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Impact of one-month DAPT followed by aspirin monotherapy in patients undergoing percutaneous coronary intervention according to clinical presentation: a post hoc analysis of the randomised One-Month DAPT trial

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KEYWORDS

- ACS/NSTE-ACS
- adjunctive pharmacotherapy
- drug-eluting stent
- stable angina

Abstract

Background: The impact of 1-month dual antiplatelet therapy (DAPT) followed by aspirin monotherapy according to clinical presentation has not been elucidated.

Aims: This study aimed to compare the impact of 1-month DAPT followed by aspirin monotherapy after polymer-free drug-coated stent (PF-DCS) implantation (1-month DAPT after PF-DCS) vs 6-12-month DAPT followed by aspirin monotherapy after biodegradable polymer drug-eluting stent (BP-DES) implantation (6-12-month DAPT after BP-DES) according to clinical presentation.

Methods: This is a *post hoc* analysis of the One-Month DAPT trial. The primary outcome was the composite of major adverse cardiac and cerebrovascular events (MACCE; a composite of cardiac death, non-fatal myocardial infarction, target vessel revascularisation, and stroke) and major bleeding.

Results: Among 1,828 patients with stable coronary artery disease (CAD), 1-month DAPT after PF-DCS resulted in lower rates of the primary outcome than 6-12-month DAPT after BP-DES (3.9% vs 6.5%; hazard ratio [HR] 0.59, 95% confidence interval [CI]: 0.39-0.90; p=0.012). However, among 1,192 patients with acute coronary syndrome (ACS), the rates of the primary outcome were not significantly different between the two therapy groups (5.6% vs 3.6%; HR 1.57, 95% CI: 0.91-2.70; p=0.102) and a significant interaction was observed between therapy and clinical presentation regarding the primary outcome (P_{int}=0.005). A significant interaction was observed in MACCE (P_{int}=0.016), but not in major bleeding (P_{int}=0.276).

Conclusions: In patients undergoing drug-eluting stent implantation for non-complex lesions, the benefits of 1-month DAPT followed by aspirin monotherapy for a composite of ischaemic and bleeding outcomes were found in patients with stable CAD, but not in those with ACS. ClinicalTrials.gov: NCT02513810.

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Abbreviations

ACS	acute coronary syndrome
CAD	coronary artery disease
CI	confidence interval
DAPT	dual antiplatelet therapy
DES	drug-eluting stent
HR	hazard ratio
MACCE	major adverse cardiac and cerebrovascular events
PCI	percutaneous coronary intervention
PF-DCS	polymer-free drug-coated stent

Introduction

Dual antiplatelet therapy (DAPT) with aspirin and a $P2Y_{12}$ inhibitor has been recommended after drug-eluting stent (DES) implantation to prevent atherothrombotic events; however, issues have been raised regarding increased bleeding risk, medical costs, and non-compliance related to prolonged DAPT[1-3]. Therefore, previous trials have examined experimental antiplatelet therapy strategies of short-term DAPT followed by single antiplatelet therapy to balance the ischaemic and bleeding risks[4-11]. Although different strategies for DAPT after DES implantation have been recommended depending on clinical presentation, with a relatively shorter duration of DAPT in stable coronary artery disease (CAD) compared to acute coronary syndrome (ACS), studies regarding the impact of short-term DAPT followed by single antiplatelet therapy in patients with stable CAD are limited[1-3,12]. Recently, the one-month dual antiplatelet therapy followed by aspirin monotherapy after polymer-free drug-coated stent implantation (One-Month DAPT) trial demonstrated the non-inferiority of 1-month DAPT followed by aspirin monotherapy after polymer-free drug-coated stent (PF-DCS) implantation, compared to 6-12-month DAPT after biodegradable polymer drug-eluting stent (BP-DES) implantation for the 1-year composite of ischaemic and bleeding outcomes in patients undergoing percutaneous coronary intervention (PCI) for non-complex lesions[13]. Thus, the aim of the present *post hoc* analysis of the One-Month DAPT trial was to evaluate the impact of 1-month DAPT followed by aspirin monotherapy after PF-DCS implantation compared to 6-12-month DAPT after BP-DES implantation, according to clinical presentation.

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Methods

STUDY POPULATION AND DESIGN

The study design and rationale for the One-Month DAPT trial have been previously described in detail[13]. Briefly, the multicentre, prospective, open-label, randomised, non-inferiority trial evaluated 1-month DAPT followed by aspirin monotherapy after PF-DCS implantation (1-month DAPT after PF-DCS) vs 6-12-month DAPT followed by aspirin monotherapy after BP-DES implantation (6-12-month DAPT after BP-DES) in 3,020 patients at 23 centres in the Republic of Korea[13]. Patients who underwent non-emergent PCI for *de novo* coronary lesions were eligible for participation in the trial and those with complex lesion morphologies, including aorto-ostial, unprotected left main, chronic total occlusion, graft, thrombosis, heavily calcified, or extremely tortuous lesions, were excluded[13]. The DAPT after the index PCI consisted of aspirin (100 mg) and clopidogrel (75 mg) once per day[13]. The PF-DCS used in the study was a polymer-free biolimus A9-coated stent (BioFreedom; Biosensors International)[13]. The BP-DES used in the study was either a stainless-steel biolimus A9-eluting stent with a biodegradable polymer (BioMatrix NeoFlex; Biosensors International) or a cobalt-chromium sirolimus-eluting stent (Ultimaster; Terumo), based on the discretion of the operator[13]. Consenting patients were randomised in a 1:1 ratio to either of the therapies and observed up to 12 months. In this analysis, patients in the One-Month DAPT trial were classified into two groups according to the clinical presentation at index PCI as follows: those with stable CAD and those with ACS **(Figure 1)**[12,14]. The trial was approved by the institutional review board of each participating centre and followed the ethical principles of the Declaration of Helsinki. All patients provided written informed consent before participation in the trial.

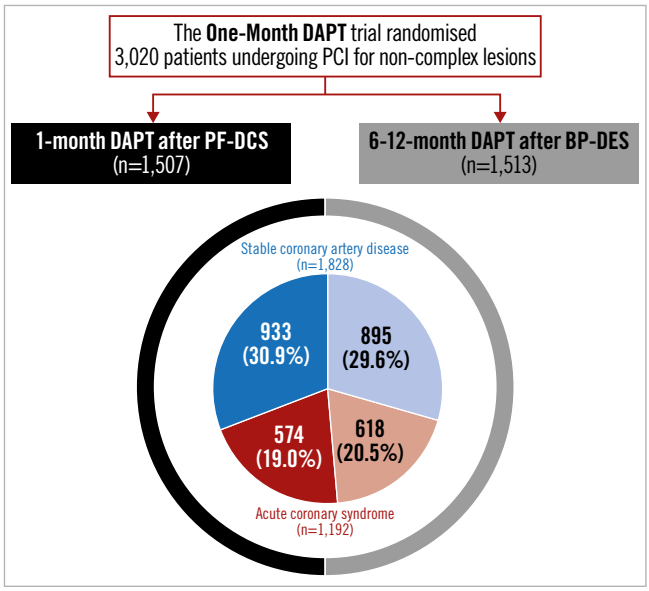


Figure 1. *Distribution of One-Month DAPT trial patients by clinical presentation and therapy strategy. BP-DES: biodegradable polymer drug-eluting stent; DAPT: dual antiplatelet therapy; PCI: percutaneous coronary intervention; PF-DCS: polymer-free drug-coated stent*

STUDY OUTCOMES AND DEFINITIONS

The primary outcome was the composite of major adverse cardiac and cerebrovascular events (MACCE) and major bleeding at 12 months after the index PCI. MACCE included the composite of cardiac death, non-fatal myocardial infarction, target vessel revascularisation, and stroke. The key secondary outcomes were MACCE and major bleeding.

Clinical events were defined according to the Academic Research Consortium[13,15]. All deaths were considered as cardiac

deaths unless a definite non-cardiac cause could be established. Myocardial infarction after discharge from hospital was defined as the presence of clinical symptoms, electrocardiographic changes, or abnormal findings on imaging studies, combined with an increase in creatine kinase-MB fraction above the upper normal limits or an increase in troponin T or I to greater than the 99th percentile of the upper normal limit[16-18]. Ischaemia-driven target vessel revascularisation was defined as repeat PCI or bypass surgery of any segment within the coronary vessel treated during the index PCI, with either of the following: (1) ischaemia symptoms or a positive stress test and angiographic diameter stenosis >50% by quantitative coronary angiographic analysis; or (2) angiographic diameter stenosis >70% by quantitative coronary angiographic analysis, with or without ischaemia symptoms or a positive stress test[17]. All cerebrovascular events including transient ischaemic attacks and reversible ischaemic neurologic deficits were considered as stroke and further classified as an ischaemic or a haemorrhagic stroke. Definite or probable stent thrombosis was defined according to the recommendations of the Academic Research Consortium[16]. In this *post hoc* analysis, major bleeding was defined according to the Thrombolysis in Myocardial Infarction (TIMI) criteria as follows: intracranial bleeding, haemorrhage with a haemoglobin decrease of at least 5 g/dL, or fatal bleeding that resulted in death within 7 days[19]. Routine follow-up of coronary angiography was not recommended in the trial. Adverse events, including ischaemic and bleeding events, were categorised by an independent clinical event committee blinded to the therapy assignments and primary results of the trial.

STATISTICAL ANALYSES

Primary analyses were performed based on the intention-to-treat population. Continuous variables were reported as mean±standard deviation or median (interquartile range) and compared using Student's t-test or the Mann-Whitney U test. Categorical variables were reported as numbers (percentages) and compared using χ^2 tests or Fisher's exact test. Event rates regarding study outcomes at 12 months were estimated using Kaplan-Meier survival analysis and compared using log-rank tests. Since patients may experience more than one component of the adverse events, each patient was assessed until the occurrence of the first event and only once during the analysis. Hazard ratios (HRs) with 95% confidence intervals (CIs) were computed using Cox regression analysis. To assess whether therapy effects (1-month DAPT after PF-DCS vs 6-12-month DAPT after BP-DES) differ according to clinical presentation (stable CAD vs ACS), formal interaction tests between the therapy and clinical presentation on the clinical outcomes were performed using Cox regression analysis. Prespecified 1-month landmark analyses were performed in patients who were alive at 31 days and did not encounter adverse events of the specific type nor were censored before this landmark[13]. Moreover, exploratory analyses after excluding the patients with acute myocardial infarction at index PCI were performed[13]. All tests were two-sided, and $p<0.05$ was considered statistically significant. Statistical analyses were performed using IBM SPSS, version 25.0 (IBM) and R 3.5.3 software (R Foundation for Statistical Computing).

Results

BASELINE CHARACTERISTICS

Between December 2015 and September 2019, 3,020 patients were enrolled in the One-Month DAPT trial: 1,828 patients presented with stable CAD, and 1,192 patients presented with ACS. The baseline clinical, angiographic, and procedural characteristics according to the clinical presentation are described in **Table 1** and **Table 2**. The stable CAD group had a lower proportion of current smokers, patients who had undergone prior PCI, patients in whom the transfemoral approach had been used, and patients with smaller diameter stenosis on pre-interventional quantitative analyses than the ACS group. In contrast, patients with stable CAD had a higher proportion of dyslipidaemia and larger minimal luminal diameter on pre-interventional quantitative analyses. Among the patients with stable CAD, 933 patients were assigned to the 1-month DAPT after PF-DCS group, and 895 patients were assigned to the 6-12-month DAPT after BP-DES group. Among the patients with ACS, 574 patients were assigned to the 1-month DAPT after PF-DCS group, and 618 patients were assigned to the 6-12-month DAPT after BP-DES group. Baseline characteristics did not differ between the two therapy groups in patients with stable CAD and ACS **(Table 1, Table 2)**.

CLINICAL OUTCOMES BY CLINICAL PRESENTATION AND THERAPY STRATEGY

The effects of 1-month DAPT after PF-DCS compared to 6-12-month DAPT after BP-DES in patients with stable CAD and ACS are presented in **Table 3** and **Figure 2**. With regard to the primary outcome, in patients with stable CAD, 1-month DAPT after PF-DCS resulted in lower rates of the primary outcome compared to 6-12-month DAPT after BP-DES (3.9% vs 6.5%; HR 0.59, 95% CI: 0.39-0.90; p=0.012) **(Figure 2A)**. However, in patients with ACS, the rates of the primary outcome were not significantly different between 1-month DAPT after PF-DCS and 6-12-month DAPT after BP-DES (5.6% vs 3.6%; HR 1.57, 95% CI: 0.91-2.70; p=0.102) **(Figure 2B)**. A significant interaction was observed between therapy and clinical presentation, indicating a different therapy effect of 1-month DAPT after PF-DCS according to clinical presentation (P_{int}=0.005) **(Figure 2C)**. Regarding secondary outcomes, in patients with stable CAD, 1-month DAPT after PF-DCS resulted in lower rates of MACCE compared to 6-12-month DAPT after BP-DES (3.9% vs 6.0%; HR 0.65, 95% CI: 0.43-0.99; p=0.044). However, in patients with ACS, rates of MACCE were not significantly different between the two therapy groups (5.3% vs 3.4%; HR 1.54, 95% CI: 0.88-2.68; p=0.128) and a significant interaction was observed, which indicates a different therapeutic effect of 1-month DAPT after PF-DCS according to clinical presentation (P_{int}=0.016). In addition, in patients with stable CAD, 1-month DAPT after PF-DCS resulted in lower rates of major bleeding compared to 6-12-month DAPT after BP-DES (0.3% vs

Table 1. Baseline characteristics.

Variables	Stable CAD (n=1,828)			ACS (n=1,192)			*p*-value[e]
	1-month DAPT after PF-DCS (n=933)	6-12-month DAPT after BP-DES (n=895)	*p*-value	1-month DAPT after PF-DCS (n=574)	6-12-month DAPT after BP-DES (n=618)	*p*-value	
Age (years)	66.6±9.9	66.6±9.7	0.977	66.4±10.0	66.6±10.9	0.738	0.804
Male	646 (69.2)	639 (71.4)	0.338	393 (68.5)	409 (66.2)	0.436	0.087
Body mass index (kg/m^2)[a]	24.8±3.1	24.7±3.1	0.299	24.6±3.2	24.7±3.0	0.711	0.463
Hypertension	630 (67.5)	595 (66.5)	0.671	377 (65.7)	407 (65.9)	0.997	0.505
Diabetes mellitus	353 (37.8)	358 (40.0)	0.367	211 (36.8)	213 (34.5)	0.444	0.071
Diabetes mellitus requiring insulin treatment	50 (5.4)	31 (3.5)	0.064	17 (3.0)	26 (4.2)	0.319	0.307
Chronic kidney disease	124 (13.3)	119 (13.3)	1.000	78 (13.6)	87 (14.1)	0.873	0.706
Dyslipidaemia	779 (83.5)	751 (83.9)	0.859	441 (76.8)	483 (78.2)	0.632	<0.001
Current smoker[b]	150 (16.1)	122 (13.7)	0.161	109 (19.0)	119 (19.3)	0.977	0.003
Prior percutaneous coronary intervention	148 (15.9)	144 (16.1)	0.946	99 (17.2)	130 (21.0)	0.113	0.024
Prior myocardial infarction	35 (3.8)	29 (3.2)	0.640	19 (3.3)	25 (4.0)	0.604	0.861
Prior stroke	58 (6.2)	72 (8.0)	0.153	34 (5.9)	37 (6.0)	1.000	0.242
Prior coronary bypass graft	11 (1.2)	18 (2.0)	0.216	9 (1.6)	6 (1.0)	0.507	0.562
Clinical presentation[c]			1.000			0.658	–
Stable coronary artery disease	933 (100)	895 (100)		–	–		
Unstable angina	–	–		534 (93.0)	570 (92.2)		
Non-ST-elevation myocardial infarction	–	–		40 (7.0)	48 (7.8)		
Left ventricular ejection fraction (%)[d]	63.3±9.4	62.9±9.5	0.407	62.9±9.8	63.1±9.3	0.743	0.730

Data are presented as mean±SD or n (%). [a]Data were available for 1,817 patients with stable CAD and 1,186 patients with ACS. [b]Data were available for 1,820 patients with stable CAD and 1,191 patients with ACS. [c]Eighty-eight patients had increased troponin level without increase in creatine kinase-MB level. [d]Data were available for 1,763 patients with stable CAD and 1,140 patients with ACS. [e]P-value for the comparison between the patients with stable CAD vs ACS. ACS: acute coronary syndrome; BP-DES: biodegradable polymer drug-eluting stent; CAD: coronary artery disease; DAPT: dual antiplatelet therapy; PF-DCS: polymer-free drug-coated stent

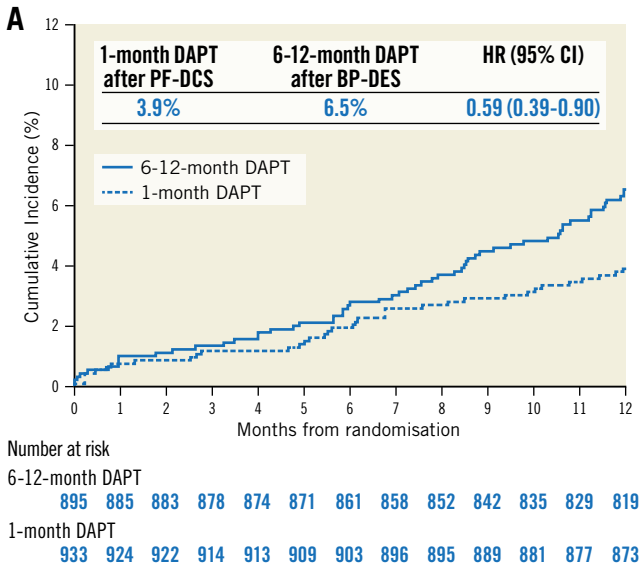
1.5%; HR 0.22, 95% CI: 0.06-0.78; p=0.010). However, in patients with ACS, rates of major bleeding did not significantly differ between the two therapy groups (0.5% vs 0.8%; HR 0.64, 95% CI: 0.15-2.68; p=0.537), but no significant interaction was observed, which indicates a similar therapeutic effect of 1-month DAPT after PF-DCS, irrespective of clinical presentation (P_{int}=0.276).

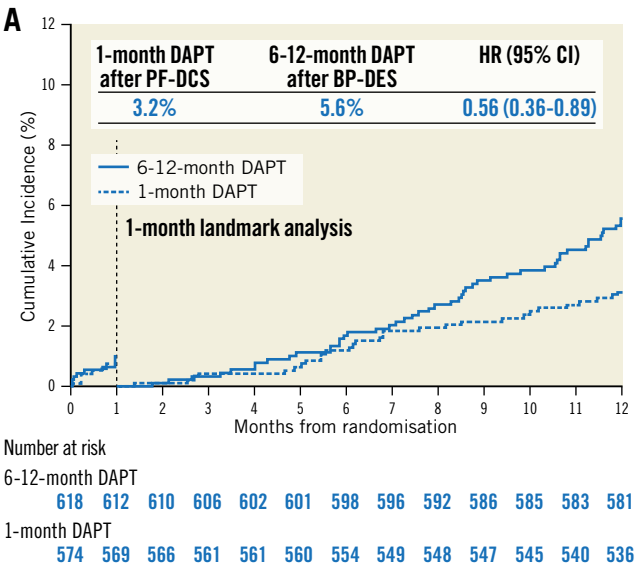
ADDITIONAL ANALYSES

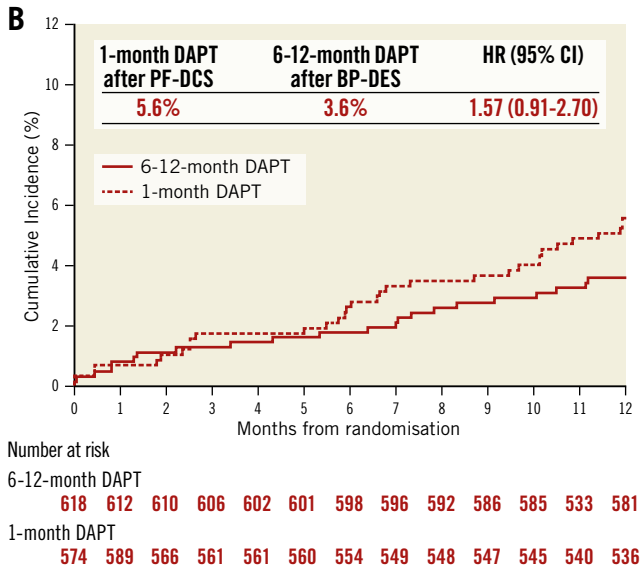
In prespecified 1-month landmark analyses, in patients with stable CAD, 1-month DAPT after PF-DCS resulted in lower rates of the primary outcome compared to 6-12-month DAPT after BP-DES (3.2% vs 5.6%; HR 0.56, 95% CI: 0.36-0.89; p=0.013) **(Figure 3A)**. However, in patients with ACS, the rates of the primary outcome were not significantly different between the two therapy groups (5.0% vs 2.8%; HR 1.77, 95% CI: 0.97-3.24; p=0.059) **(Figure 3B)** and a significant interaction was observed between therapy and clinical presentation, indicating a different therapeutic effect of 1-month DAPT after PF-DCS according to clinical presentation (P_{int}=0.003) **(Figure 3C)**. A significant interaction was observed in MACCE (P_{int}=0.009), but not in major bleeding (P_{int}=0.190) **(Supplementary Figure 1A, Supplementary Figure 1B)**. Similarly, results for the exploratory analyses were consistent after excluding the 88 patients with acute myocardial infarction at index PCI. A significant interaction was observed between therapy and clinical presentation regarding the primary outcome, indicating different therapeutic effects of 1-month DAPT after PF-DCS according to clinical presentation (P_{int}=0.003) **(Supplementary Figure 2A)**. Further, a significant interaction was observed in MACCE (P_{int}=0.010), but not in major bleeding (P_{int}=0.278) **(Supplementary Figure 2B, Supplementary Figure 2C)**. Detailed analyses for clinical outcomes regarding the 1-month landmark and after excluding the patients presenting with acute myocardial infarction are presented in **Supplementary Table 1** and **Supplementary Table 2**.

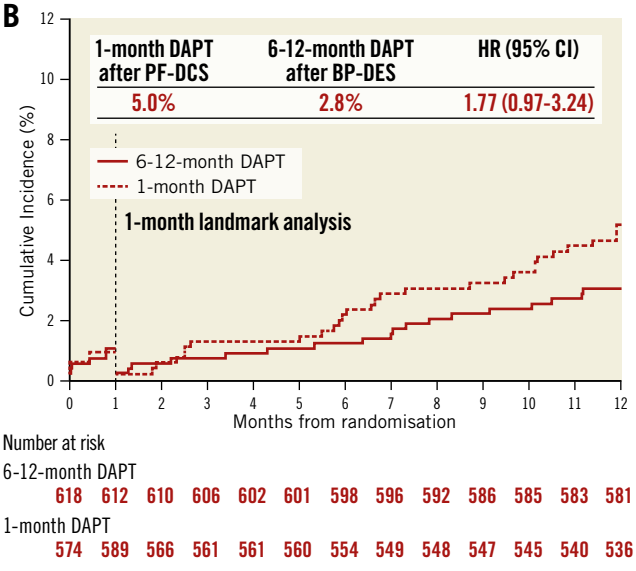
Discussion

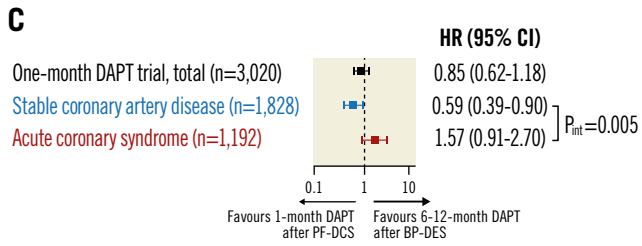
The main findings of this *post hoc* analysis of the One-Month DAPT trial were as follows **(Central illustration)**: 1) in patients undergoing PCI for non-complex lesions, the effects of 1-month DAPT after PF-DCS vs 6-12-month DAPT after BP-DES regarding the primary outcome and MACCE differed according to clinical presentation, with 1-month DAPT after PF-DCS resulting in lower rates of the primary outcome and MACCE in patients with stable CAD, but presenting no significant difference in rates of the primary outcome and MACCE in patients with ACS; 2) the effects of 1-month DAPT after PF-DCS regarding major bleeding were similar, irrespective of clinical presentation; and 3) results were consistent in 1-month landmark analyses or after excluding the patients presenting with acute myocardial infarction. Overall,











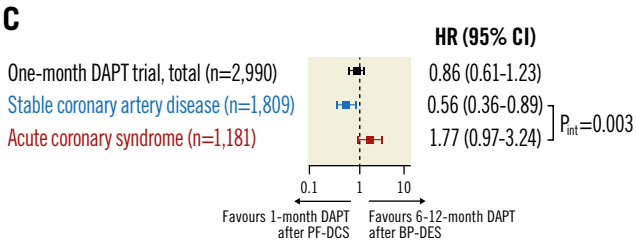


Figure 2. *Time-to-event curves and risk for primary outcome by clinical presentation and therapy strategy. Kaplan-Meier survival curves for primary outcome in patients with A) Stable CAD, and B) ACS. C) Relative risk for primary outcome by clinical presentation and therapy strategy. P_{int} indicates p-value from Cox regression test of therapy × clinical presentation interaction. ACS: acute coronary syndrome; BP-DES: biodegradable polymer drug-eluting stent; CAD: coronary artery disease; CI: confidence interval; DAPT: dual antiplatelet therapy; HR: hazard ratio; PF-DCS: polymer-free drug-coated stent*

Figure 3. *Time-to-event curves and risk for primary outcome by clinical presentation and therapy strategy in 1-month landmark analyses. Kaplan-Meier survival curves for primary outcome in patients with A) Stable CAD, and B) ACS. C) Relative risk for primary outcome by clinical presentation and therapy strategy. P_{int} indicates p-value from Cox regression test of therapy × clinical presentation interaction. ACS: acute coronary syndrome; BP-DES: biodegradable polymer drug-eluting stent; CAD: coronary artery disease; CI: confidence interval; DAPT: dual-antiplatelet therapy; HR: hazard ratio; PF-DCS: polymer-free drug-coated stent*

Table 2. Angiographic and procedural characteristics.

Variables		Stable CAD (n=1,828)			ACS (n=1,192)			*p*-value[e]
		1-month DAPT after PF-DCS (n=933)	6-12-month DAPT after BP-DES (n=895)	*p*-value	1-month DAPT after PF-DCS (n=574)	6-12-month DAPT after BP-DES (n=618)	*p*-value	
Extent of coronary artery disease	1-vessel disease	395 (42.3)	371 (41.5)	0.114	245 (42.7)	264 (42.7)	0.877	0.446
	2-vessel disease	319 (34.2)	278 (31.1)		172 (30.0)	192 (31.1)		
	3-vessel disease	219 (23.5)	246 (27.5)		157 (27.4)	162 (26.2)		
Transfemoral approach[a]		180 (19.3)	160 (17.9)	0.473	118 (20.6)	143 (23.1)	0.314	0.031
Multivessel intervention[a]		120 (12.9)	103 (11.5)	0.417	80 (13.9)	86 (13.9)	1.000	0.188
Treated lesions per patient[a]		1.19±0.44	1.18±0.44	0.676	1.21±0.45	1.20±0.44	0.798	0.333
Total number of stents per patient[b]		1.33±0.63	1.30±0.61	0.277	1.33±0.60	1.34±0.63	0.716	0.327
Total stent length per patient (mm)[b]		30.89±18.08	30.40±17.86	0.563	31.55±17.40	31.86±19.13	0.769	0.117
Number of treated lesions		**1,111**	**1,058**		**693**	**742**		
Treated lesion	Left anterior descending artery	616 (55.4)	589 (55.7)	0.827	393 (56.7)	403 (54.3)	0.212	0.750
	Left circumflex artery	209 (18.8)	189 (17.9)		139 (20.1)	137 (18.5)		
	Right coronary artery	286 (25.7)	280 (26.5)		161 (23.2)	202 (27.2)		
Type of drug-eluting stents	BioFreedom	1,108 (99.7)	0	<0.001	689 (99.4)	0	<0.001	0.117
	BioMatrix	0	698 (66.0)		0	507 (68.3)		
	Ultimaster	0	356 (33.6)		0	229 (30.9)		
	Other drug-eluting stents	2 (0.2)	4 (0.4)		2 (0.3)	6 (0.8)		
	Balloon angioplasty alone	1 (0.1)	0		2 (0.3)	0		
Pre-interventional quantitative analyses[c]	Reference vessel diameter (mm)	2.81±0.46	2.80±0.45	0.571	2.79±0.47	2.80±0.46	0.821	0.637
	Minimal lumen diameter (mm)	0.83±0.39	0.82±0.39	0.672	0.77±0.37	0.78±0.39	0.519	0.001
	Diameter stenosis (%)	70.69±12.28	70.97±12.30	0.605	72.59±11.94	72.11±12.58	0.453	<0.001
	Lesion length (mm)	20.27±10.32	20.27±9.89	0.999	20.40±9.64	20.74±12.44	0.564	0.408
Stent diameter (mm)[d]		3.08±0.43	3.07±0.42	0.495	3.08±0.44	3.06±0.41	0.335	0.719
Post-interventional quantitative analyses[c]	Reference vessel diameter (mm)	2.92±0.47	2.91±0.45	0.479	2.91±0.48	2.90±0.46	0.856	0.489
	Minimal lumen diameter (mm)	2.53±0.43	2.53±0.42	0.917	2.51±0.44	2.51±0.43	0.911	0.101
	Diameter stenosis (%)	13.19±7.94	12.71±8.34	0.168	13.62±8.01	13.34±8.54	0.535	0.064

Data are presented as mean±SD or n (%). [a]Data were analysed for 1,826 patients with stable CAD who underwent percutaneous coronary intervention (1 patient did not undergo revascularisation and 1 patient underwent bypass surgery). [b]Data were analysed for 3,015 patients who underwent stent implantation (1,824 patients with stable CAD and 1,191 patients with ACS). [c]Data were available for 2,163 lesions with stable CAD and 1,434 lesions with ACS. [d]Data were analysed for 3,601 lesions that underwent stent implantation (2,168 lesions with stable CAD and 1,433 lesions with ACS). [e]P-value for the comparison between the patients or lesions with stable CAD vs ACS. ACS: acute coronary syndrome; BP-DES: biodegradable polymer drug-eluting stent; CAD: coronary artery disease; DAPT: dual antiplatelet therapy; PF-DCS: polymer-free drug-coated stent

compared to 6-12-month DAPT followed by aspirin monotherapy after BP-DES implantation, 1-month DAPT followed by aspirin monotherapy after PF-DCS implantation may be safe for patients with stable CAD but not for those with ACS.

The use of a DES in patients with coronary artery disease showed superior clinical outcomes compared to a bare metal stent; however, maintaining DAPT is important after DES implantation to prevent ischaemic events[1-3,20]. However, major concerns have been raised about an increased risk of bleeding events as well as higher costs, non-compliance, and inconvenience due to prolonged DAPT. Diverse experimental antiplatelet therapy strategies have been proposed with short-term DAPT followed by single antiplatelet therapy after DES implantation[4-10,21]. In addition, with the strategy of DAPT duration maximally shortened to 1 month, the PF-DCS showed superior clinical outcomes compared to a bare metal stent; however, the focus was only on patients with high bleeding risk and single antiplatelet therapy followed by DAPT that was not limited to aspirin[8]. In contrast, the One-Month DAPT trial showed the non-inferiority of 1-month DAPT after PF-DCS compared to 6-12-month DAPT after BP-DES in patients undergoing PCI for non-complex lesions. Furthermore, the trial was not restricted to those with high bleeding risk and single antiplatelet therapy followed by DAPT that was limited to aspirin in both groups, and it included 1,828 (60.5%) patients with stable CAD and 1,192 (39.5%) patients with ACS.

In general, a shorter duration of DAPT after DES implantation is recommended in patients with stable CAD than in patients with ACS[1-3,12]. However, the effects of experimental antiplatelet therapy strategy with short-term DAPT followed by single antiplatelet therapy according to clinical presentation are not clearly elucidated. In the STOPDAPT-2 trial, which evaluated the impact of an experimental antiplatelet therapy strategy (1-month DAPT followed by clopidogrel monotherapy) vs a conventional strategy

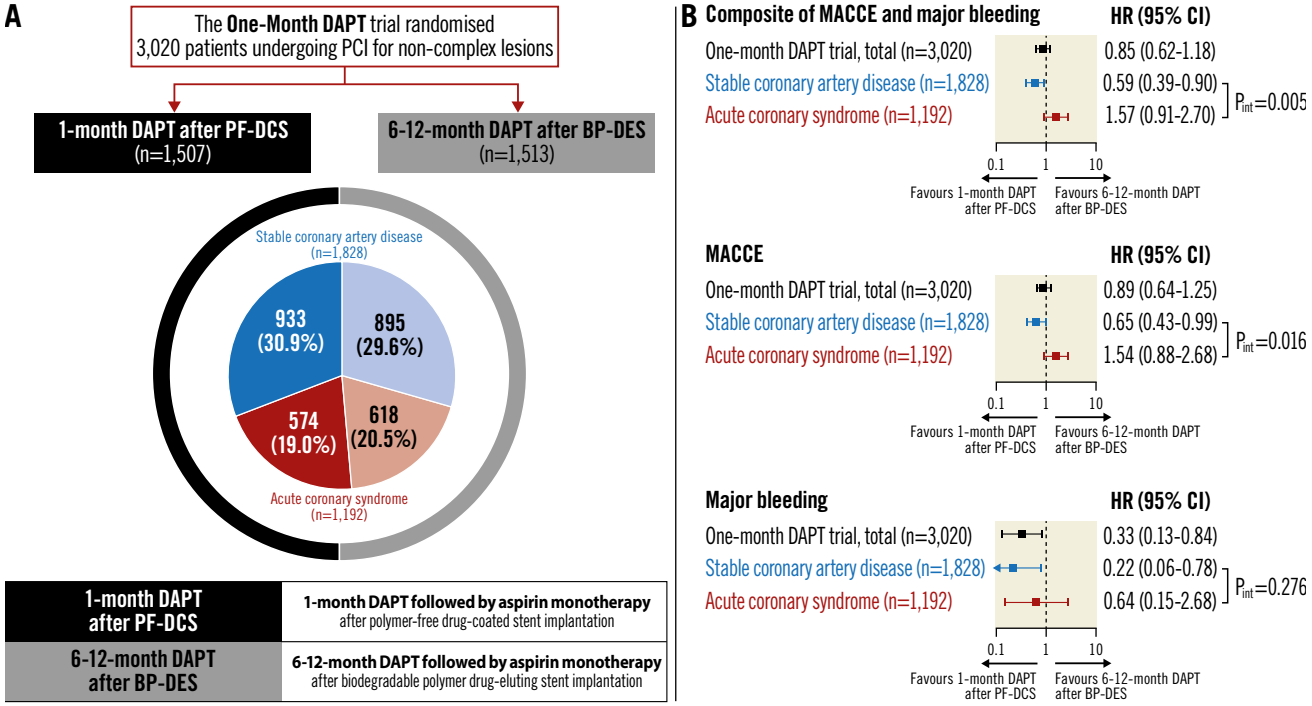
Table 3. Clinical outcomes by clinical presentation and therapy strategy.

Clinical outcomes	Stable CAD (n=1,828)			ACS (n=1,192)			*p*-value for interaction[b]
	1-month DAPT after PF-DCS (n=933)	6-12-month DAPT after BP-DES (n=895)	HR (95% CI)	1-month DAPT after PF-DCS (n=574)	6-12-month DAPT after BP-DES (n=618)	HR (95% CI)	
Primary outcome							
Composite of major adverse cardiac and cerebrovascular events[a] and major bleeding	36 (3.9)	58 (6.5)	0.59 (0.39-0.90)	32 (5.6)	22 (3.6)	1.57 (0.91-2.70)	0.005
Secondary outcome							
Ischaemic outcome							
Major adverse cardiac and cerebrovascular events	36 (3.9)	53 (6.0)	0.65 (0.43-0.99)	30 (5.3)	21 (3.4)	1.54 (0.88-2.68)	0.016
Composite of cardiac death, non-fatal myocardial infarction, target vessel revascularisation, and ischaemic stroke	33 (3.6)	46 (5.2)	0.69 (0.44-1.07)	29 (5.1)	17 (2.8)	1.84 (1.01-3.35)	0.010
All-cause death	11 (1.2)	13 (1.5)	0.81 (0.37-1.82)	2 (0.3)	7 (1.1)	0.31 (0.06-1.47)	0.275
Cardiac death	5 (0.5)	6 (0.7)	0.80 (0.25-2.63)	1 (0.2)	4 (0.7)	0.27 (0.03-2.40)	0.388
Non-fatal myocardial infarction	11 (1.2)	14 (1.6)	0.76 (0.34-1.66)	6 (1.1)	8 (1.3)	0.80 (0.28-2.31)	0.929
Target vessel revascularisation	21 (2.3)	29 (3.3)	0.69 (0.40-1.22)	20 (3.5)	10 (1.7)	2.15 (1.01-4.59)	0.019
Stent thrombosis	7 (0.8)	8 (0.9)	0.84 (0.31-2.32)	4 (0.7)	4 (0.7)	1.07 (0.27-4.29)	0.783
Definite	4	4		3	2		
Probable	3	4		1	2		
Stroke	6 (0.6)	11 (1.3)	0.52 (0.19-1.42)	7 (1.2)	5 (0.8)	1.50 (0.48-4.72)	0.176
Ischaemic	3	4		6	1		
Haemorrhagic	3	7		1	4		
Bleeding outcome							
Major bleeding	3 (0.3)	13 (1.5)	0.22 (0.06-0.78)	3 (0.5)	5 (0.8)	0.64 (0.15-2.68)	0.276
Major or minor bleeding	14 (1.5)	23 (2.6)	0.59 (0.30-1.14)	12 (2.1)	15 (2.5)	0.86 (0.40-1.83)	0.462

Data are presented as n (% of the cumulative rates at 12 months according to Kaplan-Meier event rates). [a]Major adverse cardiac and cerebrovascular events included the composite of cardiac death, non-fatal myocardial infarction, target vessel revascularisation, and stroke. [b]P-values from Cox regression test of therapy x clinical presentation interaction. ACS: acute coronary syndrome; BP-DES: biodegradable polymer drug-eluting stent; CAD: coronary artery disease; CI: confidence interval; DAPT: dual antiplatelet therapy; HR: hazard ratio; PF-DCS: polymer-free drug-coated stent

(12-month DAPT) after cobalt-chromium everolimus-eluting stent implantation, the experimental strategy was superior for the primary (composite of ischaemic and bleeding) and bleeding (TIMI major or minor) outcomes, whereas it was comparable for ischaemic outcomes (cardiovascular death, myocardial infarction, stroke, or definite stent thrombosis)[4]. While no significant interaction between therapy and clinical presentation was observed regarding the primary outcome (P_{int}=0.64), the interaction regarding ischaemic or bleeding outcome was not addressed[4]. In the GLOBAL-LEADERS trial, which evaluated the impact of an experimental antiplatelet therapy strategy (1-month DAPT followed by 23 months of ticagrelor monotherapy) vs a conventional strategy (12-month DAPT followed by 12 months aspirin monotherapy) after biodegradable polymer-based biolimus A9-eluting stent implantation, the two strategies were comparable in ischaemic (all-cause death or new Q-wave myocardial infarction) and bleeding (Bleeding Academic Research Consortium [BARC] type 3 or 5) outcomes[6]. While no significant interaction between therapy and clinical presentation was observed regarding ischaemic outcomes (P_{int}=0.93), a significant interaction was observed regarding bleeding outcomes (P_{int}=0.007) with a benefit of experimental strategy present in patients with ACS (HR 0.73, 95% CI: 0.54-0.98; p=0.037), but not in stable CAD (HR 1.32, 95% CI: 0.97-1.81; p=0.081)[6]. Only the TWILIGHT trial, which examined the impact of an experimental antiplatelet therapy strategy (3-month DAPT followed by ticagrelor monotherapy) vs a conventional strategy (12-month DAPT) after locally approved DES implantation in patients with high-ischaemic or high bleeding risk,

CENTRAL ILLUSTRATION Impact of 1-month DAPT followed by aspirin monotherapy after drug-eluting stent implantation according to clinical presentation.



The present post hoc analysis of the One-Month DAPT trial investigated the impact of 1-month DAPT followed by aspirin monotherapy after PF-DCS implantation vs 6-12-month DAPT followed by aspirin monotherapy after BP-DES implantation in patients with stable CAD, compared to those with ACS. The benefits of 1-month DAPT after PF-DCS were present in patients with stable CAD, but not in those with ACS regarding primary (composite of ischaemic and bleeding) and ischaemic outcomes, and a significant interaction was observed between therapy and clinical presentation. There was no heterogeneity in the effects of 1-month DAPT after PF-DCS regarding bleeding outcomes by clinical presentation. ACS: acute coronary syndrome; BP-DES: biodegradable polymer drug-eluting stent; CAD: coronary artery disease; CI: confidence interval; DAPT: dual antiplatelet therapy; HR: hazard ratio; MACCE: major adverse cardiac and cerebrovascular events; PCI: percutaneous coronary intervention; PF-DCS: polymer-free drug-coated stent

conducted a subgroup analysis according to clinical presentation[5,22]. A significant interaction between therapy and clinical presentation was observed regarding bleeding outcomes (BARC type 2, 3, or 5; P_{int}=0.03) with the benefit of the experimental strategy more pronounced in patients with ACS (HR 0.47, 95% CI: 0.36-0.61; p<0.001) compared to stable CAD (HR 0.76, 95% CI: 0.54-1.06; p=0.011). However, no significant interaction was observed regarding ischaemic outcomes (all-cause death, myocardial infarction, or stroke; P_{int}=0.96) and similar rates were observed between the two strategies, irrespective of clinical presentation[22]. Nevertheless, the interaction between therapy and clinical presentation regarding the composite of ischaemic and bleeding outcomes was not evaluated in either the GLOBAL-LEADERS or the TWILIGHT trial. In contrast, in the One-Month DAPT trial which specifically focused on patients undergoing PCI for non-complex lesions, the composite of ischaemic and bleeding outcomes was evaluated with DAPT duration shortened to 1 month followed by $P2Y_{12}$ inhibitor discontinuation instead of aspirin discontinuation, regarding antiplatelet therapy, and only PF-DCS was used regarding DES in the experimental strategy[13]. In this *post hoc* analysis according to clinical presentation, a significant interaction between therapy and clinical presentation was observed regarding composite outcomes with a benefit of 1-month DAPT after PF-DCS present in patients with stable CAD, but not in ACS. The results were similar for ischaemic outcomes, but not for bleeding outcomes. These findings were also confirmed in 1-month landmark analyses or after excluding the patients presenting with acute myocardial infarction. Taken together, in patients undergoing PCI for non-complex lesions, although 1-month DAPT followed by aspirin monotherapy after PF-DCS implantation might not be sufficient to find a balance between ischaemic and bleeding risks in patients with ACS, it might be considered a reasonable therapeutic approach in patients with stable CAD. Our findings are in line with a previous meta-analysis that included relatively low-ischaemic risk patients treated with DES and demonstrated different effects of short-term DAPT according to clinical presentation[23].

Compared to prolonged DAPT, short-term DAPT appeared to be safe in patients with stable CAD, whereas it was associated with higher ischaemic risk in patients with ACS[23]. Short-term DAPT was associated with lower bleeding risk regardless of clinical presentation[23]. Similarly, the recently published STOPDAPT-2 ACS trial failed to show non-inferiority of 1-2-month DAPT followed by clopidogrel monotherapy compared to 12-month DAPT regarding the composite of ischaemic and bleeding outcomes, due to numerically higher incidence of ischaemic events in spite of lower incidence of bleeding events in ACS patients undergoing PCI[11].

In this study, the benefit of short-term DAPT in patients with stable CAD was not only due to a decrease in bleeding events, but also a decrease in ischaemic events. A similar trend of decreased ischaemic events along with decreased bleeding events with short-term DAPT was also observed in previous studies of STOPDAPT-2 and a secondary analysis of the TWILIGHT trial regarding the diabetes mellitus subgroup[4,24]. These findings may imply that bleeding and ischaemic events are not independent; instead, they are interlinked events. This interlinked feature between bleeding and ischaemic events is also in line with previous studies which demonstrated that high bleeding risk based on the Predicting Bleeding Complications in Patients Undergoing Stent Implantation and Subsequent Dual Antiplatelet Therapy (PRECISE-DAPT) score or the Academic Research Consortium for high bleeding risk (ARC-HBR) criteria were associated with higher bleeding events as well as ischaemic events when validated for a large unselected cohort of the Bern PCI registry[25,26]. In this respect, as found in patients with stable CAD undergoing PCI for non-complex lesions in the One-Month DAPT trial, the strategy of 1-month DAPT followed by aspirin monotherapy which primarily aimed to decrease bleeding events may also have been beneficial in decreasing ischaemic events. However, even in patients undergoing PCI for non-complex lesions, those presenting with ACS may require a longer duration of DAPT or more potent single antiplatelet agents after a shorter duration of DAPT compared to those with stable CAD[1-3].

Study limitations

This study has several limitations. First, the therapy strategies used in the One-Month DAPT trial consisted of different antiplatelet therapies combined with different DES between the two groups. Although this may be distinct from previous trials regarding the experimental strategy, a careful interpretation of our findings is required. Second, randomisation was not stratified by clinical presentation in the One-Month DAPT trial and this might have contributed to imbalances in the number of patients allocated to each therapy group within the patients with stable CAD and ACS. Third, although stable CAD or ACS subgroups were not individually powered to yield conclusions on the effect of 1-month DAPT, with a low proportion of patients with acute myocardial infarction, a significant interaction was observed between therapy and clinical presentation regarding the primary outcome. Fourth, the general application of our findings to patients undergoing PCI needs caution since the study was primarily based on patients with non-complex lesions. Therefore, our findings need to be considered only as hypothesis-generating and warrant further prospective confirmation.

Conclusions

In patients undergoing PCI for non-complex lesions, the benefits of 1-month DAPT followed by aspirin monotherapy after PF-DCS implantation compared to 6-12-month DAPT followed by aspirin monotherapy after BP-DES implantation, with respect to the composite of ischaemic and bleeding outcomes, were different according to clinical presentation. The benefits were present in patients with stable CAD, but not in those with ACS. Given that this is a *post hoc* analysis based on the One-Month DAPT trial, current findings should be considered as hypothesis-generating and require further prospective trials.

Impact on daily practice

After PCI, it is necessary to determine the appropriate minimal duration of DAPT to achieve a balance between bleeding and ischaemic risks, which may differ according to clinical presentation. In patients undergoing percutaneous coronary intervention for non-complex lesions, the benefits of 1-month DAPT followed by aspirin monotherapy after PF-DCS implantation regarding a composite of ischaemic and bleeding outcomes were different according to clinical presentation; the benefits were present in patients with stable CAD, but not in those with ACS. However, these findings of a *post hoc* analysis need to be considered as hypothesis-generating.

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Conflict of interest statement

The authors have no conflicts of interest to declare.

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Supplementary data

Supplementary Table 1. Clinical outcomes by clinical presentation and therapy strategy in 1-month landmark analyses.

Supplementary Table 2. Clinical outcomes by clinical presentation and therapy strategy after excluding the patients with acute myocardial infarction at index PCI.

Supplementary Figure 1. Risk for MACCE and major bleeding by clinical presentation and therapy strategy in 1-month landmark analyses.

Supplementary Figure 2. Risk for clinical outcomes by clinical presentation and therapy strategy after excluding the patients with acute myocardial infarction at index PCI.

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Supplementary data

Supplementary Table 1. Clinical outcomes by clinical presentation and therapy strategy in 1-month landmark analyses.

Clinical outcomes	Stable CAD			ACS			p-value for interaction[b]
	1-month DAPT after PF-DCS	6–12-month DAPT after BP-DES	HR (95% CI)	1-month DAPT after PF-DCS	6–12-month DAPT after BP-DES	HR (95% CI)	
Primary outcome							
Composite of major adverse cardiac and cerebrovascular events[a] and major bleeding	29/924 (3.2)	49/885 (5.6)	0.56 (0.36-0.89)	28/569 (5.0)	17/612 (2.8)	1.77 (0.97-3.24)	0.003
Secondary outcome							
Ischaemic outcome							
Major adverse cardiac and cerebrovascular events	29/924 (3.2)	45/886 (5.1)	0.62 (0.39-0.98)	26/569 (4.6)	16/612 (2.6)	1.75 (0.94-3.26)	0.009
Composite of cardiac death, non-fatal myocardial infarction, target vessel revascularisation, and ischaemic stroke	27/924 (3.0)	38/886 (4.3)	0.68 (0.42-1.11)	25/569 (4.4)	12/612 (2.0)	2.25 (1.13-4.47)	0.006
All-cause death	7/927 (0.8)	11/892 (1.2)	0.61 (0.24-1.58)	1/572 (0.2)	5/615 (0.8)	0.21 (0.03-1.83)	0.347
Cardiac death	2/927 (0.2)	4/892 (0.5)	0.48 (0.09-2.63)	0/572	2/615 (0.3)	-	-
Non-fatal myocardial infarction	7/924 (0.8)	9/887 (1.0)	0.75 (0.28-2.01)	5/571 (0.9)	4/612 (0.7)	1.33 (0.36-4.95)	0.491
Target vessel revascularisation	18/925 (2.0)	25/888 (2.9)	0.69 (0.38-1.27)	19/571 (3.3)	9/615 (1.5)	2.26 (1.02-5.01)	0.020

Stent thrombosis	3/925 (0.3)	6/891 (0.7)	0.48 (0.12-1.93)	2/571 (0.4)	1/614 (0.2)	2.13 (0.19-23.52)	0.293
Definite	1	3		2	1		
Probable	2	3		0	0		
Stroke	4/927 (0.4)	11/892 (1.3)	0.35 (0.11-1.10)	5/570 (0.9)	5/615 (0.8)	1.07 (0.31-3.69)	0.194
Ischaemic	2	4		4	1		
Haemorrhagic	2	7		1	4		
Bleeding outcome							
Major bleeding	2/927 (0.2)	12/891 (1.4)	0.16 (0.04-0.71)	3/572 (0.5)	5/615 (0.8)	0.64 (0.15-2.68)	0.190
Major or minor bleeding	9/923 (1.0)	18/887 (2.1)	0.48 (0.22-1.07)	8/568 (1.4)	10/610 (1.7)	0.85 (0.34-2.16)	0.362

Data are presented as number of patients with event/number of patients at risk (% of the cumulative rates at 12 months according to Kaplan-Meier event rates).

ACS: acute coronary syndrome; BP-DES: biodegradable polymer drug-eluting stent; CAD: coronary artery disease; CI: confidence interval; DAPT: dual antiplatelet therapy; HR, hazard ratio; PF-DCS: polymer-free drug-coated stent.

[a]Major adverse cardiac and cerebrovascular events included the composite of cardiac death, nonfatal myocardial infarction, target-vessel revascularisation, and stroke.

[b]P-values from Cox regression test of therapy × clinical presentation interaction.

Supplementary Table 2. Clinical outcomes by clinical presentation and therapy strategy after excluding the patients with acute myocardial infarction at index PCI.

Clinical outcomes	Stable CAD (n=1,828)			ACS (n=1,104)			p-value for interaction[b]
	1-month DAPT after PF-DCS (n=933)	6–12-month DAPT after BP-DES (n=895)	HR (95% CI)	1-month DAPT after PF-DCS (n=534)	6–12-month DAPT after BP-DES (n=570)	HR (95% CI)	
Primary outcome							
Composite of major adverse cardiac and cerebrovascular events[a] and major bleeding	36 (3.9)	58 (6.5)	0.59 (0.39-0.90)	27 (5.1)	16 (2.8)	1.80 (0.97-3.34)	0.003
Secondary outcome							
Ischaemic outcome							
Major adverse cardiac and cerebrovascular events	36 (3.9)	53 (6.0)	0.65 (0.43-0.99)	25 (4.7)	15 (2.7)	1.78 (0.94-3.37)	0.010
Composite of cardiac death, non-fatal myocardial infarction, target-vessel revascularisation, and ischaemic stroke	33 (3.6)	46 (5.2)	0.69 (0.44-1.07)	24 (4.5)	11 (2.0)	2.33 (1.14-4.76)	0.004
All-cause death	11 (1.2)	13 (1.5)	0.81 (0.37-1.82)	2 (0.4)	4 (0.7)	0.53 (0.10-2.90)	0.654
Cardiac death	5 (0.5)	6 (0.7)	0.80 (0.25-2.63)	1 (0.2)	1 (0.2)	1.07 (0.07-17.08)	0.854
Non-fatal myocardial infarction	11 (1.2)	14 (1.6)	0.76 (0.34-1.66)	5 (0.9)	3 (0.5)	1.77 (0.42-7.39)	0.307
Target-vessel revascularisation	21 (2.3)	29 (3.3)	0.69 (0.40-1.22)	17 (3.2)	6 (1.1)	3.02 (1.19-7.65)	0.008

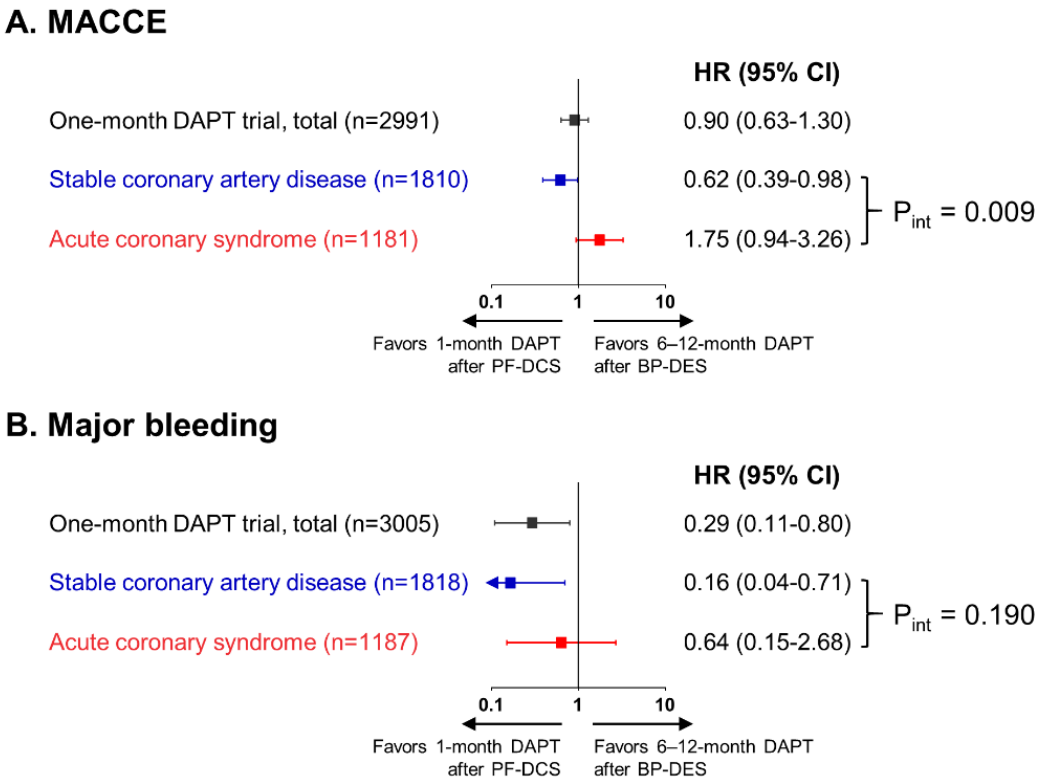
Stent thrombosis	7 (0.8)	8 (0.9)	0.84 (0.31-2.32)	3 (0.6)	1 (0.2)	3.19 (0.33-30.69)	0.292
Definite	4	4		2	0		
Probable	3	4		1	1		
Stroke	6 (0.6)	11 (1.3)	0.52 (0.19-1.42)	5 (0.9)	5 (0.9)	1.06 (0.31-3.67)	0.384
Ischaemic	3	4		4	1		
Haemorrhagic	3	7		1	4		
Bleeding outcome							
Major bleeding	3 (0.3)	13 (1.5)	0.22 (0.06-0.78)	3 (0.6)	5 (0.9)	0.64 (0.15-2.66)	0.278
Major or minor bleeding	14 (1.5)	23 (2.6)	0.59 (0.30-1.14)	12 (2.3)	11 (1.9)	1.16 (0.51-2.63)	0.203

Data are presented as n (% of the cumulative rates at 12 months according to Kaplan-Meier event rates).

ACS: acute coronary syndrome; BP-DES: biodegradable polymer drug-eluting stent; CAD: coronary artery disease; CI: confidence interval; DAPT: dual antiplatelet therapy; HR: hazard ratio; PF-DCS: polymer-free drug-coated stent; PCI: percutaneous coronary intervention.

[a]Major adverse cardiac and cerebrovascular events included the composite of cardiac death, non-fatal myocardial infarction, target-vessel revascularisation, and stroke.

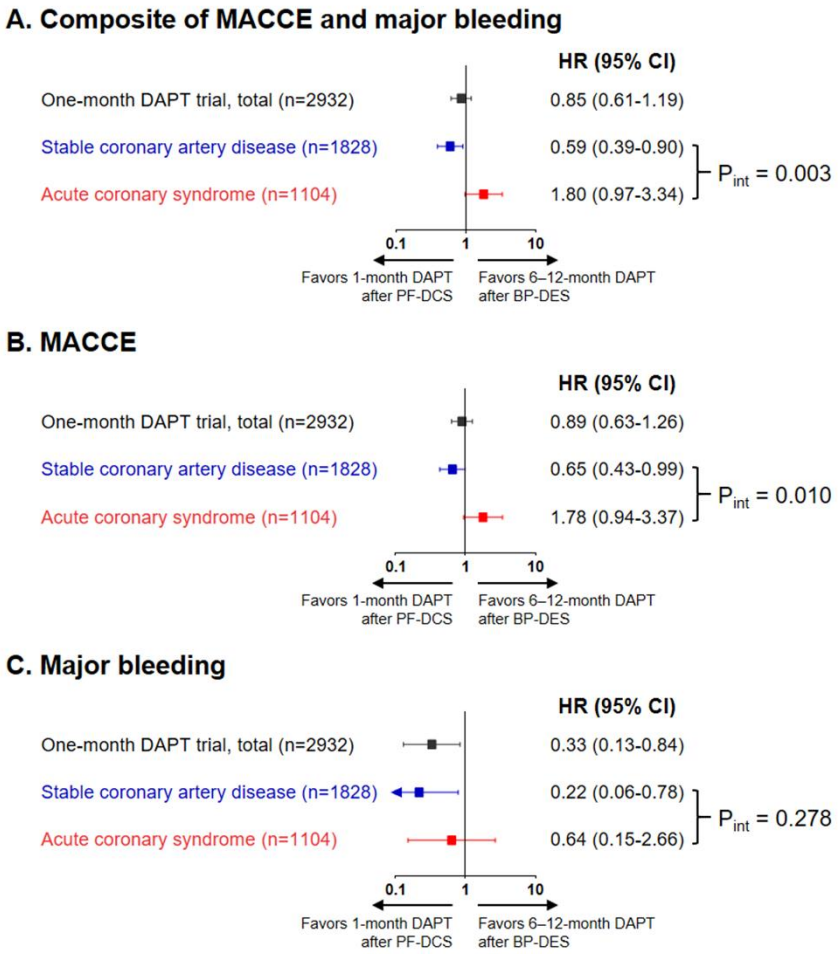
[b]P-values from Cox regression test of therapy × clinical presentation interaction.



Supplementary Figure 1. Risk for MACCE and major bleeding by clinical presentation and therapy strategy in 1-month landmark analyses.

Relative risk for (A) MACCE and (B) major bleeding by clinical presentation and therapy strategy. P_{int} indicates p-values from Cox regression test of therapy × clinical presentation interaction.

BP-DES: biodegradable polymer drug-eluting stent; CI: confidence interval; DAPT: dual antiplatelet therapy; HR: hazard ratio; MACCE: major adverse cardiac and cerebrovascular events; PF-DCS: polymer-free drug-coated stent.



Supplementary Figure 2. Risk for clinical outcomes by clinical presentation and therapy strategy after excluding the patients with acute myocardial infarction at index PCI. Relative risk for (A) primary outcome, (B) MACCE, and (C) major bleeding by clinical presentation and therapy strategy. P_{int} indicates p-values from Cox regression test of therapy × clinical presentation interaction.

BP-DES: biodegradable polymer drug-eluting stent; CI: confidence interval; DAPT: dual antiplatelet therapy; HR: hazard ratio; MACCE: major adverse cardiac and cerebrovascular events; PF-DCS: polymer-free drug-coated stent; PCI: percutaneous coronary intervention.