



Clopidogrel Monotherapy After 1-Month Dual Antiplatelet Therapy in Percutaneous Coronary Intervention: From the STOPDAPT-2 Total Cohort

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BACKGROUND: The benefit of clopidogrel monotherapy after 1-month dual antiplatelet therapy (DAPT) compared with 12-month DAPT with aspirin and clopidogrel was demonstrated in the STOPDAPT-2 (Short and Optimal Duration of Dual Antiplatelet Therapy After Everolimus-Eluting Cobalt-Chromium Stent-2), but not in the STOPDAPT-2 acute coronary syndrome (ACS); however, both trials were underpowered based on the actual event rates.

METHODS: We obtained the prespecified pooled population of 5997 patients as the STOPDAPT-2 total cohort (STOPDAPT-2: N=3009/STOPDAPT-2 ACS: N=2988; ACS: N=4136/chronic coronary syndrome [CCS]: N=1861), comprising 2993 patients assigned to 1-month DAPT followed by clopidogrel monotherapy, and 3004 patients assigned to 12-month DAPT with aspirin and clopidogrel after percutaneous coronary intervention. The primary end point was the composite of cardiovascular (cardiovascular death, myocardial infarction, definite stent thrombosis, or any stroke) or bleeding (Thrombolysis in Myocardial Infarction major/minor) end points at 1 year.

RESULTS: One-month DAPT was noninferior to 12-month DAPT for the primary end point (2.84% versus 3.04%; hazard ratio [HR], 0.94 [95% CI, 0.70–1.27]; $P_{\text{noninferiority}}=0.001$; $P_{\text{superiority}}=0.68$). There was no significant risk-difference for the cardiovascular end point between the 1- and 12-month DAPT groups (2.40% versus 1.97%; HR, 1.24 [95% CI, 0.88–1.75]; $P_{\text{noninferiority}}=0.14$; $P_{\text{superiority}}=0.23$). There was a lower risk of the bleeding end point with 1-month DAPT relative to 12-month DAPT (0.50% versus 1.31%; HR, 0.38 [95% CI, 0.21–0.70]; $P_{\text{superiority}}=0.002$). One-month DAPT relative to 12-month DAPT was associated with a lower risk for major bleeding regardless of ACS or CCS (ACS: HR, 0.46 [95% CI, 0.23–0.94]; $P=0.03$, and CCS: HR, 0.26 [95% CI, 0.09–0.79]; $P=0.02$; $P_{\text{interaction}}=0.40$), while it was associated with a numerical increase in cardiovascular events in ACS patients, but not in CCS patients, although not statistically significant and without interaction (ACS: HR, 1.50 [95% CI, 0.99–2.27]; $P=0.053$, and CCS: HR, 0.74 [95% CI, 0.38–1.45]; $P=0.39$; $P_{\text{interaction}}=0.08$).

CONCLUSIONS: Clopidogrel monotherapy after 1-month DAPT compared with 12-month DAPT with aspirin and clopidogrel had a benefit in reducing major bleeding events without being associated with increase in cardiovascular events.

REGISTRATION: URL: <https://www.clinicaltrials.gov>; Unique identifiers: NCT02619760, NCT03462498.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: acute coronary syndrome ■ antiplatelet therapy ■ chronic coronary syndrome ■ coronary stent ■ percutaneous coronary intervention

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WHAT IS KNOWN

- In the STOPDAPT-2 trial (Short and Optimal Duration of Dual Antiplatelet Therapy After Everolimus-Eluting Cobalt-Chromium Stent-2), clopidogrel monotherapy after 1-month dual antiplatelet therapy (DAPT) was demonstrated to be noninferior to 12-month DAPT with aspirin and clopidogrel in terms of net clinical benefit, while it was inconclusive in the pooled acute coronary syndrome (ACS) population from the STOPDAPT-2 and STOPDAPT-2 ACS with numerical increase in cardiovascular event despite being associated with reduction in bleeding event.
- However, given the event rates lower than anticipated, both the STOPDAPT-2 and the STOPDAPT-2 ACS trials were underpowered.

WHAT THE STUDY ADDS

- We obtained the prespecified pooled population of 5997 patients as the STOPDAPT-2 Total Cohort (3009 patients from the STOPDAPT-2, and 2988 patients from the STOPDAPT-2 ACS; ACS: 4136 patients and chronic coronary syndrome: 1861 patients), in which clopidogrel monotherapy after 1-month DAPT compared with 12-month DAPT had a benefit in reducing major bleeding events without being associated with increase in cardiovascular events.
- The treatment-by-subgroup interaction was not significant for ACS and chronic coronary syndrome, although clopidogrel monotherapy after 1-month DAPT compared with 12-month DAPT was associated with numerical increase in cardiovascular events in patients with ACS, but not in patients with chronic coronary syndrome.
- Clopidogrel monotherapy after 1-month DAPT would be a reasonable regimen in patients who underwent successful percutaneous coronary intervention, however, given a numerical increase in cardiovascular events with clopidogrel monotherapy after 1-month DAPT in patients with ACS, further studies would be warranted to explore the optimal antithrombotic strategies in patients with ACS.

Dual antiplatelet therapy (DAPT) with aspirin and a P2Y₁₂ inhibitor for at least 1 year has been recommended after percutaneous coronary intervention (PCI) using drug-eluting stent.^{1,2} However, shorter durations of DAPT have been explored due to the growing concerns on the increase in bleeding events associated with prolonged DAPT, particularly in patients with high bleeding risk.^{3–6} Recently, 5 clinical trials enrolling a total of >30000 patients have suggested a benefit of very short (1- to 3-month) DAPT with subsequent P2Y₁₂ inhibitor monotherapy after PCI in reducing bleeding events without increasing cardiovascular events compared with prolonged DAPT (12- to 15-month).^{6–12} In these trials,

Nonstandard Abbreviations and Acronyms

ACS	acute coronary syndrome
CCS	chronic coronary syndrome
DAPT	dual antiplatelet therapy
HR	hazard ratio
MASTER-DAPT	The Management of High Bleeding Risk Patients Post Biore-sorbable Polymer Coated Stent Implantation With an Abbreviated Versus Standard DAPT Regimen
PCI	percutaneous coronary intervention
STOPDAPT-2	Short and Optimal Duration of Dual AntiPlatelet Therapy After Everolimus-Eluting Cobalt-Chromium Stent-2

ticagrelor monotherapy was the dominant strategy after stopping DAPT at 1 to 3 months after PCI. Nevertheless, clopidogrel monotherapy after 1-month DAPT compared with standard 12-month DAPT with aspirin and clopidogrel suggested a benefit of reducing major bleeding without increase in cardiovascular events in the STOPDAPT-2 trial (Short and Optimal Duration of Dual Antiplatelet Therapy After Everolimus-Eluting Cobalt-Chromium Stent-2) that enrolled patients with both chronic coronary syndrome (CCS) and acute coronary syndrome (ACS).⁸ On the other hand, the benefit and harm of 1-month DAPT was inconclusive in the STOPDAPT-2 ACS due to a numerical increase in cardiovascular events despite being associated with reduction in major bleeding.¹³ However, given the observed event rates lower than anticipated, both the prior 2 trials were considered to be underpowered in evaluating the benefit and harm of clopidogrel monotherapy after 1-month DAPT. Therefore, we sought to evaluate the effect of clopidogrel monotherapy after 1-month DAPT relative to standard 12-month DAPT combining 2 trials as the STOPDAPT-2 Total Cohort. Moreover, we aimed to explore the possible differences in the effects of 1-month DAPT relative to 12-month DAPT between patients with CCS and ACS.

METHODS

Study Population

Data will be available from corresponding author upon reasonable requests. STOPDAPT-2 (December 2015 to December 2017; 90 centers; NCT02619760) and STOPDAPT-2 ACS (March 2018 to June 2020; 74 centers; NCT03462498) trials are physician-initiated, prospective, multicenter, open-label, adjudicator blinded randomized clinical trials in Japan, where we compared the experimental strategy of 1-month DAPT followed by clopidogrel monotherapy with the standard strategy of 12-month DAPT with aspirin and clopidogrel after PCI using

cobalt-chromium everolimus-eluting stent (ABBOTT) implantation.^{8,13} The study protocol for the STOPDAPT-2 ACS trial was identical to that of the STOPDAPT-2 trial except for the exclusive enrollment of ACS patients in the former. The details of the STOPDAPT-2 and STOPDAPT-2 ACS trials were reported previously.^{8,13} Briefly, patients without in-hospital major complications were enrolled and randomized in a 1-to-1 ratio either to the 1-month DAPT group or 12-month DAPT group before discharge from the index hospitalization. During the initial 1-month period (30–59 days) after PCI, all the patients were to receive DAPT with aspirin 81 to 200 mg/day and a P2Y₁₂ inhibitor (clopidogrel 75 mg/day or prasugrel 3.75 mg/day at the discretion of the attending physicians). At 1-month visit, the patients in the 1-month DAPT group were to receive clopidogrel monotherapy, while the patients in the 12-month DAPT group were to receive DAPT with aspirin and clopidogrel up to 12 months. In patients who had received prasugrel, it was switched to clopidogrel without loading at 1 month in both groups. In the present study, we obtained the prespecified pooled population of 5997 patients as the STOPDAPT-2 Total Cohort (3009 patients from the STOPDAPT-2, and 2988 patients from the STOPDAPT-2 ACS), comprising 2993 patients in the 1-month DAPT group and 3004 patients in the 12-month DAPT group (Figure 1).

The STOPDAPT-2 total cohort was divided into the 2 subgroups of patients with CCS and with ACS (Figure 1). ACS was defined as one of the following diagnosis treated within 1 week after onset: ST-segment–elevation myocardial infarction, non–ST-segment–elevation myocardial infarction, or unstable angina based on the previous guidelines,¹⁴ and CCS was defined as patients who were indicated for PCI for reasons other than ACS. The ethical committees in all the participating centers approved the study protocol, and written informed consents were obtained from all patients.

Outcome Measures

The clinical outcomes were assessed at 1 year after the index PCI. The primary and major secondary end points in the present study were identical to those adopted in the STOPDAPT-2 and STOPDAPT-2 ACS. The primary end point was a composite of cardiovascular (death from cardiovascular cause, myocardial infarction, definite stent thrombosis, or any stroke) or bleeding (Thrombolysis in Myocardial Infarction major or minor bleeding events.¹⁵ The major secondary cardiovascular and bleeding end points were the cardiovascular and bleeding components of the primary end point, respectively. The definitions of myocardial infarction, and stent thrombosis were derived from the Academic Research Consortium.¹⁶ The definitions of other secondary end points were described in the [Supplemental Appendix](#). The independent clinical event committee adjudicated the clinical events in a blinded fashion to the assigned group.

Statistical Analysis

Categorical variables were presented as number and percentage and were compared using the χ^2 test. Continuous variables were expressed as mean \pm SD or median with interquartile range and were compared using the Student *t* test or Wilcoxon rank-sum test depending on their distributions. The cumulative incidence of each end point was estimated via the Kaplan-Meier method and the differences between assigned groups were compared via the

log-rank test. We also performed 30 days and 6 months landmark analyses after index PCI. The relative effects of 1-month DAPT to 12-month DAPT for the end points were expressed as HRs with 95% CIs by the Cox proportional hazard model. In the current study, HRs were adjusted with the clinical presentation (ACS versus CCS) and trials (STOPDAPT-2 versus STOPDAPT-2 ACS). For the primary and major secondary cardiovascular end points in the STOPDAPT-2 Total Cohort, noninferiority analysis of 1-month DAPT relative to 12-month DAPT with a relative margin of 1.5 on the hazard ratio scale was followed by superiority analysis, while for the major secondary bleeding end point, only superiority analysis was performed. Other secondary end points were presented for descriptive purpose only without calculating *P*. In the subgroup analysis, the differences in the effects of 1-month DAPT relative to 12-month DAPT between ACS and CCS for the primary and major secondary end points were evaluated by the interaction terms in the models. Sensitivity analyses for the primary and major secondary cardiovascular and bleeding end points were conducted in the post hoc subgroups stratified by ST-segment–elevation myocardial infarction versus non–ST-segment–elevation acute coronary syndrome presentation and GRACE score categories in the ACS population,¹⁷ and acute myocardial infarction versus non-acute myocardial infarction presentation and PARIS risk score categories in the total pooled population.¹⁸ We calculated the sample sizes in the STOPDAPT-2 and STOPDAPT-2 ACS trials separately (85% and 90% of power, respectively^{8,13}), and this study combined the both trials without sample size calculations or power calculation for this study. For the noninferiority testing, *P* were 1-tailed and *P* < 0.025 were considered statistically significant. For other comparisons, *P* were 2-tailed and *P* < 0.05 were considered statistically significant. All analysis was performed with JMP version 15.2 software (SAS Institute Inc, Cary, NC).

RESULTS

Study Population

Among the 5997 patients in the STOPDAPT-2 Total Cohort, there were 4136 patients (69.0%) with ACS (1-month DAPT: N=2058 and 12-month DAPT: N=2078) and 1861 patients (31.0%) with CCS (1-month DAPT group: N=935 and 12-month DAPT group: N=926; Figure 1). Among 4136 patients with ACS, 1148 and 2988 patients were derived from the STOPDAPT-2 and STOPDAPT-2 ACS trials, respectively, while all 1861 patients with CCS were derived from the STOPDAPT-2 trial.

Baseline Characteristics and Medications

In the STOPDAPT-2 Total Cohort, mean age was 67.8 years, and 78.4% were men. The prevalence of diabetes and Academic Research Consortium-high bleeding risk was 33.9% and 31.6%, respectively. Radial approach was dominant (87.9%), and intravascular imaging was utilized at PCI in 97.5% of patients. Staged PCI procedures were performed in 13.2% of patients, and 2 or more vessels were treated in 17.9% of patients. The dose of aspirin was 100 mg in 98.2% of patients, and the types of P2Y₁₂

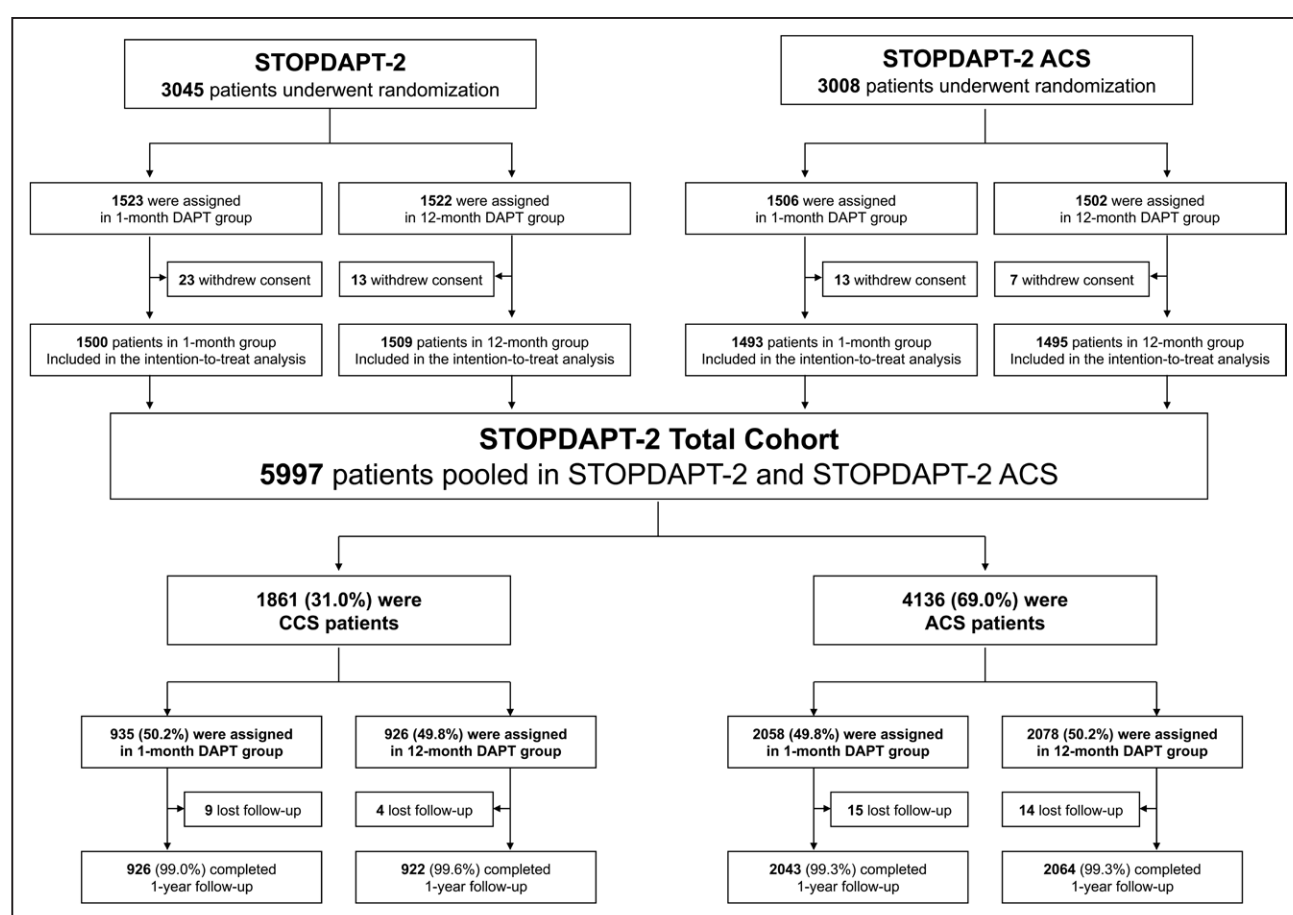


Figure 1. Study flow for the STOPDAPT-2 (Short and Optimal Duration of Dual Antiplatelet Therapy After Everolimus-Eluting Cobalt-Chromium Stent-2) total cohort and acute coronary syndrome (ACS)/chronic coronary syndrome (CCS) subgroup analysis. DAPT indicates dual antiplatelet therapy.

inhibitors in the initial 1-month period were clopidogrel and prasugrel in 57.2%, and 42.7% of patients, respectively. At discharge from the index hospitalization, statins and high-intensity statins were prescribed in 92.6% and 24.8% of patients, respectively (Table S1).

Patients with ACS were younger, more often men, and less often had previous cardiovascular medical history such as prior PCI, coronary artery bypass grafting, myocardial infarction, stroke, atrial fibrillation, and peripheral artery disease than patients with CCS. Patients with ACS also less often had comorbidities such as anemia, cancer, chronic kidney disease, hypertension, diabetes as well as Academic Research Consortium-high bleeding risk than patients with CCS. Emergency procedure was notably more prevalent in patients with ACS than in patients with CCS; nevertheless, patients with ACS more often underwent PCI with radial approach than CCS patients. As a P2Y₁₂ inhibitor, prasugrel was more often used in ACS patients than in CCS patients, while clopidogrel was more often used in CCS patients than in ACS patients. Regarding medication at discharge, the prescription rates of β -blocker, angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers, and statins were higher in patients

with ACS than those with CCS. The prevalence of high-intensity statins use was remarkably higher in ACS patients than in CCS patients (Table S1).

Baseline characteristics and medications were well balanced between the 1-month DAPT and 12-month DAPT groups in the STOPDAPT-2 Total Cohort as well as in both ACS and CCS patients (Tables S2 and S3).

The vast majority of patients received the assigned antiplatelet therapy based on the study protocol during follow-up (Figures S1 and S2).

Clinical Outcomes in the STOPDAPT-2 Total Cohort

Clinical follow-up at 1 year was completed in 99.3% of patients (Figure 1). The primary end point occurred in 84 patients (2.84%) in the 1-month DAPT group and in 90 patients (3.04%) in the 12-month DAPT group. For the primary end point, clopidogrel monotherapy after 1-month DAPT was noninferior, but not superior to 12-month DAPT with aspirin and clopidogrel (hazard ratio [HR], 0.94 [95% CI, 0.70–1.27], *P* for noninferiority=0.001; *P* for superiority=0.68; Figures 2 and 3; Table S4).

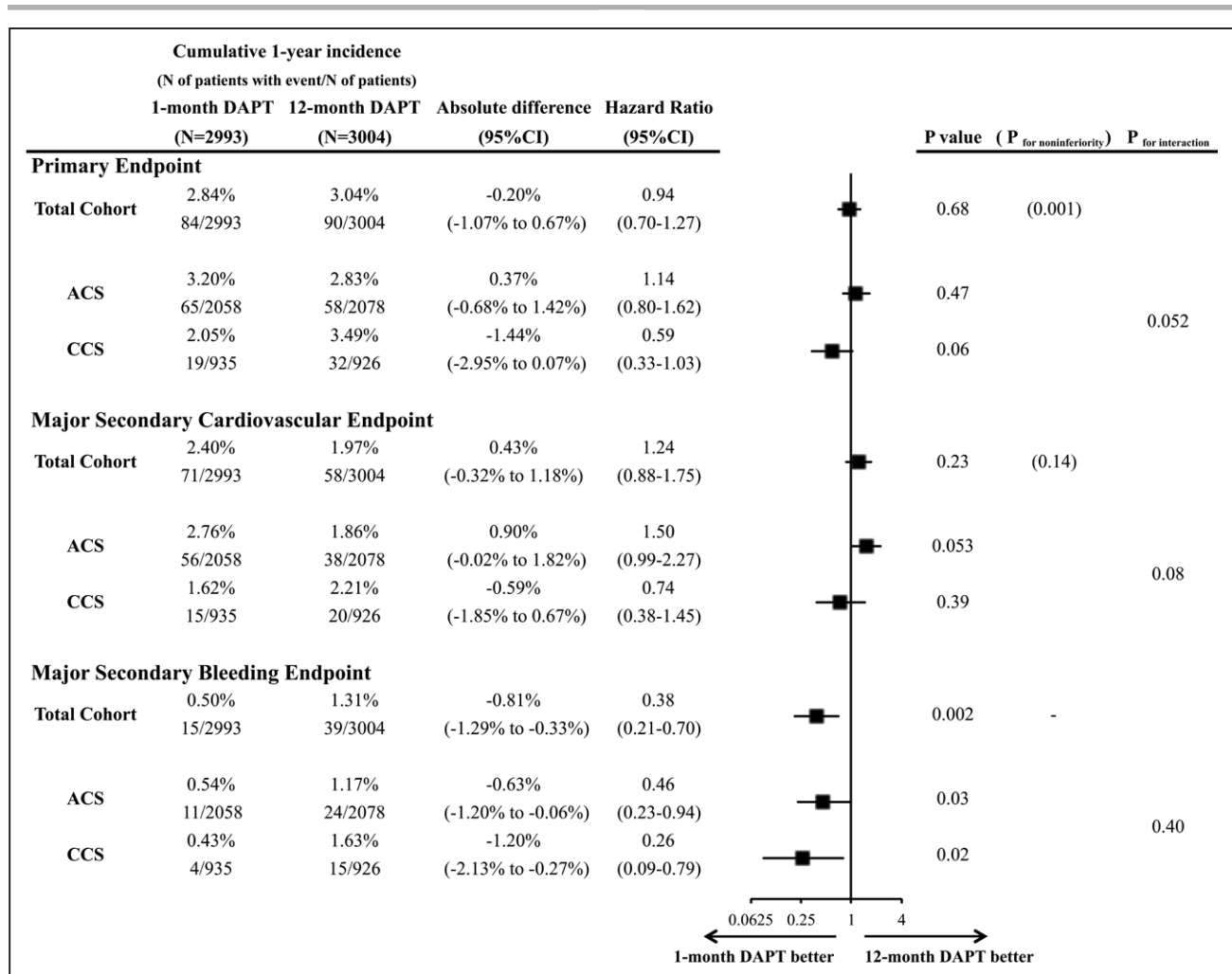


Figure 2. Forrest plots for the effect of 1-month relative to 12-mo dual antiplatelet therapy (DAPT) for the primary and major secondary end points in the STOPDAPT-2 (Short and Optimal Duration of Dual Antiplatelet Therapy After Everolimus-Eluting Cobalt-Chromium Stent-2) total cohort and in acute coronary syndrome (ACS)/chronic coronary syndrome (CCS) subgroups.

The major secondary cardiovascular end point occurred in 71 patients (2.40%) in the 1-month DAPT group and in 58 patients (1.97%) in the 12-month DAPT group. For the major secondary cardiovascular end point, noninferiority of 1-month DAPT relative to 12-month DAPT was not attested, but there was no significant risk-difference between the 1- and 12-month DAPT groups (HR, 1.24 [95% CI, 0.88–1.75], *P* for noninferiority=0.14; *P* for superiority=0.23; Figures 2 and 3; Table S4).

The cumulative 1-year incidence of the major secondary bleeding end point was lower in the 1-month DAPT group (15 patients, 0.50%) than in the 12-month DAPT group (39 patients, 1.31%) (HR, 0.38 [95% CI, 0.21–0.70], *P* for superiority=0.002; Figures 2 and 3; Table S4).

The results for the primary and the major secondary cardiovascular and bleeding end points were consistent in the 30 days landmark analyses (Figure S3).

The cumulative 1-year incidences of serious cardiovascular events such as cardiovascular death, large myocardial infarction (CKMB \geq 10*ULN), and stroke were very low and not different between the 1- and 12-month DAPT

groups (0.54% versus 0.57%; 0.28% versus 0.14%; 0.67% versus 0.72%). Definite stent thrombosis occurred in 9 patients (0.31%) and in 4 patients (0.14%) in the 1- and 12-month DAPT groups, respectively (Table S4).

Clinical Outcomes in the ACS and CCS Subgroups

The primary end point occurred in 65 patients (3.20%) in the 1-month DAPT group and in 58 patients (2.83%) in the 12-month DAPT in ACS patients (HR, 1.14 [95% CI, 0.80–1.62]; *P*=0.47), while in CCS patients, it occurred in 19 patients (2.05%) in the 1-month DAPT group and in 32 patients (3.49%) in the 12-month DAPT (HR, 0.59 [95% CI, 0.33–1.03]; *P*=0.06). The effects of 1-month DAPT relative to 12-month DAPT for the primary end point were directionally inconsistent in the ACS and CCS subgroups, but the treatment-by-subgroup interaction was not significant (*P* for interaction=0.052; Figures 2 and 4; Table S4).

The major secondary cardiovascular end point occurred in 56 patients (2.76%) in the 1-month DAPT

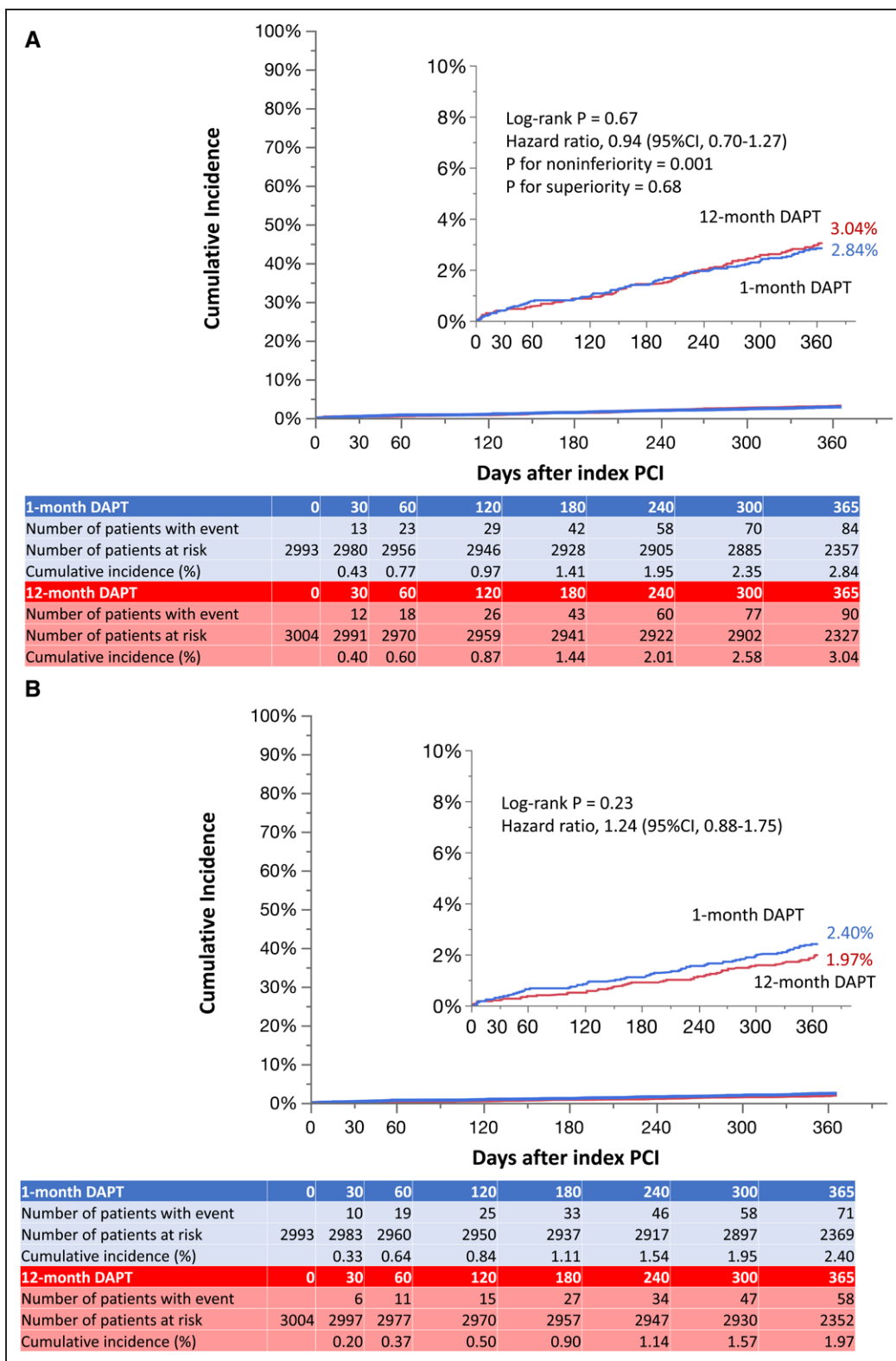


Figure 3. Cumulative incidence of the primary and major secondary end points in the STOPDAPT-2 (Short and Optimal Duration of Dual Antiplatelet Therapy After Everolimus-Eluting Cobalt-Chromium Stent-2) total cohort: 1- vs 12-mo dual antiplatelet therapy (DAPT).

Time-to-event curves during 1-y after index percutaneous coronary intervention (PCI): (A) for the primary end point, (B) for the major secondary cardiovascular end point, and (C) for the major secondary bleeding end point in the STOPDAPT-2 total cohort. TIMI indicates Thrombolysis in Myocardial Infarction. (Continued)

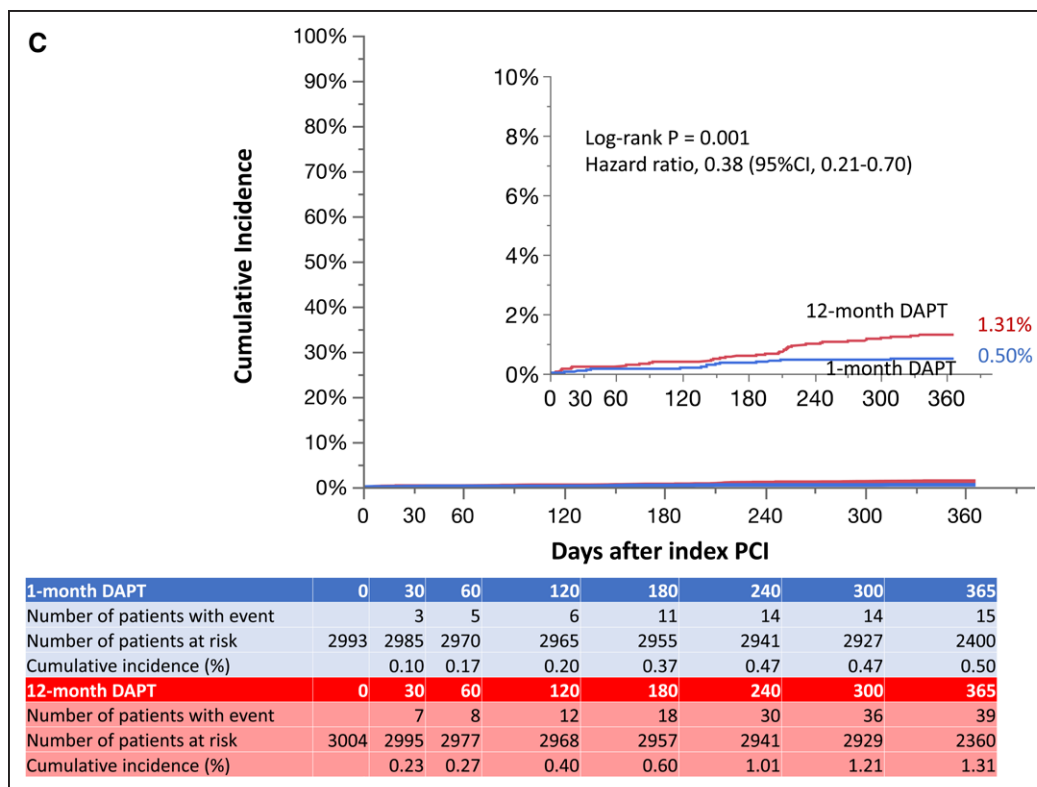


Figure 3 Continued.

group and in 38 patients (1.86%) in the 12-month DAPT group in ACS patients (HR, 1.50 [95% CI, 0.99–2.27]; $P=0.053$), while in CCS patients, it occurred in 15 patients (1.62%) in the 1-month DAPT group and in 20 patients (2.21%) in the 12-month DAPT group (HR, 0.74 [95% CI, 0.38–1.45]; $P=0.39$). The effects of 1-month DAPT relative to 12-month DAPT for the major secondary cardiovascular end point were also directionally inconsistent in the ACS and CCS subgroups, but the treatment-by-subgroup interaction was not significant (P for interaction=0.08; Figures 2 and 4; Table S4).

The cumulative 1-year incidence of the major secondary bleeding end point was lower in the 1-month DAPT group (ACS: 11 patients, 0.54%, and CCS: 4 patients, 0.43%) than in the 12-month DAPT group (ACS: 24 patients, 1.17%, and CCS: 15 patients, 1.63%) in both ACS and CCS patients. The lower risk of 1-month DAPT relative to 12-month DAPT for the major secondary bleeding end point was consistent in the ACS and CCS subgroups without interaction (HR, 0.46 [95% CI, 0.23–0.94]; $P=0.03$ and HR, 0.26 [95% CI, 0.09–0.79], $P=0.02$; P for interaction=0.40; Figures 2 and 4; Table S4).

The results for the primary and major secondary cardiovascular and bleeding end points in the 30 days and 6 months landmark analyses were consistent with those in the main analyses through 1 year for both ACS and CCS subgroups (Figures S4 and S5). As for the bleeding end points in ACS subgroup, the incidence rate before 6-month was similar between 1-month and 12-month

DAPT groups, but the incidence rate beyond 6-month was significantly higher in the 12-month DAPT group than in the 1-month DAPT group (Figure S5).

There was no significant difference in the cumulative 1-year incidences of the primary, major secondary cardiovascular, and major secondary bleeding end points between ACS and CCS patients (3.01% versus 2.77%; $P=0.27$; 2.31% versus 1.92%, $P=0.12$; 0.85% versus 1.03%, $P=0.70$), while definite stent thrombosis occurred only in ACS patients (13 patients, 0.33%; Table S5).

Sensitivity Analyses

There were no significant interactions for the primary, major secondary cardiovascular, and major secondary bleeding end points across all the subgroups of ST-segment-elevation myocardial infarction versus non-ST-segment-elevation acute coronary syndrome presentation in the ACS population, GRACE score categories in the ACS population, acute myocardial infarction versus non-acute myocardial infarction presentation in the total pooled population, and PARIS thrombotic and bleeding risk score categories in the total pooled population (Figures S6 through S10).

DISCUSSION

The main findings of the present study were the followings: (1) clopidogrel monotherapy after 1-month DAPT compared with 12-month DAPT with aspirin and

clopidogrel had a benefit in reducing major bleeding events without being associated with increase in cardiovascular events in the STOPDAPT-2 Total Cohort; (2)

Clopidogrel monotherapy after 1-month DAPT relative to 12-month DAPT with aspirin and clopidogrel was associated with lower risk for major bleeding regardless of

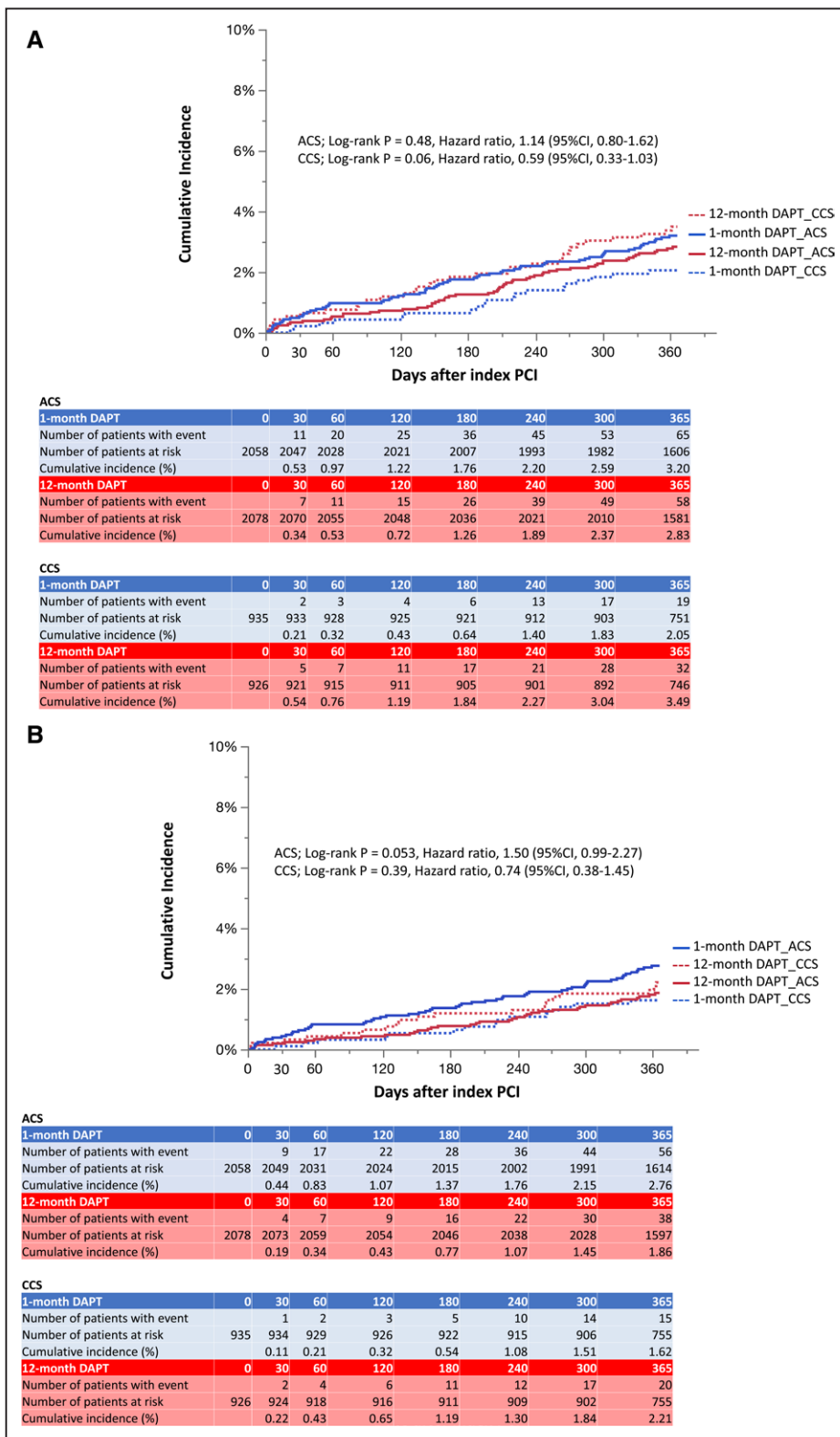


Figure 4. Kaplan-Meier curves for the primary and major secondary end points stratified by acute coronary syndrome (ACS) and chronic coronary syndrome (CCS): 1- vs 12-mo dual antiplatelet therapy (DAPT).

Time-to-event curves during 1-y after index percutaneous coronary intervention (PCI): (A) for the primary end point, (B) for the major secondary cardiovascular end point, and (C) for the major secondary bleeding end point stratified by ACS and CCS. (Continued)

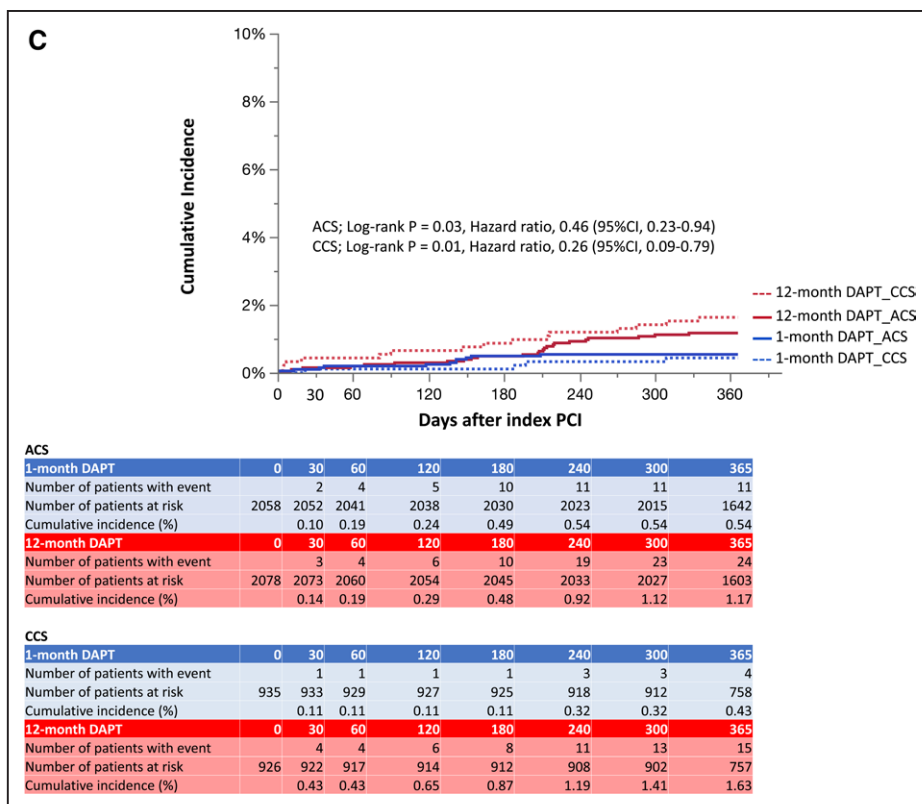


Figure 4 Continued.

ACS or CCS, while it was associated with a numerical increase in cardiovascular events in ACS patients, but not in CCS patients, though not statistically significant and without interaction.

Implications From the STOPDAPT-2 Total Cohort

In our previous report in the pooled population of ACS patients from the STOPDAPT-2 and STOPDAPT-2 ACS trials, the benefit and harm of clopidogrel monotherapy after 1-month DAPT compared with 12-month DAPT with aspirin and clopidogrel was inconclusive due to a numerical increase in cardiovascular events despite being associated with reduction in major bleeding. The results might be confusing given the positive results in the STOPDAPT-2 trial that enrolled both ACS and CCS patients. However, given the actual event rates lower than anticipated, both the STOPDAPT-2 and STOPDAPT-2 ACS trials were underpowered in evaluating the benefit and harm of clopidogrel monotherapy after 1-month DAPT. In the present STOPDAPT-2 Total Cohort including a larger number of patients, clopidogrel monotherapy after 1-month DAPT was noninferior for the primary end point representing a net clinical benefit and superior for the major secondary bleeding end point to 12-month DAPT with aspirin and clopidogrel. The rate of the major secondary cardiovascular end point was not significantly different between 1- and 12-month DAPT groups.

Moreover, the rates of serious cardiovascular events such as cardiovascular death, large myocardial infarction, and stroke were very low and not different between the 1- and 12-month DAPT groups. Therefore, in its totality, clopidogrel monotherapy after 1-month DAPT would be a reasonable regimen in patients who underwent PCI using cobalt-chromium everolimus-eluting stent.

Implications From the Subgroup Analysis for ACS and CCS

It might remain confusing that the effect of 1-month DAPT relative to 12-month DAPT for cardiovascular events was directionally opposite in the ACS and CCS subgroups. We think this finding might largely be explained by the lack of adequate power in the subgroup analysis, because it is mechanistically implausible to find that the effects of clopidogrel monotherapy after 1-month DAPT could be in the opposite directions between the ACS and CCS subgroups. However, we would still be concerned on the observed numerical increase in cardiovascular events with clopidogrel monotherapy after 1-month DAPT in patients with ACS. Globally, the standard regimen after PCI in ACS patients is 12-month DAPT with aspirin and a newer P2Y₁₂ inhibitor, such as ticagrelor or prasugrel.^{1,2,19,20} Among the 6 trials exploring P2Y₁₂ inhibitor monotherapy after very short DAPT, the majority of ACS patients received monotherapy with a newer P2Y₁₂ inhibitor, mostly

ticagrelor, after stopping DAPT.^{6,7,9–11} Given the absence of a signal suggesting increase in cardiovascular events with monotherapy with newer P2Y₁₂ inhibitors after very short DAPT, clopidogrel monotherapy might not be the optimal antithrombotic regimen after very short DAPT in patients with ACS who underwent successful PCI.^{6,7,9–11} Nevertheless, clopidogrel monotherapy might be associated with less bleeding than monotherapy with a newer P2Y₁₂ inhibitor.^{7–11,13,21} Indeed, in the MASTER-DAPT trial (The Management of High Bleeding Risk Patients Post Bioresorbable Polymer Coated Stent Implantation With an Abbreviated Versus Standard DAPT Regimen), abbreviated DAPT compared with standard DAPT was associated with reduction in bleeding events without increase in cardiovascular events, in which half of the study population were patients with ACS, and clopidogrel was the most commonly used antiplatelet agent as a monotherapy.²² Therefore, further studies are warranted to define the optimal antiplatelet monotherapy after PCI in ACS patients. Resistance to clopidogrel due to CYP2C19 polymorphisms, which is commonly found in Japanese, might be one of the reasons for the numerical increase in cardiovascular events in ACS patients in the present study. Currently, STOPDAPT-3 trial (NCT 04609111) is ongoing to explore the completely aspirin free strategy with reduced-dose prasugrel monotherapy starting just before PCI in patients with ACS and/or high bleeding risk.

Study Limitations

The individual STOPDAPT-2 and STOPDAPT-2 ACS trials pooled in the STOPDAPT-2 Total Cohort had limitations such as open-label design, use of a net clinical benefit for the primary end point and low event rate of its each component, timing of randomization (at baseline, but not at 1-month when the study medications were changed), representation of lower risk patients than those in the real clinical practice, and inadequate power for evaluating the primary and major secondary end points. There are other important limitations in the STOPDAPT-2 Total Cohort. First, we pooled the patients from the 2 trials conducted in different time period; all patients with CCS were derived from STOPDAPT-2, while patients with ACS were derived from both STOPDAPT-2 and STOPDAPT-2 ACS, which could reflect the change of clinical practice over time rather than the disease-specific difference between ACS and CCS, although we included the enrolled study period as a risk-adjusting factor. Second, the subgroup analysis in patients with ACS and CCS was underpowered and its results should be regarded as hypothesis generating. Considering that the event rate for the major secondary cardiovascular end point was especially low in the subgroups of ACS and CCS, comparison between 1- and 12-month DAPT should be difficult in patients with ACS. Third, we did

not assess the influence of clopidogrel resistance due to CYP2C19 polymorphisms on clinical outcomes. Fourth, the percentage of women was only about one-fifths of all the patients. The results of a subgroup analysis in an individual patient level meta-analysis of trials evaluating P2Y₁₂ inhibitor monotherapy after coronary revascularization suggested that P2Y₁₂ inhibitor monotherapy compared with DAPT lowered the risk of ischemic events in women, but not in men.⁶ Therefore, caution is warranted in adapting the present study results for women. Fifth, the prevalence of high-intensity statins therapy in the present study was lower than that in the daily clinical practice in other countries such as the United States and Europe. With further penetration of high-intensity statins therapy, we might expect further decrease in the rate of cardiovascular event, leading to a smaller absolute difference in the rate of cardiovascular event between the 1- and 12-month DAPT groups.

Conclusions

Clopidogrel monotherapy after 1-month DAPT compared with 12-month DAPT with aspirin and clopidogrel had a benefit in reducing major bleeding events without being associated with increase in cardiovascular events.

ARTICLE INFORMATION

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Supplemental Material

Supplemental Appendix
Tables S1–S5
Figures S1–S10

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