	8 (0.7)	0.21				
Repeat revascularisation	150 (4.4)	45 (4.0)	0.52	1.10 (0.79, 1.52)	0.59	1.23 (0.86, 1.77)	0.25
Any target vessel	104 (3.1)	33 (3.0)	0.79				
All non-target vessel	46 (1.4)	12 (1.1)	0.45				
Stroke	35 (1.0)	10 (0.9)	0.66	1.18 (0.59, 2.39)	0.64	1.25 (0.58, 2.69)	0.57
Definite stent thrombosis	7 (0.2)	4 (0.3)	0.38	0.58 (0.17, 1.97)	0.38	0.62 (0.17, 2.25)	0.47

*Values are presented as numbers and Kaplan-Meier incidences. CI: confidence interval; MACCE: major adverse cardiac and cerebrovascular events; MI: myocardial infarction

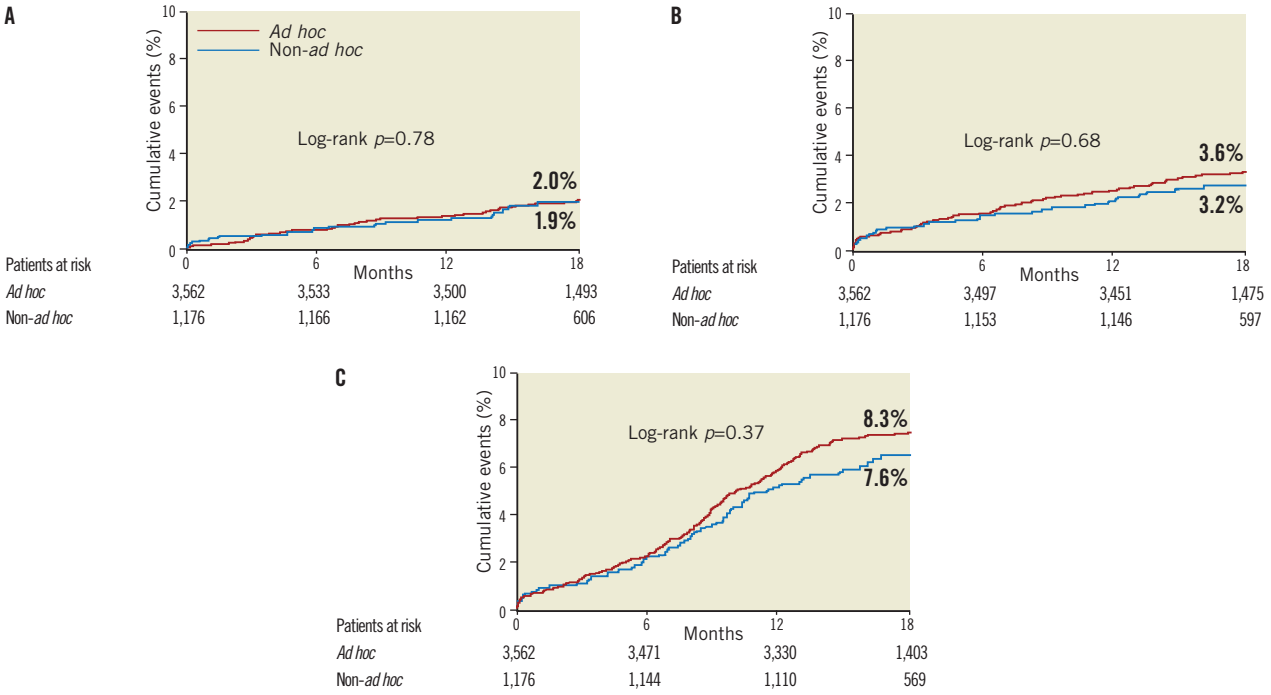

Figure 2. *Unadjusted 18-month event curves. Kaplan-Meier event curves for: A) all-cause death; B) composite of death, myocardial infarction (MI), and stroke; and C) major adverse cardiac or cerebrovascular events.*

Subgroup	MACCE *Ad hoc* no/ total no. (%)	MACCE Non-*ad hoc* no/ total no. (%)	Adjusted HR (95% CI)	*p*-value	*p*-value for interaction
Age					0.39
≥70 yr	112/1,177 (10.2)	25/338 (7.6)	1.37 (0.87, 2.15)	0.17	
<70 yr	148/2,385 (6.7)	50/838 (6.3)	1.06 (0.75,1.49)	0.75	
Sex					0.88
Male	164/2,245 (7.8)	55/846 (6.9)	1.13 (0.82, 1.56)	0.47	
Female	96/1,317 (7.9)	20/330 (6.1)	1.24 (0.76, 2.03)	0.39	
Diabetes mellitus					0.57
Yes	120/1,295 (10.2)	36/413 (8.9)	1.16 (0.78, 1.73)	0.46	
No	140/2,267 (6.5)	39/763 (5.4)	1.19 (0.83,1.73)	0.35	
ACS					0.79
Yes	130/1,803 (7.7)	51 /826 (6.5)	1.21 (0.87,1.70)	0.26	
No	130/1,759 (8.0)	24/350 (7.1)	1.15 (0.73, 1.81)	0.54	
Renal failure					0.44
Yes	26/139 (20.5)	4/40 (10.0)	2.00 (0.65, 6.19)	0.23	
No	234/3,423 (7.3)	71/113 6 (6.5)	1.14 (0.87,1.51)	0.34	
Multivessel disease					0.13
Yes	148/1,707 (9.4)	54/634 (8.8)	1.01 (0.72, 1.39)	0.98	
No	112/1,855 (6.4)	21 /542 (4.2)	1.57 (0.96, 2.56)	0.073	
Ejection fraction					0.56
<50%	48/377 (13.4)	10/111 (10.0)	1.44 (0.71, 2.95)	0.31	
≥50%	212/3,185 (7.2)	65/1,065 (6.3)	1.16 (0.87, 1.56)	0.32	
Stent types					0.061
Sirolimus stent	118/1,794 (7.2)	41/541 (7.7)	0.89 (0.61, 1.30)	0.56	
Everolimus stent	142/1,768 (8.4)	34/635 (5.8)	1.52 (1.03, 2.24)	0.036	

Figure 3. *Adjusted hazard ratios (HR) of ad hoc percutaneous coronary intervention (PCI) for major adverse cardiac or cerebrovascular events (MACCE) in different subgroups. ACS: acute coronary syndrome*

In contrast to the New York State registry, our study showed similar long-term outcomes of *ad hoc* PCI compared with non-*ad hoc* PCI for angina patients. Although patients receiving *ad hoc* PCI had less complex clinical and angiographic features than those in the New York State registry, the unadjusted and adjusted risks of 18-month mortality, MI, stroke and repeat revascularisation were comparable between *ad hoc* and non-*ad hoc* PCI. The pattern was identical regardless of the presence of traditional PCI risks, such as old age, female sex, diabetes mellitus, multivessel disease or renal failure. The difference between our study and the New York State registry may be explained by several potential reasons[1]. First, our study might have included patients with more unstable conditions than the NY registry. Therefore, the benefit of *ad hoc* PCI might have been diminished due to the unstable patients in our study. Second, the prevalence of *ad hoc* PCI was diverse across the investigating centres. Therefore, different procedural patterns across hospitals might have influenced the results. Third, because non-*ad hoc* PCI was intentionally selected for patients at high procedural risk, patients receiving a non-*ad hoc* PCI might have been treated with greater care. Fourth, as indicated in the adjusted results, the strategy of *ad hoc* or non-*ad hoc* PCI may not have altered outcomes for patients with stable coronary disease. This hypothesis is supported by previous randomised studies showing that prompt revascularisation with PCI for patients with stable angina did not influence the risk of death or any hard clinical events compared with provisional revascularisation[17,20]. Nonetheless, it is of note that *ad hoc* PCI, which decreases hospital stay and problems related to a staged procedure, may lead to feasible outcomes in stable patients at relatively low procedural risk.

In spite of its clinical feasibility, however, *ad hoc* PCI should be performed with caution. In fact, *ad hoc* PCI increased the risk of MACCE for patients receiving everolimus-eluting stents in this study. In spite of unclear mechanism, it should be noted that *ad hoc* PCI may potentially inflate unnecessary procedures due to the "oculo-stenotic"' reflex. In our study, a substantial proportion of patients received *ad hoc* PCI although the indication for revascularisation was not favourable to PCI[19,21]. For instance, 47% of patients with left main or multivessel disease were treated without a pause after angiography. Previous studies have already shown that angiographic complete revascularisation may not improve clinical outcomes in stable patients with multivessel coronary disease[4]. On-site evaluation of objective ischaemia using fractional flow reserve may prevent the potential risk of overtreatment due to angiography-guided procedure during *ad hoc* PCI[5,22].

Study limitations

Our study has limitations. First, although patients were recruited in a prospective cohort, this analysis was performed retrospectively. Therefore, important factors in the selection between *ad hoc* versus non-*ad hoc* procedures were not considered appropriately. For instance, the prevalence and clinical impact of non-invasive assessment of myocardial ischaemia could not be analysed in this study. Second, because of a non-randomised study design, our observation is exploratory and cannot exclude the impact of selection bias in spite of rigorous statistical adjustment. However, our study provides important information on healthcare policy because this issue cannot be confirmed by a randomised clinical study. In fact, without enough data, the current guidelines recommend that *ad hoc* PCI should not be performed for high-risk patients for whom the superiority of PCI compared with other strategies is not clear[19,21]. Third, our study did not analyse the cost-effectiveness of *ad hoc* PCI due to the lack of financial information. This issue needs to be investigated in future studies. Finally, the appropriateness of PCI was not counted in this registry due to a lack of baseline information. Therefore, the impact of appropriate PCI between *ad hoc* and non-*ad hoc* PCI could not be analysed.

Conclusion

In conclusion, our study demonstrates that *ad hoc* PCI is widely used and leads to similar long-term clinical outcomes compared with non-*ad hoc* PCI for patients at a relatively low risk of procedures. However, it should be performed with evaluation of objective ischaemia using non-invasive or invasive tests to decrease the potential risk of unnecessary procedures. Staged PCI should also be considered for patients at high risk for PCI, to allow for appropriate selection of the revascularisation strategy and to enhance patient understanding of treatment risks and benefits.

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Conflict of interest statement

Y-H. Kim has received lecture fees from AstraZeneca, MSD, and Medtronic. S-J. Park has received research grants and lecture fees from Abbott Vascular, Boston Scientific, Cordis, and Medtronic. The other authors have no conflicts of interest to declare.

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