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ORIGINAL ARTICLE
Thrombosis and antithrombotic therapy

Aspirin vs. clopidogrel monotherapy beyond 1 month after complex percutaneous coronary intervention: a pre-specified subgroup analysis of the STOPDAPT-3 trial

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Aims There were no previous studies comparing aspirin vs. $P2Y_{12}$ inhibitor monotherapy following short dual antiplatelet therapy (DAPT) after complex percutaneous coronary intervention (PCI).

Methods and results We conducted a pre-specified subgroup analysis based on complex PCI in the 1-year results of the STOPDAPT-3 (ShorT and OPtimal Duration of Dual AntiPlatelet Therapy-3) trial, which randomly compared 1-month DAPT followed by aspirin monotherapy (aspirin group) with 1-month prasugrel monotherapy followed by clopidogrel monotherapy (clopidogrel group). The main analysis in the present study was the 30-day landmark analysis. The co-primary endpoints were cardiovascular events (a composite of cardiovascular death, myocardial infarction, definite stent thrombosis, or stroke) and major bleeding (Bleeding Academic Research Consortium 3 or 5). In the 30-day landmark analysis ($N = 5833$), there were 1415 patients (24.3%) who underwent complex PCI. There was a significant interaction between complex PCI and the effect of the aspirin group relative to the clopidogrel group for cardiovascular events (complex PCI: 3.3% vs. 5.2%, non-complex PCI: 4.3% vs. 3.6%, interaction $P = 0.04$) and net adverse clinical events (complex PCI: 4.8% vs. 7.2%, non-complex PCI: 5.3% vs. 4.4%, interaction $P = 0.02$), but not for bleeding events (complex PCI: 2.1% vs. 2.7%, non-complex PCI: 1.7% vs. 1.4%, interaction $P = 0.35$).

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Conclusions There was a significant interaction between complex PCI and the effect of aspirin monotherapy relative to clopidogrel monotherapy beyond 1 month and up to 1 year for cardiovascular events due to numerically lower risk of aspirin monotherapy in patients with complex PCI, while the effect of aspirin monotherapy relative to clopidogrel monotherapy was not different for bleeding regardless of complex PCI.

Clinical trial registration ShorT and OPtimal duration of Dual AntiPlatelet Therapy after everolimus-eluting cobalt-chromium stent-3 [STOPDAPT-3]; NCT04609111.

Keywords Antiplatelet therapy • Coronary stent • Percutaneous coronary intervention • Procedural complexity

Introduction

Several randomized clinical trials have suggested that the strategy of short duration of dual antiplatelet therapy (DAPT) up to 1–3 months followed by $P2Y_{12}$ inhibitor monotherapy reduced major bleeding events without increasing cardiovascular events after percutaneous coronary intervention (PCI).[1–5] However, the procedural complexity of PCI has been acknowledged as a determinant for cardiovascular events, and short DAPT compared with prolonged DAPT has been reported to increase the risk of cardiovascular events after complex PCI.[6] On the other hand, another study showed that $P2Y_{12}$ inhibitor monotherapy after very short DAPT compared with standard DAPT did not increase cardiovascular events regardless of complex PCI.[7,8] As of now, there are no data regarding the optimal antiplatelet monotherapy after very short DAPT in patients who underwent complex PCI. Recently, 1-year results of the STOPDAPT-3 (ShorT and OPtimal Duration of Dual AntiPlatelet Therapy-3) trial reported that aspirin monotherapy compared with clopidogrel monotherapy was associated with comparable cardiovascular and bleeding outcomes beyond 1 month and up to 1 year after PCI.[9,10] In the present study, we conducted a pre-specified subgroup analysis stratified by complex and non-complex PCI using the 1-year follow-up data from the STOPDAPT-3 trial.

Methods

Study design and population

The STOPDAPT-3 (NCT04609111) was a physician-initiated, prospective, multicentre, open-label, adjudicator blinded randomized clinical trial, where we compared the group of 1-month prasugrel monotherapy followed by clopidogrel monotherapy with the group of 1-month DAPT followed by aspirin monotherapy in patients planned for PCI in terms of cardiovascular and bleeding endpoints. The details for the study design and the overall results at 30 days and at 1 year were previously reported (Supplemental Appendix A–B).[9,10] Briefly, the trial enrolled patients with acute coronary syndrome or those with high bleeding risk by the criteria of the Academic Research Consortium irrespective of acute coronary syndrome who were planned for PCI with cobalt–chromium everolimus-eluting stents (Xience series, ABBOTT vascular). Patients were randomly assigned in a one-to-one fashion to the 1-month aspirin-free prasugrel monotherapy or the 1-month DAPT with aspirin and prasugrel. At 1 month (between 30 and 59 days after the index PCI), patients who had received DAPT were switched to aspirin (81–100 mg/day) monotherapy (aspirin group), and patients who had received prasugrel monotherapy were switched to clopidogrel (75 mg/day) monotherapy (clopidogrel group). Each group of patients were to continue the assigned antiplatelet monotherapy up to 1 year. The ethics committees in all the participating centres approved the study protocol, and informed consent was obtained from all patients.

Application of complex percutaneous coronary intervention criteria

The present study was the pre-specified subgroup analysis stratified by the complex and non-complex PCI. In the present study, patients were divided into two subgroups based on the complex PCI criteria. Giustino et al.[6] proposed procedural complexity criteria called 'complex PCI', and the criteria were endorsed by the clinical guidelines of the European Society of Cardiology and the Japanese Circulation Society.[11,12] Complex PCI was defined as a procedure at the index PCI and the staged PCI with at least one of the following procedural criteria: 3 vessels treated, $\geq$3 stents implanted, $\geq$3 lesions treated, bifurcation with 2 stents implanted, total stent length >60 mm, or chronic total occlusion as the target lesion.[6] The definition of complex PCI was consistent with that in our previous publications on this issue.[8,13]

Endpoints

The co-primary cardiovascular endpoint was a composite of cardiovascular death, myocardial infarction, definite stent thrombosis, or ischaemic stroke, and the co-primary bleeding endpoint was major bleeding defined as the Bleeding Academic Research Consortium (BARC) type 3 or 5.[14] The major secondary endpoint was a composite of cardiovascular death, myocardial infarction, definite stent thrombosis, ischaemic stroke, or major bleeding (BARC 3 or 5), which represented net adverse clinical events for cardiovascular and bleeding events. Myocardial infarction and stent thrombosis were defined by the Academic Research Consortium criteria.[15] The definitions of other secondary endpoints are described in the supplemental materials (Supplemental Appendix C–D). The independent clinical event committee adjudicated all the clinical events in a blinded fashion to the assigned group.

Statistical analysis

The main analysis in the present study was the 30-day landmark analysis for the comparison between aspirin and clopidogrel monotherapy beyond 30 days and up to 1 year. In the 30-day landmark analysis, we excluded those patients who had the endpoint event of interest before 30 days, and thus the number of patients included in the 30-day landmark analysis was different according to the endpoint event of interest. We also conducted the overall 1-year analysis evaluating throughout 1 year. The overall 1-year analysis set consisted of 5962 patients after excluding 3 patients who did not receive PCI for the absence of suitable coronary lesions, and 37 patients who withdrew consent (*Figure 1*). The 30-day landmark analysis set consisted of 5833 patients after excluding 129 patients who died by 30 days or lost to follow-up at 30 days (*Figure 1*).

Categorical variables were presented as number and percentage and were compared using the χ^2 test. Continuous variables were expressed as mean ± standard deviation or median with interquartile range and were compared using Student's *t*-test or the Wilcoxon rank-sum test depending on their distributions. The cumulative incidences of the endpoints were estimated by the Kaplan–Meier method. The effects of patients with

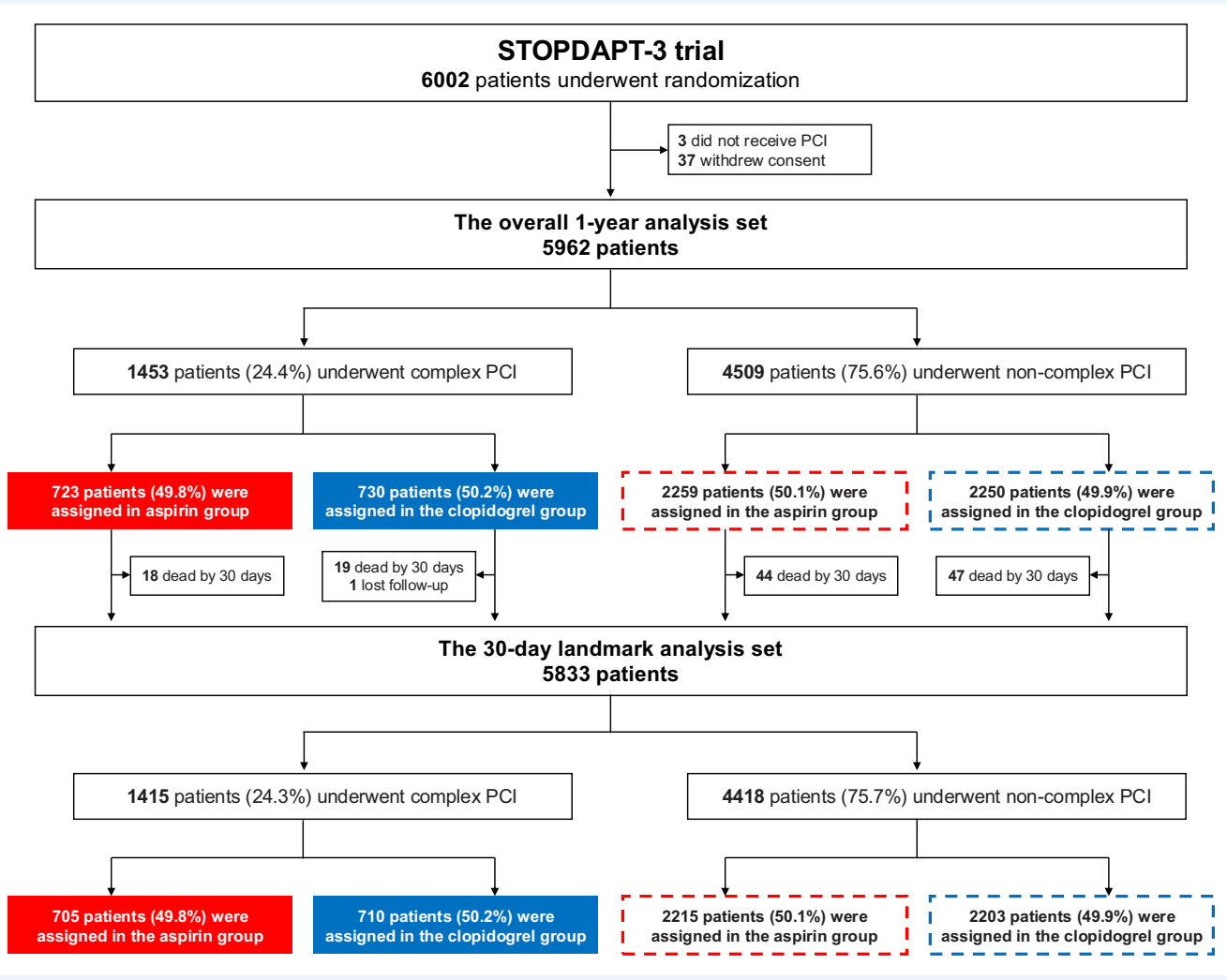


Figure 1 Study flow. PCI, percutaneous coronary intervention.

complex PCI relative to those with non-complex PCI, and the effects of the aspirin group relative to the clopidogrel group for the endpoints were expressed as hazard ratios (HRs) with 95% confidence intervals (CIs) by the Cox proportional hazard model. In the present study, we analysed the treatment-by-subgroup interactions in the effects of the aspirin group compared with the clopidogrel group in complex PCI and non-complex PCI subgroups. All reported *P* values were two-sided. *P* values <0.05 were considered statistically significant. All analysis was performed with R version 4.2.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Study population

Among 5833 patients in the 30-day landmark analysis, there were 1415 patients (24.3%) who underwent complex PCI (aspirin group: $N = 705$, and clopidogrel group: $N = 710$), and 4418 patients (75.7%) who underwent non-complex PCI (aspirin group: $N = 2215$, and clopidogrel group: $N = 2203$) (*Figure 1*). Regarding the criteria for complex PCI, >60 mm total stent length (19.4%) and ≥3 stents implanted (12.1%) were more prevalent than other criteria, whereas bifurcation with 2 stents (1.2%) was less prevalent than other criteria (*Table 1*).

Baseline characteristics

Among 5833 patients in the 30-day landmark analysis, patients with complex PCI were older and more often men compared with those without (*Table 2*). Patients with complex PCI less often presented as acute coronary syndrome, but more often had acute heart failure compared with those without. Patients with complex PCI more often had comorbidities such as history of heart failure, hypertension, hyperlipidaemia, diabetes, left ventricular systolic dysfunction, anaemia, and chronic kidney disease than those without. The prevalence of the high bleeding risk by the criteria of the Academic Research Consortium was higher in patients with complex PCI than in those without. Procedural characteristics were largely different between patients with and without complex PCI. The rate of intracoronary imaging use was >90% regardless of complex PCI. In terms of medications, total heparin dose during the index PCI was slightly higher in patients with complex PCI than in those without. The prescription rates of mineralocorticoid receptor antagonist and β-blockers were higher in patients with complex PCI than in those without. Baseline characteristics in the overall 1-year analysis are shown in Supplementary material online, *Table S1*.

Baseline characteristics were well balanced between the aspirin and clopidogrel groups regardless of complex PCI, except for the higher

Table 1 Prevalence of complex percutaneous coronary intervention

	(A) 30-day landmark analysis set			(B) Overall 1-year analysis set		
	Overall N = 5833	Aspirin group N = 2920	Clopidogrel group N = 2913	Overall N = 5962	Aspirin group N = 2982	Clopidogrel group N = 2980
Target of 3 vessels	263 (4.5)	135 (4.6)	128 (4.4)	264 (4.4)	135 (4.5)	129 (4.3)
≥3 stents implanted	707 (12.1)	354 (12.1)	353 (12.1)	720 (12.1)	359 (12.0)	361 (12.1)
≥3 lesions treated	481 (8.2)	241 (8.3)	240 (8.2)	485 (8.1)	242 (8.1)	243 (8.2)
Bifurcation with two stents	72 (1.2)	32 (1.1)	40 (1.4)	78 (1.3)	34 (1.1)	44 (1.5)
Total stent length >60 mm	1109 (19.4)	556 (19.3)	553 (19.4)	1141 (19.5)	471 (19.5)	570 (19.6)
Target of chronic total occlusion	283 (4.9)	148 (5.1)	135 (4.6)	285 (4.8)	149 (5.0)	136 (4.6)
Complex PCI	1415 (24.3)	705 (24.1)	710 (24.4)	1453 (24.3)	723 (24.2)	730 (24.5)

PCI, percutaneous coronary intervention.

prescription rate of proton pump inhibitors in the aspirin group than in the clopidogrel group in the 30-day landmark and the overall 1-year analyses (see Supplementary material online, *Tables S2* and *S3*).

As we previously reported, the vast majority of the study patients received the assigned antiplatelet therapy according to the study protocol. Nevertheless, the prescription rate of the assigned antiplatelet therapy was numerically lower and the prescription rate of DAPT beyond 30 days was numerically higher in patients with complex PCI than in those without (see Supplementary material online, *Figure S1*).

Clinical outcomes: complex percutaneous coronary intervention vs. non-complex percutaneous coronary intervention

In the overall 1-year analysis, the cumulative incidence of the co-primary cardiovascular endpoint at 1 year was higher in patients with complex PCI than in those without (9.1% vs. 7.3%, HR, 1.27; 95% CI, 1.03–1.55; $P = 0.02$), whereas it was not different between patients with and without complex PCI in the 30-day landmark analysis (4.3% vs. 3.9%, HR, 1.09; 95% CI, 0.81–1.47; $P = 0.58$) (see Supplementary material online, *Tables S4* and *S5*). The cumulative incidences of the myocardial infarction and coronary revascularization were higher in patients with complex PCI than in those without in the overall 1-year and 30-day landmark analyses (see Supplementary material online, *Tables S4* and *S5*).

In the overall 1-year analysis, the cumulative incidence of the co-primary bleeding endpoint at 1 year was not different between patients with and without complex PCI (7.0% vs. 6.1%, HR, 1.14; 95% CI, 0.91–1.44; $P = 0.25$), whereas it was higher in patients with complex PCI than in those without in the 30-day landmark analysis (2.4% vs. 1.6%, HR, 1.54; 95% CI 1.01–2.36; $P = 0.04$) (see Supplementary material online, *Tables S4* and *S5*).

Clinical outcomes in the 30-day landmark analysis: aspirin group vs. clopidogrel group in patients with and without complex percutaneous coronary intervention

In the 30-day landmark analysis, the cumulative incidence of the co-primary cardiovascular endpoint at 1 year was 3.3% in the aspirin group and 5.2% in the clopidogrel group in patients with complex PCI (HR, 0.52; 95% CI, 0.36–1.05; $P = 0.08$), while it was 4.3% in the aspirin group and 3.6% in the clopidogrel group in patients without complex PCI (HR, 1.18; 95% CI 0.87–1.60; $P = 0.27$) (*Figure 2A*). There was a significant treatment-by subgroup interaction in patients with and without complex PCI for the co-primary cardiovascular endpoint (P for interaction = 0.04). The cumulative incidence of definite stent thrombosis at 1 year was 0.3% in the aspirin group and 0.1% in the clopidogrel group in patients with complex PCI, while it was 0.1% in the aspirin group and 0.1% in the clopidogrel group in patients without complex PCI (*Table 3*).

The cumulative incidence of the co-primary bleeding endpoint at 1 year was 2.1% in the aspirin group and 2.7% in the clopidogrel group in patients with complex PCI (HR, 0.78; 95% CI, 0.39–1.56; $P = 0.48$), while it was 1.7% in the aspirin group and 1.4% in the clopidogrel group in patients without complex PCI (HR, 1.17; 95% CI, 0.72–1.90; $P = 0.54$) (*Figure 2B*). There was no significant treatment-by subgroup interaction in patients with and without complex PCI for the co-primary bleeding endpoint (P for interaction = 0.35).

Clinical outcomes in the overall 1-year analysis: aspirin group vs. clopidogrel group in patients with and without complex percutaneous coronary intervention

In the overall 1-year analysis, the cumulative incidence of the co-primary cardiovascular endpoint at 1 year was 8.3% in the aspirin group and 9.8% in the clopidogrel group in patients with complex PCI (HR, 0.85; 95% CI 0.61–1.20; $P = 0.37$), while it was 7.3% in the aspirin group and 7.3% in the clopidogrel group in patients without complex PCI (HR, 0.99; 95% CI 0.80–1.23; $P = 0.94$) (*Figure 3A*). There was no significant treatment-by subgroup interaction in patients with and without complex PCI for the co-primary cardiovascular endpoint (P for interaction = 0.47).

The cumulative incidence of the co-primary bleeding endpoint at 1 year was 6.2% in the aspirin group and 7.8% in the clopidogrel group in patients with complex PCI (HR, 0.79; 95% CI, 0.53–1.17; $P = 0.24$), while it was 6.6% in the aspirin group and 5.6% in the clopidogrel group in patients without complex PCI (HR, 1.19; 95% CI 0.94–1.52; $P = 0.15$) (*Figure 3B*). There was no significant treatment-by subgroup interaction in patients with and without complex PCI for the co-primary cardiovascular endpoint (P for interaction = 0.08).

Table 2 Baseline characteristics in the 30-day landmark analysis: complex percutaneous coronary intervention vs. non-complex percutaneous coronary intervention

	Complex PCI *N* = 1415	Non-complex PCI *N* = 4418	*P* value
Patient demographics			
Age (year)	72.2 ± 11.2	71.3 ± 11.8	0.01
≥75	669 (47.3)	1981 (44.8)	0.11
Men	1126 (79.6)	3344 (75.7)	0.003
Body mass index (kg/m^2)	24.0 ± 3.7	23.9 ± 3.8	0.39
<25	926 (65.4)	2891 (65.4)	1.00
Clinical presentation			
Acute coronary syndrome	995 (70.3)	3358 (76.0)	<0.001
ST-segment elevation myocardial infarction	570 (40.3)	1887 (42.7)	
Non-ST-segment elevation myocardial infarction	253 (17.9)	821 (18.6)	
Unstable angina	172 (12.2)	650 (14.7)	
Non-acute coronary syndrome	420 (29.7)	1060 (24.0)	<0.001
Cardiogenic shock	63 (4.5)	172 (3.9)	0.35
Current heart failure	287 (20.3)	751 (17.0)	0.01
History and comorbidities			
Prior PCI	201 (14.2)	711 (16.1)	0.09
Prior coronary artery bypass grafting	33 (2.3)	89 (2.0)	0.47
Prior myocardial infarction	105 (7.4)	346 (7.8)	0.61
Prior stroke	133 (9.4)	405 (9.2)	0.79
Prior heart failure	359 (25.4)	942 (21.3)	0.001
Atrial fibrillation	123 (8.7)	419 (9.5)	0.37
Peripheral artery disease	90 (6.4)	240 (5.4)	0.19
Hypertension	1157 (81.8)	3329 (75.4)	<0.001
Hyperlipidaemia	986 (69.7)	2951 (66.8)	0.04
Diabetes	719 (50.8)	1906 (43.1)	<0.001
With insulin therapy	100 (7.1)	213 (4.8)	0.001
Current smoker	335 (23.7)	1047 (23.7)	0.99
Left ventricular ejection fraction (%)	54.1 ± 12.2	54.9 ± 11.7	0.03
<40	153 (11.5)	371 (9.0)	0.01
Moderate or severe mitral regurgitation	36 (2.5)	107 (2.4)	0.80
Anaemia	186 (13.1)	476 (10.8)	0.01
Thrombocytopenia	18 (1.3)	51 (1.2)	0.72
Moderate chronic kidney disease	626 (44.2)	1748 (39.6)	0.002
Severe chronic kidney disease	182 (12.9)	462 (10.5)	0.01
Estimated glomerular filtration rate <30 mL/min/1.73 m^2 not on dialysis	88 (6.2)	210 (4.8)	0.03
Haemodialysis	94 (6.6)	252 (5.7)	0.19
Cancer history	152 (10.7)	439 (9.9)	0.38
ARC-HBR	815 (57.6)	2341 (53.0)	0.002
Procedural characteristics at the index PCI			
Staged PCI	861 (60.8)	347 (7.9)	<0.001
Number of procedures	2.0 (1.0–2.0)	1.0 (1.0–1.0)	<0.001
Number of target lesions	2.0 (2.0–3.0)	1.0 (1.0–1.0)	<0.001
≥3	481 (34.0)	0 (0.0)	<0.001
Target of two vessels or more	975 (68.9)	541 (12.2)	<0.001
Target of three vessels	258 (18.2)	0 (0.0)	<0.001
Target of chronic total occlusion	283 (20.0)	0 (0.0)	<0.001
Target of bifurcation lesion	633 (44.7)	1025 (23.2)	<0.001
Bifurcation with two stents	72 (5.1)	0 (0.0)	<0.001
Target lesion location			
Left main coronary artery	170 (12.0)	167 (3.8)	<0.001
Left anterior descending coronary artery	999 (70.6)	2499 (56.6)	<0.001

Table 2 Continued

	Complex PCI *N* = 1415	Non-complex PCI *N* = 4418	*P* value
Left circumflex coronary artery	572 (40.4)	770 (17.4)	<0.001
Right coronary artery	866 (61.2)	1408 (31.9)	<0.001
Bypass graft	5 (0.4)	12 (0.3)	0.62
Number of implanted stents	2.0 (2.0–3.0)	1.0 (1.0–1.0)	<0.001
≥3	707 (50.0)	0 (0.0)	<0.001
Minimal stent diameter (mm)	2.5 (2.25–3.0)	3.0 (2.5–3.5)	<0.001
Total stent length (mm)	71.0 (61.0–94.0)	28.0 (18.0–38.0)	<0.001
>60	1109 (79.0)	0 (0.0)	<0.001
Radial approach only	958 (67.7)	3547 (80.3)	<0.001
Use of intracoronary imaging	1349 (95.3)	3987 (90.2)	<0.001
Medication at the index PCI			
Loading of prasugrel	1412 (99.8)	4394 (99.5)	0.11
Loading of aspirin	581 (82.6)	1800 (81.3)	0.44
Total heparin dose (IU/kg) during PCI	129.0 (101.9–156.2)	118.5 (96.2–147.5)	<0.001
Post-procedural heparin use	614 (43.4)	1977 (44.8)	0.36
Medication at discharge			
Antiplatelet agents	1405 (99.5)	4376 (99.5)	0.93
Aspirin only	30 (2.1)	64 (1.5)	
Prasugrel only	674 (47.7)	2102 (47.8)	
DAPT	685 (48.5)	2158 (49.1)	
Aspirin/prasugrel	679 (48.1)	2146 (48.8)	
Anticoagulants	193 (13.7)	595 (13.5)	0.90
Warfarin	30 (2.1)	123 (2.8)	
Direct oral anticoagulants	163 (11.5)	472 (10.7)	
Renin–angiotensin system inhibitor	1054 (74.6)	3281 (74.6)	0.98
Angiotensin-converting enzyme inhibitor	452 (32.0)	1478 (33.6)	
Angiotensin-2 receptor blocker	494 (35.0)	1540 (35.0)	
Angiotensin receptor–neprilysin inhibitor	114 (8.1)	277 (6.3)	
Mineralocorticoid receptor antagonist	281 (19.9)	681 (15.5)	<0.001
β-Blockers	952 (67.4)	2792 (63.5)	0.01
Statins	1323 (93.7)	4111 (93.5)	0.79
High-intensity statin therapy	726 (51.4)	2097 (47.7)	0.02
Proton pump inhibitors	1239 (87.7)	3862 (87.8)	0.93

Categorical variables are presented as number and percentage. Continuous variables are presented as mean ± standard deviation or median with interquartile range.
ARC-HBR, Academic Research Consortium for high bleeding risk; DAPT, dual antiplatelet therapy; PCI, percutaneous coronary intervention.

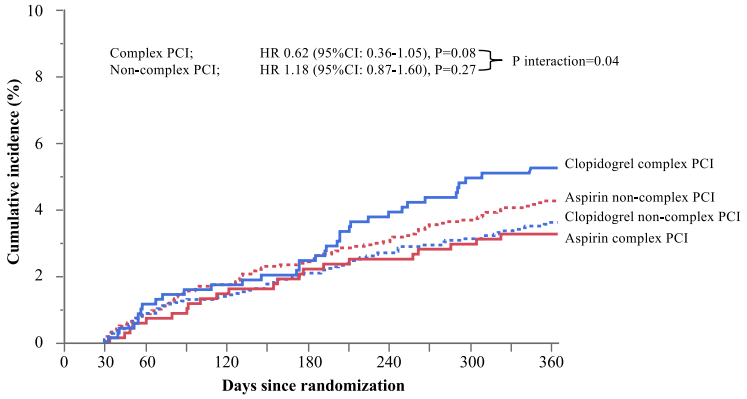
Results for the secondary endpoints in the 30-day landmark and the overall 1-year analyses are shown in *Table 3* and Supplementary material online, *Table S6*.

Discussion

The main findings in the present study were as follows: (i) The effect of aspirin monotherapy relative to clopidogrel monotherapy beyond 1 month and up to 1 year was not significant for cardiovascular events regardless of complex PCI, but there was a significant interaction between complex PCI and the effect of aspirin monotherapy relative to clopidogrel monotherapy for cardiovascular events due to numerically lower risk of aspirin monotherapy in patients with complex PCI. (ii) The effect of aspirin monotherapy relative to clopidogrel monotherapy beyond 1 month and up to 1 year was not significant for bleeding events regardless of complex PCI without significant interaction.

The European Society of Cardiology and the Japanese Circulation Society guidelines have suggested that complex PCI is a risk factor of stent-driven recurrent ischaemic events.[11,12] Indeed, patients with complex PCI had higher incidence of cardiovascular events compared with those without in the overall 1-year analysis in the present study. Giustino et al.[6] reported that prolonged DAPT (12–24 months) compared with short DAPT (3–6 months) reduced major adverse cardiac events and coronary thrombotic events after complex PCI in the individual patient data-level meta-analysis of six randomized clinical trials in which aspirin monotherapy was mainly used after stopping short DAPT. More recently, Gragnano et al.[7] showed that $P2Y_{12}$ inhibitor (ticagrelor, prasugrel, or clopidogrel) monotherapy after very short DAPT (1–3 months) compared with standard DAPT was not associated with an increased risk of cardiovascular events

(A)



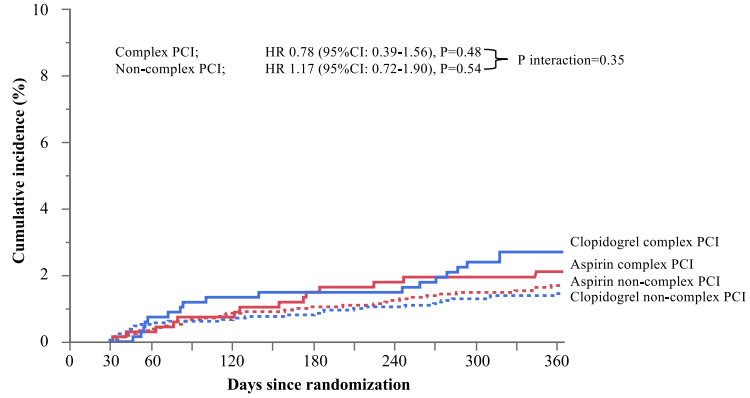
Complex PCI

Aspirin	30	60	120	180	240	300	365
Number of patients with event	0	4	10	15	17	20	22
Number of patients at risk	684	679	668	658	653	643	496
Cumulative incidence (%)	0.0	0.6	1.5	2.2	2.5	3.0	3.3
Clopidogrel	**30**	**60**	**120**	**180**	**240**	**300**	**365**
Number of patients with event	0	8	12	17	27	34	36
Number of patients at risk	693	683	676	670	658	650	507
Cumulative incidence (%)	0.0	1.2	1.7	2.5	3.9	4.9	5.2

Non-complex PCI

Aspirin	30	60	120	180	240	300	365
Number of patients with event	1	18	38	53	66	80	92
Number of patients at risk	2187	2169	2139	2115	2093	2071	1586
Cumulative incidence (%)	0.0	0.8	1.7	2.4	3.0	3.7	4.3
Clopidogrel	**30**	**60**	**120**	**180**	**240**	**300**	**365**
Number of patients with event	2	19	30	45	58	67	77
Number of patients at risk	2163	2142	2120	2094	2076	2057	1546
Cumulative incidence (%)	0.1	0.9	1.4	2.1	2.7	3.1	3.6

(B)



Complex PCI

Aspirin	30	60	120	180	240	300	365
Number of patients with event	0	2	5	10	12	13	14
Number of patients at risk	680	676	668	656	650	642	499
Cumulative incidence (%)	0.0	0.3	0.7	1.5	1.8	1.9	2.1
Clopidogrel	**30**	**60**	**120**	**180**	**240**	**300**	**365**
Number of patients with event	0	5	9	10	10	16	18
Number of patients at risk	683	671	663	659	653	643	500
Cumulative incidence (%)	0.0	0.7	1.3	1.5	1.5	2.4	2.7

Non-complex PCI

Aspirin	30	60	120	180	240	300	365
Number of patients with event	0	7	18	22	26	31	35
Number of patients at risk	2125	2107	2081	2065	2050	2036	1546
Cumulative incidence (%)	0.0	0.3	0.9	1.0	1.2	1.5	1.7
Clopidogrel	**30**	**60**	**120**	**180**	**240**	**300**	**365**
Number of patients with event	1	11	14	17	22	27	30
Number of patients at risk	2127	2106	2086	2065	2052	2035	1527
Cumulative incidence (%)	0.0	0.5	0.7	0.8	1.0	1.3	1.4

Figure 2 Kaplan–Meier curves in the 30-day landmark analysis. (*A*) co-primary cardiovascular endpoint: a composite of cardiovascular death, myocardial infarction, definite stent thrombosis, or ischaemic stroke. (*B*) co-primary bleeding endpoint: BARC 3 or 5 bleeding. BARC, Bleeding Academic Research Consortium; CI, confidence interval; DAPT, dual antiplatelet therapy; HR, hazard ratio; PCI, percutaneous coronary intervention.

Table 3 **Clinical outcomes in the 30-day landmark analysis: aspirin vs. clopidogrel stratified by complex percutaneous coronary intervention / non-complex percutaneous coronary intervention**

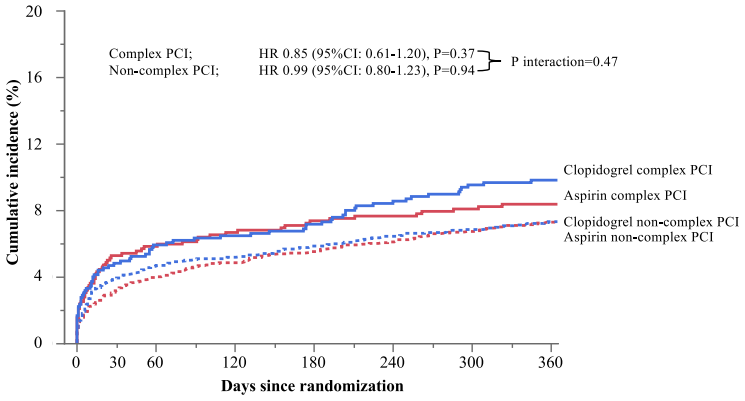
	Complex PCI			Non-complex PCI			
	Aspirin group *N* = 705	Clopidogrel group *N* = 710		Aspirin group *N* = 2215	Clopidogrel group *N* = 2203		
	Number of patients with event/number of patients (cumulative incidence at 1 year)		Hazard ratio (95% CI)	Number of patients with event/number of patients (cumulative incidence at 1 year)		Hazard ratio (95% CI)	Interaction *P*
Co-primary cardiovascular endpoint							
A composite of cardiovascular death, myocardial infarction, definite stent thrombosis, or ischaemic stroke	22/684 (3.3%)	36/693 (5.2%)	0.62 (0.36–1.05)	92/2187 (4.3%)	77/2163 (3.6%)	1.18 (0.87–1.60)	0.04
Co-primary bleeding endpoint							
BARC 3 or 5 bleeding	14/680 (2.1%)	18/683 (2.7%)	0.78 (0.39–1.56)	35/2125 (1.7%)	30/2127 (1.4%)	1.17 (0.72–1.90)	0.35
Major secondary endpoint							
A composite of cardiovascular death, myocardial infarction, definite stent thrombosis, ischaemic stroke, or BARC 3 or 5 bleeding	31/661 (4.8%)	48/670 (7.2%)	0.65 (0.42–1.03)	111/2100 (5.3%)	91/2098 (4.4%)	1.22 (0.93–1.61)	0.02
Secondary endpoints							
Death	24/705 (3.4%)	27/710 (3.8%)	0.89 (0.52–1.55)	91/2215 (4.2%)	79/2203 (3.6%)	1.14 (0.85–1.55)	0.44
Death from cardiovascular causes	8/705 (1.1%)	20/710 (2.8%)	0.40 (0.18–0.91)	50/2215 (2.3%)	46/2203 (2.1%)	1.08 (0.72–1.61)	0.03
Sudden cardiac death	2/705 (0.3%)	7/710 (1.0%)	0.29 (0.06–1.39)	21/2215 (1.0%)	9/2203 (0.4%)	2.32 (1.06–5.06)	0.02
Death from non-cardiovascular causes	16/705 (2.3%)	7/710 (1.0%)	2.30 (0.95–5.59)	41/2215 (1.9%)	33/2203 (1.5%)	1.23 (0.78–1.95)	0.22
Myocardial infarction	14/693 (2.1%)	14/700 (2.1%)	1.01 (0.48–2.13)	27/2201 (1.3%)	22/2178 (1.0%)	1.22 (0.69–2.13)	0.70
Spontaneous myocardial infarction	13/693 (1.9%)	14/700 (2.1%)	0.94 (0.44–2.00)	24/2201 (1.1%)	19/2178 (0.9%)	1.25 (0.69–2.28)	0.56
Procedural myocardial infarction	1/693 (0.1%)	0/700 (0.0%)	NA	3/2201 (0.1%)	3/2178 (0.1%)	0.99 (0.20–4.90)	NA
Myocardial infarction related to the target lesion	9/693 (1.3%)	10/700 (1.5%)	0.91 (0.37–2.24)	10/2201 (0.5%)	8/2178 (0.4%)	1.24 (0.49–3.14)	0.64
Definite or probable stent thrombosis	3/701 (0.4%)	1/706 (0.1%)	3.01 (0.31–28.95)	3/2208 (0.1%)	4/2193 (0.2%)	0.75 (0.17–3.33)	0.31
Definite	2/701 (0.3%)	1/706 (0.1%)	2.01 (0.18–22.14)	2/2208 (0.1%)	3/2193 (0.1%)	0.66 (0.11–3.97)	0.47
Probable	1/705 (0.1%)	0/710 (0.0%)	NA	1/2215 (0.0%)	1/2203 (0.0%)	0.99 (0.06–15.90)	NA
Stroke	3/696 (0.4%)	7/704 (1.0%)	0.43 (0.11–1.67)	22/2200 (1.0%)	22/2186 (1.0%)	0.99 (0.55–1.79)	0.27
Ischaemic stroke	3/696 (0.4%)	5/704 (0.7%)	0.61 (0.14–2.54)	20/2202 (0.9%)	19/2187 (0.9%)	1.05 (0.56–1.96)	0.49
Haemorrhagic stroke	0/705 (0.0%)	2/710 (0.3%)	NA	2/2213 (0.1%)	3/2202 (0.1%)	0.66 (0.11–3.96)	NA

Table 3 **Continued**

	Complex PCI			Non-complex PCI			
	Aspirin group *N* = 705	Clopidogrel group *N* = 710		Aspirin group *N* = 2215	Clopidogrel group *N* = 2203		
	Number of patients with event/number of patients (cumulative incidence at 1 year)		Hazard ratio (95% CI)	Number of patients with event/number of patients (cumulative incidence at 1 year)		Hazard ratio (95% CI)	Interaction *P*
Any coronary revascularization	39/696 (5.8%)	40/705 (5.9%)	0.99 (0.64–1.55)	87/2207 (4.1%)	85/2180 (4.0%)	1.01 (0.75–1.36)	0.96
Target lesion revascularization	19/698 (2.8%)	21/707 (3.1%)	0.92 (0.50–1.71)	26/2208 (1.2%)	27/2189 (1.3%)	0.96 (0.56–1.64)	0.93
Clinically driven	16/698 (2.4%)	18/708 (2.6%)	0.90 (0.46–1.77)	22/2209 (1.0%)	20/2190 (1.0%)	1.09 (0.60–2.00)	0.68
Non-target lesion revascularization	22/702 (3.3%)	27/708 (4.0%)	0.82 (0.47–1.44)	68/2213 (3.2%)	63/2193 (3.0%)	1.07 (0.76–1.50)	0.44
Coronary artery bypass grafting	2/703 (0.3%)	7/708 (1.0%)	0.29 (0.06–1.39)	8/2212 (0.4%)	9/2200 (0.4%)	0.88 (0.34–2.29)	0.23
Bleeding							
BARC 2, 3, or 5 bleeding	20/640 (3.2%)	25/654 (3.9%)	0.81 (0.45–1.46)	66/2039 (3.3%)	51/2048 (2.5%)	1.31 (0.91–1.88)	0.18
BARC 5	1/705 (0.1%)	1/710 (0.1%)	1.00 (0.06–16.00)	5/2215 (0.2%)	5/2203 (0.2%)	0.99 (0.29–3.43)	0.99
BARC 3	13/680 (2.0%)	17/683 (2.5%)	0.77 (0.37–1.58)	30/2125 (1.4%)	26/2127 (1.3%)	1.15 (0.68–1.95)	0.37
BARC 2	13/665 (2.0%)	12/681 (1.8%)	1.11 (0.50–2.42)	42/2125 (2.0%)	28/2123 (1.3%)	1.51 (0.93–2.43)	0.51
TIMI major or minor	11/679 (1.7%)	18/684 (2.7%)	0.61 (0.29–1.30)	30/2127 (1.4%)	28/2132 (1.3%)	1.07 (0.64–1.80)	0.23
TIMI major	8/692 (1.2%)	12/696 (1.8%)	0.67 (0.27–1.64)	26/2176 (1.2%)	25/2163 (1.2%)	1.03 (0.60–1.79)	0.42
TIMI minor	3/692 (0.4%)	7/698 (1.0%)	0.43 (0.11–1.66)	9/2166 (0.4%)	6/2171 (0.3%)	1.50 (0.54–4.23)	0.15
GUSTO moderate or severe	10/690 (1.5%)	17/692 (2.5%)	0.59 (0.27–1.28)	33/2163 (1.6%)	25/2156 (1.2%)	1.32 (0.78–2.21)	0.09
GUSTO severe	7/695 (1.0%)	12/702 (1.7%)	0.59 (0.23–1.49)	17/2191 (0.8%)	19/2178 (0.9%)	0.89 (0.46–1.71)	0.47
GUSTO moderate	3/700 (0.4%)	5/700 (0.7%)	0.60 (0.14–2.51)	17/2187 (0.8%)	10/2179 (0.5%)	1.69 (0.77–3.70)	0.21
Intracranial bleeding (BARC 3 or 5)	3/703 (0.4%)	5/708 (0.7%)	0.60 (0.14–2.53)	8/2211 (0.4%)	12/2200 (0.6%)	0.66 (0.27–1.62)	0.91
Gastrointestinal bleeding (BARC 3 or 5)	8/700 (1.2%)	6/708 (0.9%)	1.35 (0.47–3.90)	14/2200 (0.7%)	14/2193 (0.7%)	1.00 (0.47–2.09)	0.64
Gastrointestinal bleeding (BARC 2, 3, or 5)	13/694 (1.9%)	8/708 (1.1%)	1.66 (0.69–4.00)	28/2195 (1.3%)	27/2186 (1.3%)	1.03 (0.61–1.75)	0.36

BARC, Bleeding Academic Research Consortium; CI, confidence interval; GUSTO, Global Use of Strategies to Open Occluded Arteries; PCI, percutaneous coronary intervention; TIMI, Thrombolysis in Myocardial Infarction.

(A)



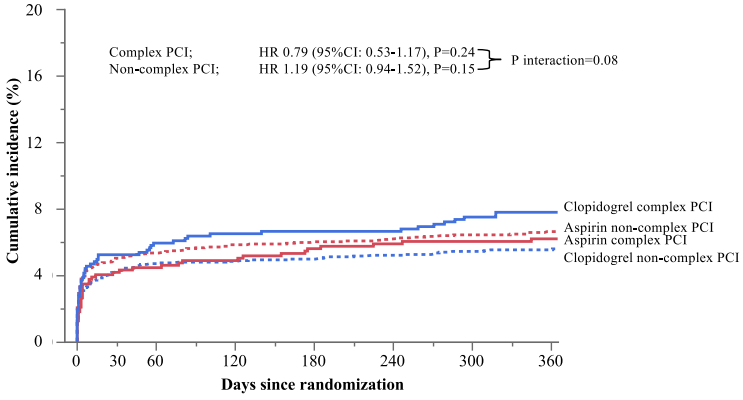
Complex PCI

Aspirin	0	30	60	120	180	240	300	365
Number of patients with event		38	42	48	53	55	58	60
Number of patients at risk	723	684	679	668	658	653	643	496
Cumulative incidence (%)		5.3	5.8	6.6	7.3	7.6	8.1	8.3
Clopidogrel	**0**	**30**	**60**	**120**	**180**	**240**	**300**	**365**
Number of patients with event		35	43	47	52	62	69	71
Number of patients at risk	730	693	683	676	670	658	650	507
Cumulative incidence (%)		4.8	5.9	6.5	7.1	8.5	9.5	9.8

Non-complex PCI

Aspirin	0	30	60	120	180	240	300	365
Number of patients with event		72	89	109	124	137	151	163
Number of patients at risk	2259	2187	2169	2139	2115	2093	2071	1586
Cumulative incidence (%)		3.2	3.9	4.8	5.5	6.1	6.7	7.3
Clopidogrel	**0**	**30**	**60**	**120**	**180**	**240**	**300**	**365**
Number of patients with event		88	105	116	131	144	153	163
Number of patients at risk	2250	2163	2142	2120	2094	2076	2057	1546
Cumulative incidence (%)		3.9	4.7	5.2	5.8	6.4	6.8	7.3

(B)



Complex PCI

Aspirin	0	30	60	120	180	240	300	365
Number of patients with event		30	32	35	40	42	43	44
Number of patients at risk	723	680	676	668	656	650	642	499
Cumulative incidence (%)		4.2	4.4	4.9	5.6	5.9	6.0	6.2
Clopidogrel	**0**	**30**	**60**	**120**	**180**	**240**	**300**	**365**
Number of patients with event		38	43	47	48	48	54	56
Number of patients at risk	730	683	671	663	659	653	643	500
Cumulative incidence (%)		5.2	5.9	6.5	6.6	6.6	7.5	7.8

Non-complex PCI

Aspirin	0	30	60	120	180	240	300	365
Number of patients with event		113	120	131	135	139	144	148
Number of patients at risk	2259	2125	2107	2081	2065	2050	2036	1546
Cumulative incidence (%)		5.0	5.3	5.8	6.0	6.2	6.4	6.6
Clopidogrel	**0**	**30**	**60**	**120**	**180**	**240**	**300**	**365**
Number of patients with event		95	105	108	111	116	121	124
Number of patients at risk	2250	2127	2106	2086	2065	2052	2035	1527
Cumulative incidence (%)		4.2	4.7	4.8	5.0	5.2	5.4	5.6

Figure 3 Kaplan–Meier curves in the overall 1-year analysis. (*A*) co-primary cardiovascular endpoint: a composite of cardiovascular death, myocardial infarction, definite stent thrombosis, or ischaemic stroke. (*B*) co-primary bleeding endpoint: BARC 3 or 5 bleeding. BARC, Bleeding Academic Research Consortium; CI, confidence interval; DAPT, dual antiplatelet therapy; HR, hazard ratio; PCI, percutaneous coronary intervention.

after complex PCI in the individual patient data-level meta-analysis of five randomized clinical trials. In addition, the subgroup analysis of the STOPDAPT-2 Total Cohort (ShorT and OPtimal Duration of Dual AntiPlatelet Therapy-2 Total Cohort) showed that clopidogrel monotherapy after 1-month DAPT compared with standard DAPT was not associated with an increased risk of cardiovascular events regardless of complex PCI.[8] When considering the above studies, it might be hypothesized that $P2Y_{12}$ inhibitor monotherapy might be a preferred antiplatelet monotherapy after stopping short DAPT regimen. Indeed, the HOST-EXAM (HOST-EXtended Antiplatelet Monotherapy) trial demonstrated that clopidogrel monotherapy reduced cardiovascular events compared with aspirin monotherapy in patients with chronic phase after PCI.[16] The 5-year follow-up of the STOPDAPT-2 trial also showed that clopidogrel monotherapy was associated with numerically lower risk of cardiovascular events compared with aspirin monotherapy beyond 1 year after PCI.[17] Moreover, in an individual patient data-level meta-analysis of randomized clinical trials comparing $P2Y_{12}$ inhibitor monotherapy with aspirin monotherapy in patients with coronary artery disease, $P2Y_{12}$ inhibitor monotherapy reduced cardiovascular events compared with aspirin monotherapy.[18] However, there were no previous clinical trials comparing aspirin monotherapy to $P2Y_{12}$ inhibitor monotherapy following short or very short DAPT after complex PCI. In the present study, the incidence of cardiovascular events beyond 1 month and up to 1 year was not different between aspirin monotherapy and clopidogrel monotherapy regardless of complex PCI. There was a significant interaction between complex PCI and the effect of aspirin monotherapy relative to clopidogrel monotherapy for cardiovascular events and the net clinical benefit due to numerically lower risk of aspirin monotherapy in patients with complex PCI. Aspirin monotherapy might be an attractive regimen after stopping short DAPT in patients undergoing complex PCI. However, the positive interaction in the present study should be interpreted with cautious, because the positive interaction was derived from a small subgroup and the results in the entire study population of the 1-year analysis of the STOPDAPT-3 trial were neutral.[10] In addition, the result in the 1-year analysis of the STOPDAPT-3 trial was not consistent with the previous studies comparing $P2Y_{12}$ inhibitor monotherapy with aspirin monotherapy conducted in the chronic phase after PCI.[16,17] Further studies would be warranted to evaluate the optimal antiplatelet monotherapy after short DAPT in patients who underwent complex PCI.

The previous studies reported that patients undergoing complex PCI had higher incidence of bleeding events compared with those undergoing non-complex PCI.[6–8] The incidence of bleeding events was higher in patients with complex PCI than in those without complex PCI in the 30-day landmark analysis in the present study. In the main analysis of the 1-year results of the STOPDAPT-3, the incidence of major bleeding was not different between aspirin monotherapy and clopidogrel monotherapy, which was consistent with the trials conducted in the chronic phase after PCI such as the 5-year results of the STOPDAPT-2 and an individual patient data-level meta-analysis.[10,17,18] In the present study, the incidence of major bleeding was also not different between aspirin monotherapy relative to clopidogrel monotherapy regardless of complex PCI without significant interaction. In the HOST-EXAM trial, clopidogrel monotherapy was associated with lower incidence of major bleeding compared with aspirin monotherapy.[16] The higher prescription rate of proton pump inhibitors in the STOPDAPT-3 trial compared with the HOST-EXAM trial might be one of the reasons to cancel out the benefit of clopidogrel over aspirin in reducing bleeding events. To reduce bleeding events after complex PCI, further studies would be needed to evaluate optimal antiplatelet monotherapy and to explore the necessity of prophylactic use of proton pump inhibitors in patients taking $P2Y_{12}$ inhibitor or aspirin monotherapy.

Limitations

The original 1-year results of the STOPDAPT-3 trial had important limitations.[10] Most importantly, the randomization was made only once at the timing of the index PCI and not 1 month. Strictly speaking, this trial was not a randomized comparison between aspirin and clopidogrel used as monotherapy after 1 month. However, the number of study patients was large enough and the number of patients having events within 1 month was not significantly different regardless of complex PCI, and the balance of baseline characteristics in the groups was well maintained in the 30-day landmark analysis.[9,10,13] The influence of immortal bias associated with the landmark analysis should be considered. However, it might not be considered large enough to change the results, because the overall 1-year analysis confirmed the consistency of the results. In addition, the changes in the antiplatelet therapy (prasugrel monotherapy to clopidogrel monotherapy in the no-aspirin group and DAPT to aspirin monotherapy in the DAPT group) were mandated not just at 30 days, but between 30 and 59 days after the index PCI. There are other important limitations of this study. First, the present pre-specified subgroup analysis was underpowered, and should be interpreted as exploratory. Second, the prevalence of complex PCI was low. The prevalence of bifurcation with two stents, which was reported as the strongest risk factor for ischaemic events, was much lower than in previous studies.[6] Third, the vast majority of the study patients underwent PCI guided by intracoronary imaging devices, which is quite different from the practice in the United States and Europe. The effect of aspirin monotherapy relative to clopidogrel monotherapy might be modified by intracoronary imaging use, especially in patients with complex PCI. Fourth, the prescription rate of DAPT beyond 30 days was numerically higher in patients with complex PCI than in those without.

Conclusion

There was a significant interaction between complex PCI and the effect of aspirin monotherapy relative to clopidogrel monotherapy beyond 1 month and up to 1 year for cardiovascular events due to numerically lower risk of aspirin monotherapy in patients with complex PCI. The effect of aspirin monotherapy relative to clopidogrel monotherapy beyond 1 month and up to 1 year was not different for bleeding events regardless of complex PCI. The positive interaction between complex PCI and the effect of aspirin vs. clopidogrel monotherapy for cardiovascular events should be interpreted with cautious due to the neutral results in the entire study population.

Supplementary material

Supplementary material is available at *European Heart Journal—Cardiovascular Pharmacotherapy* online.

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Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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