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P2Y12 Inhibitor Monotherapy or Dual Antiplatelet Therapy After Complex Percutaneous Coronary Intervention: Individual Participant Meta-analysis

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ABSTRACT

Background. It remains unclear whether $P2Y_{12}$ inhibitor monotherapy preserves ischemic protection while limiting bleeding risk compared with dual antiplatelet therapy (DAPT) after complex percutaneous coronary intervention (PCI).

Objectives. To assess the effects of $P2Y_{12}$ inhibitor monotherapy versus standard DAPT in relation to PCI complexity.

Methods. We pooled patient-level data from randomized controlled trials comparing $P2Y_{12}$ inhibitor monotherapy and standard DAPT on centrally-adjudicated outcomes after coronary revascularization. Complex PCI was defined as any of six criteria: 3 vessels treated, ≥3 stents implanted, ≥3 lesions treated, bifurcation with 2 stents implanted, total stent length >60 mm, or chronic total occlusion. The primary efficacy endpoint was all-cause mortality, myocardial infarction, and stroke. The key safety endpoint was Bleeding Academic Research Consortium (BARC) type 3 or 5 bleeding.

Results. Of 22,941 patients undergoing PCI from five trials, 4,685 (20.4%) with complex PCI had higher rates of ischemic events. The primary efficacy endpoint did not differ with $P2Y_{12}$ inhibitor monotherapy versus DAPT among patients with complex (HR: 0.87; 95% CI: 0.64-1.19) and noncomplex PCI (HR: 0.91; 95% CI: 0.76-1.09; p-interaction=0.770). The treatment effect was consistent across the components of the complex PCI definition. Compared with DAPT, $P2Y_{12}$ inhibitor monotherapy reduced the incidence of BARC type 3 or 5 bleeding in complex PCI (HR: 0.51; 95% CI: 0.31-0.84) and noncomplex PCI patients (HR: 0.49; 95% CI: 0.37-0.64; p-interaction=0.920).

Conclusions. $P2Y_{12}$ inhibitor monotherapy was associated with similar rate of fatal and ischemic events and lower risk of major bleeding compared with DAPT, irrespective of PCI complexity.

Study Registration: PROSPERO, CRD42020176853.

Condensed abstract:

In this IPD meta-analysis of randomized trials, including 4,685 and 18,256 patients with complex and noncomplex PCI, respectively, we examined the effect of $P2Y_{12}$ inhibitor monotherapy versus standard DAPT in relation to procedural complexity on centrally adjudicated endpoints. $P2Y_{12}$ inhibitor monotherapy was associated with similar risks of fatal and ischemic events compared with DAPT, irrespective of PCI complexity. The treatment effect on ischemic endpoints remained consistent across the components of the complex PCI definition. $P2Y_{12}$ monotherapy significantly reduced major bleeding and net adverse clinical events rates compared with DAPT; the magnitude of this effect was consistent regardless of PCI complexity.

Keywords: percutaneous coronary intervention; complex PCI; $P2Y_{12}$ inhibitors; Aspirin; DAPT; meta-analysis.

Abbreviations List

BARC = Bleeding Academic Research Consortium
CI = Confidence Interval
DAPT = Dual Antiplatelet Therapy
HR = Hazard Ratio
NNTB = Number-needed-to-treat to benefit
PCI = Percutaneous Coronary Intervention
TIMI = Thrombolysis in Myocardial Infarction

INTRODUCTION

Patients undergoing complex percutaneous coronary intervention (PCI) have an increased risk of ischemic events and often receive an extended dual antiplatelet therapy (DAPT) to ensure long-term atherothrombotic protection (1–3). This approach is supported by a retrospective analysis of 9,577 patients from six randomized trials, in which a prolonged DAPT (≥1 year), instead of 3- or 6-month DAPT followed by aspirin monotherapy, was associated with a greater ischemic risk reduction among patients with complex PCI (4). Yet, in a subsequent study, including 14,963 patients from 8 randomized controlled trials, long-term DAPT provided ischemic benefit only in the absence of high bleeding risk features, but not if such features were present (5). Moreover, in a sub-analysis of a randomized controlled trial including high bleeding risk patients, 1-month DAPT followed by single antiplatelet therapy, mainly consisting of $P2Y_{12}$ inhibitor alone, or standard DAPT were consistently associated with similar rates of major adverse cardiac or cerebral events among complex and noncomplex PCI patients (6).

Aspirin cessation after 1- to 3-month DAPT and continuation with $P2Y_{12}$ inhibitor monotherapy has evidence of favorably affecting the balance between bleeding and ischemic risks among unselected patients undergoing coronary revascularization (7,8). This strategy was associated with similar rates of fatal and ischemic events and lower risk of major bleeding compared with standard DAPT in an individual participant data (IPD) meta-analysis of six randomized trials including 23,308 patients (8) and is recommended as an alternative approach by international guidelines (1–3). Post-hoc analyses of individual trials (9–13) have not conclusively ascertained the trade-off between the safety and efficacy of early transitioning to $P2Y_{12}$ inhibitor monotherapy in complex PCI patients, and concerns remain that early aspirin withdrawal could be associated with potential harm in high-risk subsets.

In the present analysis, we used IPD from the Sidney-2 Collaboration (8) to investigate the treatment effect of $P2Y_{12}$ inhibitor monotherapy versus standard DAPT on centrally adjudicated outcomes among patients undergoing complex and noncomplex PCI.

METHODS

Study design

Sidney-2 was an IPD meta-analysis of randomized controlled trials designed to compare $P2Y_{12}$ inhibitor monotherapy with DAPT on centrally adjudicated outcome data in patients who underwent coronary revascularization (8). Methodological aspects of this IPD meta-analysis were reported previously (8). The study protocol was prospectively registered in PROSPERO and is available online (www.crd.york.ac.uk/prospero, CRD42020176853). Methods and reporting followed the guidelines of the Preferred Reporting Items for a Systematic Review and Meta-analysis of Individual Participant Data (PRISMA-IPD) (14). All trials were approved by ethics committee. All patients provided written informed consent for participation in the individual studies.

Data extraction and quality assessment

All principal investigators of the included trials provided IPD in an anonymized electronic dataset. Data were checked for completeness and consistency against the results of the original publications, and all queries that emerged at integrity checks were resolved with principal investigators. The quality of all included trials was assessed using version 2 of the Cochrane risk-of-bias tool (15).

Study population

The present study was designed to evaluate the safety and efficacy associated with $P2Y_{12}$ inhibitor monotherapy versus DAPT in patients undergoing complex and noncomplex PCI. For this purpose, we excluded patients who did not undergo PCI. Complex PCI included interventions with at least one of the following angiographic features: 3 vessels treated, ≥3 stents implanted, ≥3 lesions treated, total stent length >60 mm, bifurcation with 2 stents implanted, or chronic total occlusion as target lesion (4). An alternative and more extended version of the complex PCI definition including, in addition to all previous components, the use of atherectomy devices, left main intervention, or surgical bypass graft as target vessel, was adopted in a sensitivity analysis.

Study endpoints

The pre-specified primary efficacy endpoint was the composite of all-cause mortality, myocardial infarction, and stroke throughout the duration of the randomized comparison of protocol-mandated $P2Y_{12}$ inhibitor monotherapy versus DAPT. The pre-specified key safety endpoint was Bleeding Academic Research Consortium (BARC) type 3 or 5 bleeding. Secondary endpoints included the individual components of the primary endpoint, cardiovascular and non-cardiovascular mortality, ischemic and hemorrhagic stroke, definite and/or probable stent thrombosis, bleeding according to the BARC and Thrombolysis in Myocardial Infarction (TIMI) scales, and net adverse clinical events (NACE) (a composite of the primary efficacy and key safety endpoints). All events were centrally adjudicated. Outcome definitions were largely consistent across trials (**Supplemental Tables 1-3**).

Statistical analysis

We used a one-step approach to analyze the data from all trials simultaneously using a mixed-effect Cox regression model with baseline hazards stratified by trial and a random intercept to account for variation between trials in treatment effect. The primary analysis was performed in the intention-to-treat population and included clinical events occurring after the time when the protocol specified the change from DAPT to $P2Y_{12}$ inhibitor monotherapy in the experimental group. All events which occurred during the initial DAPT phase, if present, common to both experimental and treatment groups, were censored. Treatment effects were assessed as hazard ratios (HRs) and 95% confidence intervals (CIs). Data were analyzed up to the longest available time-point with protocol-specified $P2Y_{12}$ inhibitor monotherapy in the experimental group and DAPT in the control group. The heterogeneity of the treatment effect between trials was quantified using the variance of the random slope Tau^2. Pre-specified sensitivity analyses were based on a two-step approach using a DerSimonian-Laird random-effects model to combine trial-level estimates. Between-trial heterogeneity for the two-step model was estimated using I^2. The consistency of treatment effects of $P2Y_{12}$ inhibitor monotherapy versus DAPT between the complex PCI and noncomplex PCI groups

was evaluated with formal interaction testing. Additional analyses were done by stratifying patients according to the individual complex PCI components and number of criteria fulfilled. Per-protocol, on-treatment, and sensitivity analyses were performed as secondary analyses. All tests were two-sided, and a p-value of <0.05 was considered to be statistically significant. Analyses were done in Stata Release 17.1 (StataCorp LP, College Station, Texas) and R version 4.0.3 (R Foundation, Vienna, Austria). Further details on statistical analysis are described in the **Online Appendix**.

RESULTS

A total of 23,308 patients from six randomized controlled trials were included in this IPD meta-analysis. We excluded 334 patients (1.4%) who underwent surgical revascularization in one trial (16) and 33 patients (0.14%) who did not undergo PCI in one other trial (17) (**Supplemental Figure 1**). Therefore, the study cohort consists of 22,941 patients from five studies, of whom 4,685 (20.4%) underwent complex PCI and 18,256 (79.6%) noncomplex PCI. The prevalence of the complex PCI criteria is shown in the **Central Illustration** and **Supplemental Table 5**.

Baseline clinical and angiographic characteristics for patients with complex and noncomplex PCI are presented in **Tables 1 and 2**. Mean age was 64.9 years in both groups. Patients undergoing complex PCI were more likely to be male or being affected by diabetes mellitus, presented more frequently with a diagnosis of acute myocardial infarction without ST-segment elevation and less often with ST-segment elevation myocardial infarction compared with noncomplex PCI patients. Procedural characteristics were largely imbalanced between complex and noncomplex PCI groups. Patients with complex PCI had a greater extent of coronary artery disease with a higher number of treated coronary vessels and lesions; they received a greater number of coronary stents with a higher total stent length. Baseline characteristics according to the randomized treatment and PCI complexity were well balanced between groups (**Supplemental Tables 6 and 7**). The median treatment duration was 334 days (range: 9-12 months). The risk of bias assessment showed some concerns for four out of five

trials included in the present study related to the open-label treatment allocation (**Supplemental Table 4**).

Clinical outcomes according to PCI complexity

The primary efficacy endpoint of all-cause death, myocardial infarction, and stroke occurred more often in the complex PCI group compared with the noncomplex PCI group (3.86% vs. 2.98%; HR: 1.28; 95% CI: 1.04-1.59; p=0.02) (**Supplemental Table 8, Supplemental Figure 2**). The risk of the key safety endpoint of BARC type 3 or 5 bleeding was numerically but not statistically significant higher in complex PCI patients (1.66% vs. 1.31%; HR: 1.18; 95% CI: 0.87-1.59; p=0.292). The risk of NACE was higher in patients with complex compared with noncomplex PCI (5.27% vs. 4.1%; HR: 1.24; 95% CI: 1.01-1.52; p=0.041). The rates of secondary endpoints, including all-cause and cardiovascular mortality, myocardial infarction, stroke, BARC type 2, 3 or 5 bleeding, and definite or probable stent thrombosis, were numerically but not statistically significant higher in the complex PCI group when assessed in isolation.

Efficacy endpoints according to the randomized treatment and PCI complexity

Efficacy endpoints according to the randomized treatment and PCI complexity are presented in **Table 3**. The composite endpoint of all-cause mortality, myocardial infarction, and stroke occurred in 75 (3.61%) and 222 (2.75%) patients on $P2Y_{12}$ inhibitor monotherapy and 85 (4.1%) and 247 (3.21%) patients on DAPT in the complex PCI (HR: 0.87; 95% CI: 0.64-1.19; p=0.379) and noncomplex PCI groups (HR: 0.91; 95% CI: 0.76-1.09; p=0.299), respectively, with no significant treatment-by-subgroup interaction for PCI complexity (p-interaction=0.770) (**Central Illustration, Figure 1, Supplemental Figure 3**). Among patients undergoing complex PCI and noncomplex PCI, the risks of all-cause death (HR: 0.92; 95% CI: 0.55-1.55; p=0.762, and HR: 0.77; 95% CI: 0.57-1.03; p=0.075; p-interaction=0.450), cardiovascular death (HR: 0.88; 95% CI: 0.46-1.69; p=0.703, and HR: 0.64; 95% CI: 0.44-0.94; p=0.022; p-interaction=0.430), myocardial infarction (HR: 0.71; 95% CI: 0.47-

1.06; p=0.09, and HR: 1.03; 95% CI: 0.80-1.32; p=0.838; p-interaction=0.110), stroke (HR: 1.69; 95% CI: 0.67-4.30; p=0.268, and HR: 0.96; 95% CI: 0.61-1.51; p=0.852; p-interaction=0.380), and definite or probable stent thrombosis (HR: 0.54; 95% CI: 0.20-1.45; p=0.219, and HR: 0.96; 95% CI: 0.52-1.77; p=0.895; p-interaction=0.380) did not differ between the two treatment strategies, with no evidence of treatment-by-subgroup interaction for any of the ischemic endpoints (**Table 3, Figure 2**). The effect of $P2Y_{12}$ inhibitor monotherapy versus DAPT for the primary endpoint was consistent across the components of the complex PCI definition and the number of criteria fulfilled (**Figure 3**). The treatment effect for the primary endpoint was consistent across predefined subgroups in the complex PCI group (**Supplemental Figure 4**). There was a treatment-by-subgroup interaction for sex in the noncomplex PCI group (p-interaction=0.010), suggesting that $P2Y_{12}$ inhibitor monotherapy reduces the risk of the primary endpoint in females (HR: 0.59; 95% CI: 0.40-0.87) but not males (HR: 1.03; 95% CI: 0.84-1.27) with noncomplex PCI (**Supplemental Figure 5**). This corresponded to a number-needed-to-treat-to-benefit (NNTB) of 66 (95% CI: 40-200) in female patients. When the components of the primary endpoint were stratified by sex, no significant interaction was found for individual outcomes (**Supplemental Figures 6 and 7**). In both complex and noncomplex PCI groups, the effect of monotherapy on the primary endpoint or its components was consistent when stratified by the use of clopidogrel or newer $P2Y_{12}$ inhibitors in the experimental arm (**Supplemental Figures 8 and 9**). In a secondary analysis restricted to studies with newer $P2Y_{12}$ inhibitors monotherapy, the treatment effect was consistent across subgroups except for sex in the noncomplex PCI cohort (p-interaction=0.027) (**Supplemental Figures 10 and 11**). In an analysis restricted to studies with clopidogrel monotherapy, the treatment effect remained consistent across all subgroups (**Supplemental Figures 12 and 13**).

Safety endpoints according to the randomized treatment and PCI complexity

$P2Y_{12}$ inhibitor monotherapy significantly reduced the risk of the key safety endpoint of BARC type 3 or 5 bleeding compared with DAPT in patients undergoing complex PCI (1.08% vs. 2.25%; HR:

0.51; 95% CI: 0.31-0.84; p=0.008; NNTB: 83; 95% CI: 50-250) and noncomplex PCI (0.86% vs. 1.76%; HR: 0.49; 95% CI 0.37-0.64; p<0.001; NNTB: 111; 95% CI: 76-200) with no evidence of heterogeneity for the treatment effect in relation to PCI complexity (p-interaction=0.920) (**Central Illustration, Figure 1, Supplemental Figure 14**). The benefits of $P2Y_{12}$ inhibitor monotherapy was significant for other bleeding endpoints and NACE, with no evidence of interaction between complex and noncomplex PCI patients (**Table 3, Figure 2**). The treatment effect on BARC type 3 or 5 bleeding was consistent across pre-defined subgroups, with the exception of a treatment-by-subgroup interaction for clinical presentation (acute coronary syndrome: HR: 0.38; 95% CI: 0.26-0.54; chronic coronary syndrome: HR: 0.77; 95% CI: 0.49-1.21; p-interaction=0.048) and type of $P2Y_{12}$ inhibitor in the control group (newer $P2Y_{12}$ inhibitors: HR: 0.37; 95% CI: 0.26-0.53; clopidogrel: HR: 0.82; 95% CI: 0.51-1.31; p-interaction=0.0050) in the noncomplex PCI group (**Supplemental Figures 15 and 16**).

Sensitivity and secondary analyses

Sensitivity analyses including the initial DAPT phase after randomization in four out of five trials, showed consistent results for the primary efficacy endpoint, with no evidence for heterogeneity in the treatment effect between complex and noncomplex PCI patients (**Supplemental Table 9**). In the complex PCI group, all-cause death occurred in 35 (1.18%) patients on $P2Y_{12}$ inhibitor monotherapy and 43 (1.38%) with DAPT (HR: 0.81; 95% CI: 0.52-1.27; p=0.355) when GLOBAL LEADERS instead of GLASSY was pooled with the other trials. The corresponding figures in the noncomplex PCI group were 109 (0.92%) with $P2Y_{12}$ inhibitor monotherapy and 128 (1.32%) with DAPT (HR: 0.86; 95% CI: 0.66-1.11; p=0.234), with no evidence of significant interaction between groups (p-interaction=0.920). At per-protocol analysis and on-treatment analysis excluding one trial due to lack of information (18), there was no excess of ischemic events and evidence for lower bleeding risk with $P2Y_{12}$ inhibitor monotherapy in patients with and without complex PCI (**Supplemental Tables 10 and 11**). The hazard ratio of the primary endpoint censoring events that occurred nine months after

initiating the $P2Y_{12}$ inhibitor monotherapy in the experimental arm (to achieve a uniform length of follow-up across studies) was 0.89 (95% CI: 0.63-1.25; p=0.487) and 0.92 (95% CI: 0.76-1.12; p=0.428) in the complex PCI and noncomplex PCI groups, respectively, without significant interaction (p-interaction=0.830) (**Supplemental Table 12**). The treatment effect was consistent when patients presenting with acute or chronic coronary syndromes were appraised separately (**Supplemental Tables 13 and 14**). In an additional sensitivity analysis, implementing an alternative and more extended version of the complex PCI definition, the study results for the primary and all secondary endpoints remained entirely consistent (**Supplemental Table 15**).

DISCUSSION

The main findings of this IPD meta-analysis, including 22,941 patients undergoing PCI with drug-eluting stents from five randomized controlled trials, which compared the effects of $P2Y_{12}$ inhibitor monotherapy versus standard DAPT on centrally adjudicated outcomes in relation to the procedural complexity, can be summarized as follows:

1) Patients undergoing complex PCI had significantly greater risk of ischemic events and numerically higher rate of bleeding than those receiving noncomplex interventions;
2) $P2Y_{12}$ inhibitor monotherapy was associated with similar risks of fatal and ischemic events compared with DAPT, irrespective of PCI complexity; the treatment effect of $P2Y_{12}$ inhibitor monotherapy on ischemic outcomes remained consistent across complex PCI criteria, types of $P2Y_{12}$ inhibitor, and clinical presentation;
3) $P2Y_{12}$ monotherapy significantly reduced the risk of major bleeding and net adverse clinical events compared with DAPT; the magnitude of this effect was consistent among patients with complex and noncomplex PCI.
4) The main findings were corroborated by all subgroup and sensitivity analyses that confirmed consistent bleeding benefits of $P2Y_{12}$ inhibitor monotherapy over DAPT, without a trade-off in ischemic protection.

International guidelines currently endorse, with a class I recommendation, six to twelve months of DAPT after PCI, irrespective of clinical presentation (1–3). This approach is grounded in the evidence indicating the potential benefit of extended DAPT duration in reducing the risk of stent-related and spontaneous ischemic events, which is anticipated to be higher in patients with extensive coronary artery disease and complex stenting (1–4). The introduction of newer-generation drug-eluting stents has greatly reduced the incidence of stent-related complications, which are currently responsible for only a minority of ischemic recurrences after revascularization (19,20). Hence, the benefit of a long-term DAPT mainly derives from preventing thrombotic events in non-stented coronary segments and non-coronary vasculature (20). The intensification and/or prolongation of DAPT involve a trade-off between decreasing ischemic risk and increasing bleeding risk (1–6), with both affecting subsequent mortality (21,22). Patients necessitating complex PCI commonly have concomitant comorbidities, which confer elevated bleeding risk and could act as a treatment modifier for DAPT duration (5,6). More recent evidence suggests that PCI complexity does not justify *per se* a longer course of DAPT and that the overall benefit-risk ratio should instead inform decision-making on DAPT selection (5,6). In this context, implementation of antiplatelet strategies that maximize both efficacy and safety in patients with complex PCI remains crucial.

The present study, including patient-level data from 5 randomized controlled trials reporting centrally adjudicated outcomes, represents the largest analysis examining the effect of aspirin removal after 1 or 3 months of DAPT and continuation with $P2Y_{12}$ inhibitor monotherapy versus standard DAPT in relation to PCI complexity. We found that monotherapy with an oral $P2Y_{12}$ inhibitor was not associated with potential harm after complex or noncomplex PCI, showing similar rates of fatal and ischemic events to DAPT and no signals of excess myocardial infarction or stent thrombosis. The treatment effect was consistent across the individual components of the complex PCI definition and the degrees of procedural complexity or when a modified and more comprehensive definition of complex intervention was adopted (10). Confirmatory analyses were done in the per-protocol and on-treatment populations and across subgroups of interest. The effect of monotherapy remained

consistent irrespective of the type of $P2Y_{12}$ inhibitor. However, newer $P2Y_{12}$ inhibitors ticagrelor and prasugrel were over- and under-represented, respectively, in the study population, and clopidogrel monotherapy was only tested in Asian cohorts compared with a clopidogrel-based DAPT. The observation of a possible benefit on the primary endpoint with $P2Y_{12}$ inhibitor monotherapy in female patients with noncomplex interventions extends our previous findings and suggests a possible sex disparity (8) but remains hypothesis-generating.

In terms of bleeding endpoints, we observed a significant and sustained reduction in major bleeding with $P2Y_{12}$ inhibitor monotherapy compared with standard DAPT, which was uniform in magnitude between patients with and without complex PCI, and attained about 50% relative reduction in both groups. The consistency of the effect was retained when an alternative bleeding scale was adopted for grading severity. We ran several analyses, which suggested that the observed effect on bleeding was robust and reproducible across subgroups and potentially more relevant in patients presenting with acute coronary syndromes, which is in keeping with previous observations (23).

Our pooled analysis of five randomized trials expands on previous post-hoc analyses of individual trials (9–13). The low number of patients included in prior studies resulted in substantial imprecisions around the ischemic and bleeding endpoint estimates (10–13). Investigator-reported events without central adjudication were analyzed in one study (9), introducing possible inaccuracy in outcome classification. Heterogeneous definitions of PCI complexity were adopted across previous post-hoc analyses, therefore producing study-specific results (9–13). Our IPD meta-analysis enabled us to uniformly implement two sets of angiographic criteria (i.e., the original Giustino criteria (4) and an alternative and more comprehensive version of these criteria) to consistently define complex PCI across all study databases. In addition, previous analyses included events occurring during the initial DAPT phase, which was identical in both experimental and control arms (9,11–13) and might have biased treatment estimates toward the null (9,11–13). Both ischemic and bleeding complications have been shown to cluster within the first months after complex interventions (4,9,11–13). In the current analysis, we censored 35% of all primary endpoint events, 48% cardiovascular deaths, 63% definite

or probable stent thromboses, and 41% BARC type 3 or 5 bleedings in the complex PCI group. These events had occurred during the initial DAPT phase and, therefore, should not be considered for examining the risks and benefits associated with the removal of aspirin.

Study Limitations

The current study should be interpreted in view of several limitations. This is a sub-analysis of an IPD meta-analysis; the study findings should be considered hypothesis-generating and require confirmatory randomized investigations. The complex PCI group was not powered to draw definite conclusions on the safety and efficacy of $P2Y_{12}$ inhibitor monotherapy compared with DAPT. Yet, the magnitude and direction of treatment effects in patients with complex and noncomplex PCI were largely consistent with the primary analysis (8). Chronic total occlusion procedures were not available for two trials (13,17), and the use of atherectomy devices was available in one trial only (10). Although the lack of these items might have interacted with the treatment effect, individual components had limited power to detect heterogeneity due to the small size of each subgroup. The effect of the type of $P2Y_{12}$ inhibitor according to PCI complexity requires further investigation. In an open-label and underpowered trial, monotherapy with clopidogrel after 1 to 2 months of DAPT failed to attest noninferiority to standard DAPT for the net clinical benefit in acute coronary syndrome patients (24). This trial was not included in the Sidney-2 meta-analysis because it was completed after the preparation of the IPD dataset. The present analysis is subject to the limitations of the original studies, including the open-label design in four of five trials (9,11–13,17). Noteworthy, all studies implemented central event adjudication, and endpoint definitions were largely consistent across trials.

CONCLUSIONS

Among patients undergoing complex PCI, monotherapy with an oral $P2Y_{12}$ inhibitor was associated with similar risks of all-cause mortality, myocardial infarction, and stroke compared with standard DAPT, irrespective of procedural complexity. $P2Y_{12}$ monotherapy significantly reduced the incidence of major bleeding and net adverse clinical events compared with DAPT, with a consistent effect between patients with complex and noncomplex interventions.

PERSPECTIVES

Competency in Patient Care and Procedural Skills:

$P2Y_{12}$ inhibitor monotherapy after 1 or 3 months of DAPT was associated with a similar risk of fatal and ischemic events and lower incidence of major bleeding compared with standard DAPT, irrespective of PCI complexity.

Translational Outlook:

Additional randomized research is needed to better understand whether the type of $P2Y_{12}$ inhibitor affects the safety and efficacy of aspirin-free strategies with $P2Y_{12}$ inhibitor monotherapy compared with conventional DAPT regimens in patients undergoing complex and noncomplex PCI with current-generation drug-eluting stents.

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FIGURE TITLES AND LEGEND

Central illustration. $P2Y_{12}$ inhibitor monotherapy or standard DAPT after complex PCI.
Complex PCI was defined as having at least 1 of the following criteria: 3 vessels treated, ≥3 stents implanted, ≥3 lesions treated, total stent length >60 mm, bifurcation with 2 stents implanted, or chronic total occlusion as target lesion. Among patients undergoing complex PCI, $P2Y_{12}$ inhibitor monotherapy was associated with similar risks of fatal and ischemic events and lower risks of major bleeding and net adverse clinical events compared with standard DAPT. The treatment effect was consistent among patients with and without complex PCI.

Figure 1. Treatment effect of $P2Y_{12}$ inhibitor monotherapy versus DAPT on the primary efficacy and key safety endpoints in patients undergoing complex and noncomplex PCI.
Kaplan-Meier estimates and hazard ratios for (A) the primary efficacy endpoint of all-cause death, myocardial infarction, and stroke and (B) the key safety endpoint of BARC type 3 or 5 bleeding according to the randomized treatment and PCI complexity. Kaplan-Meier curves are from one-step fixed-effect meta-analysis. BARC=Bleeding Academic Research Consortium; DAPT=dual antiplatelet therapy; P2Y12i=$P2Y_{12}$ inhibitor monotherapy.

Figure 2. Treatment effect of $P2Y_{12}$ inhibitor monotherapy versus DAPT on secondary endpoints in patients undergoing complex and noncomplex PCI.
Kaplan-Meier estimates and hazard ratios for (A) all-cause mortality, (B) cardiovascular mortality, (C) myocardial infarction, (D) stroke, (E) definite or probable stent thrombosis, and (F) net adverse clinical events (NACE) according to randomized treatment and PCI complexity. Kaplan-Meier curves are from one-step fixed-effect meta-analysis. DAPT=dual antiplatelet therapy; P2Y12i=$P2Y_{12}$ inhibitor monotherapy.

Figure 3. Treatment effect of $P2Y_{12}$ inhibitor monotherapy versus DAPT across the components of the complex PCI definition and the number of complex PCI criteria fulfilled.

Risk of the primary efficacy endpoint of (A) all-cause mortality, myocardial infarction, and stroke across the individual components of the complex PCI definition and (B) according to the number of complex PCI criteria fulfilled.

604 **Table 1.** Baseline clinical characteristics according to PCI complexity.
605

	Complex PCI (N=4685)	Noncomplex PCI (N=18256)	p value
Study ID			
GLASSY	1597 (34.1%)	5879 (32.2%)	0.014
SMART-CHOICE	486 (10.4%)	2440 (13.4%)	<0.001
STOPDAPT-2	329 (7.0%)	2674 (14.6%)	<0.001
TICO	570 (12.2%)	2434 (13.3%)	0.035
TWILIGHT	1703 (36.4%)	4829 (26.5%)	<0.001
Age, years (SD)	64.9 ± 10.3	64.9 ± 10.7	0.776
Age ≥65 years	2443 (52.1%)	9583 (52.5%)	0.682
Female sex	974 (20.8%)	4373 (24.0%)	<0.001
Height, meters (SD)	1.7 ± 0.1	1.7 ± 0.1	<0.001
Weight, kg (SD)	78.1 ± 17.2	76.2 ± 17.3	<0.001
Mean BMI, kg/m2 (SD)	27.2 ± 4.8	26.8 ± 4.8	<0.001
Geographic region			
Asia	1727 (36.9%)	8257 (45.2%)	<0.001
North America	685 (14.6%)	2287 (12.5%)	<0.001
Western Europe	1976 (42.2%)	5839 (32.0%)	<0.001
Eastern Europe	297 (6.3%)	1873 (10.3%)	<0.001
Diabetes mellitus	1547 (33.0%)	5715 (31.3%)	0.025
Insulin-treated diabetes	368 (8.4%)	1172 (7.0%)	0.003
Current cigarette smoker	1272 (27.2%)	4875 (26.7%)	0.543
Hypercholesterolemia	2942 (63.1%)	11488 (63.8%)	0.367
Hypertension	3196 (68.3%)	12538 (68.7%)	0.536
Liver disease	9 (0.2%)	24 (0.2%)	0.374
PAD	282 (6.9%)	983 (6.2%)	0.137
Previous MI	929 (19.8%)	3393 (18.6%)	0.053
Previous PCI	1374 (29.3%)	5578 (30.6%)	0.102

Previous CABG	280 (6.0%)	968 (5.3%)	0.069
Prior stroke	129 (2.8%)	565 (3.1%)	0.224
Prior bleeding	52 (1.1%)	213 (1.2%)	0.744
History of CKD	775 (16.9%)	3033 (16.8%)	0.902
Chronic lung disease	181 (5.0%)	630 (4.7%)	0.485
Clinical presentation			
CCS	1827 (39.0%)	7379 (40.4%)	0.077
ACS	2857 (61.0%)	10875 (59.6%)	0.077
Unstable angina	1153 (40.4%)	4215 (38.8%)	0.121
Non-STEMI	1151 (40.3%)	3955 (36.4%)	<0.001
STEMI	553 (19.4%)	2705 (24.9%)	<0.001
Aspirin on admission	2829 (65.0%)	10051 (64.5%)	0.588
PRECISE-DAPT (SD)*	16.8 ± 9.5	16.5 ± 9.5	0.026
PRECISE-DAPT ≥25	784 (17.7%)	2941 (16.8%)	0.156
Creatinine clearance (MDRD), ml/min (IQR)	82.9 (68.6; 98.1)	84.8 (70.2; 100.5)	<0.001
Hemoglobin, g/dl (SD)	14.0 ± 1.7	14.0 ± 2.0	0.382
LVEF, % (SD)	54.4 ± 11.5	56.7 ± 11.0	<0.001

Data expressed as n (%) or means ± standard deviations (SD) or median (interquartile range [IQR]).
*The PRECISE-DAPT score includes 5 items: age, creatinine clearance, white-blood-cell count, hemoglobin, and history of bleeding.
ACS=acute coronary syndrome; BMI=body-mass index; CABG=coronary artery bypass grafting; CCS=chronic coronary syndrome; CKD=chronic kidney disease; g/dl=grams per deciliter; LVEF=left ventricular ejection fraction; ml/min=milliliter per minute; MDRD=Modification of Diet in Renal Disease; MI=myocardial infarction; PAD=peripheral artery disease; PCI=percutaneous coronary intervention; STEMI=ST-segment elevation myocardial infarction.

613 **Table 2.** Baseline procedural characteristics according to PCI complexity.
614

	Complex PCI (N=4685)	Noncomplex PCI (N=18256)	p value
Radial access	3217 (68.7%)	13185 (72.2%)	<0.001
Femoral access	1451 (31.0%)	4893 (26.8%)	<0.001
Brachial access	23 (0.5%)	198 (1.1%)	<0.001
Unfractioned heparin	2690 (64.1%)	10325 (65.3%)	0.141
LMWH	247 (6.4%)	916 (7.0%)	0.203
GP IIb/IIIa inhibitors	225 (5.8%)	636 (4.8%)	0.015
Bivalirudin	1655 (39.4%)	6086 (38.5%)	0.269
Number of vessels treated at index PCI			
One vessel	2498 (53.4%)	16077 (88.2%)	<0.001
Two vessels	1789 (38.2%)	2156 (11.8%)	<0.001
Three vessels or more	395 (8.4%)	0 (0.0%)	<0.001
Number of lesions treated at index PCI			
One lesion	1577 (33.7%)	15083 (82.7%)	<0.001
Two lesions	1767 (37.7%)	3150 (17.3%)	<0.001
Three or more lesions	1338 (28.6%)	0 (0.0%)	<0.001
LAD	2838 (60.6%)	9445 (51.7%)	<0.001
Left circumflex artery	1785 (38.1%)	4517 (24.7%)	<0.001
Right coronary artery	2230 (47.6%)	5562 (30.5%)	<0.001
Left main	296 (6.3%)	428 (2.3%)	<0.001
Venous or arterial graft	58 (1.4%)	172 (1.1%)	0.112
Bifurcation	1295 (27.6%)	2285 (12.5%)	<0.001
Bifurcation lesion treated with at least 2 stents	676 (14.4%)	0 (0.0%)	<0.001
Thrombus	568 (12.1%)	2538 (13.9%)	0.001
TIMI pre-PCI 0-1	1179 (30.2%)	2855 (19.1%)	<0.001
N. of implanted stents	3.0 (2.0; 3.0)	1.0 (1.0; 1.0)	<0.001
Overlapping stents	2151 (72.1%)	2046 (15.2%)	<0.001
Total stent length	66.0 (52.0; 81.0)	24.0 (18.0; 36.0)	<0.001

New generation DES	4661 (99.5%)	18170 (99.9%)	<0.001
Minimum diameter of implanted stents (SD)	2.69 ± 0.39	2.99 ± 0.48	<0.001
Maximum diameter of implanted stents (SD)	3.26 ± 0.46	3.10 ± 0.48	<0.001
Aspirin at randomization	2317 (49.5%)	9173 (50.2%)	0.334
$P2Y_{12}$ at randomization	4685 (100.0%)	18256 (100.0%)	-
Clopidogrel	988 (21.1%)	5888 (32.3%)	<0.001
Prasugrel	44 (0.9%)	188 (1.0%)	0.580
Ticagrelor	3653 (78.0%)	12180 (66.7%)	<0.001
ACE-inhibitors or ARBs at randomization	3039 (64.9%)	11660 (63.9%)	0.209
ß-blockers at randomization	3391 (72.4%)	12467 (68.3%)	<0.001
Statins at randomization	4375 (94.2%)	17050 (94.9%)	0.070
PPI at randomization	2088 (58.5%)	7695 (59.4%)	0.314

Data expressed as n (%) or means±standard deviations or median [IQR]
ACE-inhibitors=angiotensin-converting enzyme-inhibitors; ARBs=angiotensin receptor blockers; DES=drug-eluting stent; GP=glycoprotein; LAD=left anterior descending artery; LIMA=left internal mammary artery; LMWH=low-molecular-weight heparin; PCI=percutaneous coronary intervention; PPI=proton pump inhibitors; TIMI=Thrombolysis in Myocardial Infarction.

620 **Table 3.** Clinical outcomes according to PCI complexity and randomized treatment group.

	Complex PCI (N=4685)					Noncomplex PCI (N=18256)					
Outcome	**$P2Y_{12}$ Inhibitor (N=2368)**	**Aspirin + $P2Y_{12}$ Inhibitor (N=2317)**	**HR (95% CI)**	**Tau^2**	**p value**	**$P2Y_{12}$ Inhibitor (N=9083)**	**Aspirin + $P2Y_{12}$ Inhibitor (N=9173)**	**HR (95% CI)**	**Tau^2**	**p value**	**p-interaction**
Death, MI, or stroke	75 (3.61%)	85 (4.10%)	0.87 (0.64-1.19)	0	0.379	222 (2.75%)	247 (3.21%)	0.91 (0.76-1.09)	0	0.299	0.770
Death or MI	67 (3.26%)	80 (3.88%)	0.82 (0.60-1.14)	0.017	0.242	189 (2.29%)	213 (2.81%)	0.90 (0.74-1.09)	0	0.274	0.660
Death											
All cause	28 (1.31%)	30 (1.42%)	0.92 (0.55-1.55)	0	0.762	79 (0.91%)	104 (1.42%)	0.77 (0.57-1.03)	0	0.075	0.450
Cardiovascular	17 (0.82%)	19 (0.90%)	0.88 (0.46-1.69)	0	0.703	44 (0.51%)	69 (0.91%)	0.64 (0.44-0.94)	0	0.022	0.430
Non-cardiovascular	10 (0.44%)	9 (0.43%)	1.12 (0.46-2.76)	0	0.803	32 (0.37%)	32 (0.47%)	1.01 (0.62-1.65)	0	0.972	0.700
Myocardial infarction	41 (2.03%)	57 (2.79%)	0.71 (0.47-1.06)	0	0.09	123 (1.53%)	121 (1.54%)	1.03 (0.80-1.32)	0.088	0.838	0.110
Stroke											
Any	12 (0.51%)	7 (0.31%)	1.69 (0.67-4.3)	0	0.268	36 (0.49%)	38 (0.44%)	0.96 (0.61-1.51)	0.54	0.852	0.380
Ischemic	9 (0.38%)	3 (0.13%)	3.00 (0.81-11.08)	0	0.1	26 (0.38%)	33 (0.38%)	0.79 (0.47-1.33)	0.55	0.377	0.099
Hemorrhagic	2 (0.09%)	2 (0.09%)	0.97 (0.14-6.91)	0	0.978	4 (0.04%)	0 (0%)	-	-	0.999	>0.99
Stent thrombosis											
Definite	6 (0.36%)	9 (0.51%)	0.55 (0.18-1.63)	0	0.28	17 (0.20%)	17 (0.23%)	1.01 (0.51-1.97)	0	0.984	0.410
Probable	0 (0%)	2 (0.09%)	-	-	-	6 (0.07%)	5 (0.05%)	1.01 (0.29-3.48)	0	0.99	-
Possible	8 (0.42%)	10 (0.46%)	0.79 (0.31-20.0)	0.066	0.619	19 (0.22%)	38 (0.56%)	0.50 (0.29-0.87)	0.12	0.015	0.400

Definite or probable	6 (0.36%)	11 (0.60%)	0.54 (0.20-1.45)	0	0.219	21 (0.25%)	21 (0.27%)	0.96 (0.52-1.77)	0	0.895	0.380
Any	13 (0.74%)	21 (1.06%)	0.61 (0.31-1.22)	0.10	0.161	39 (0.46%)	58 (0.83%)	0.66 (0.44-0.99)	0.024	0.046	0.900
BARC bleeding											
2, 3 or 5	65 (3.12%)	116 (5.64%)	0.54 (0.40-0.74)	0	<0.001	230 (2.93%)	376 (4.63%)	0.61 (0.52-0.72)	0.027	<0.001	0.470
3 or 5	24 (1.08%)	46 (2.25%)	0.51 (0.31-0.84)	0	0.008	73 (0.86%)	151 (1.76%)	0.49 (0.37-0.64)	0.080	<0.001	0.920
5	2 (0.11%)	2 (0.14%)	0.98 (0.14-6.96)	0	0.984	1 (0.02%)	3 (0.05%)	0.33 (0.03-3.22)	0	0.343	0.610
TIMI bleeding											
Major	10 (0.43%)	22 (1.06%)	0.45 (0.21-0.95)	0	0.035	32 (0.39%)	68 (0.81%)	0.39 (0.17-0.87)	0.58	0.022	0.750
Minor	36 (1.84%)	54 (2.64%)	0.65 (0.43-0.99)	0	0.044	100 (1.36%)	186 (2.31%)	0.53 (0.42-0.68)	0	<0.001	0.450
Major or minor	46 (2.28%)	75 (3.68%)	0.60 (0.41-0.86)	0	0.006	131 (1.74%)	251 (3.11%)	0.52 (0.42-0.64)	0.046	<0.001	0.610
NACE	93 (4.43%)	125 (6.13%)	0.73 (0.56-0.95)	0	0.021	285 (3.51%)	373 (4.70%)	0.77 (0.66-0.9)	0.052	0.001	0.640

BARC=Bleeding Academy Research Consortium; CI=confidence interval; HR=hazard ratio; MI=myocardial infarction; NACE=net adverse clinical events, defined as a composite of all-cause death, myocardial infarction, stroke, and BARC type 3 or 5 bleeding; TIMI=Thrombolysis in Myocardial Infarction.

Central Illustration

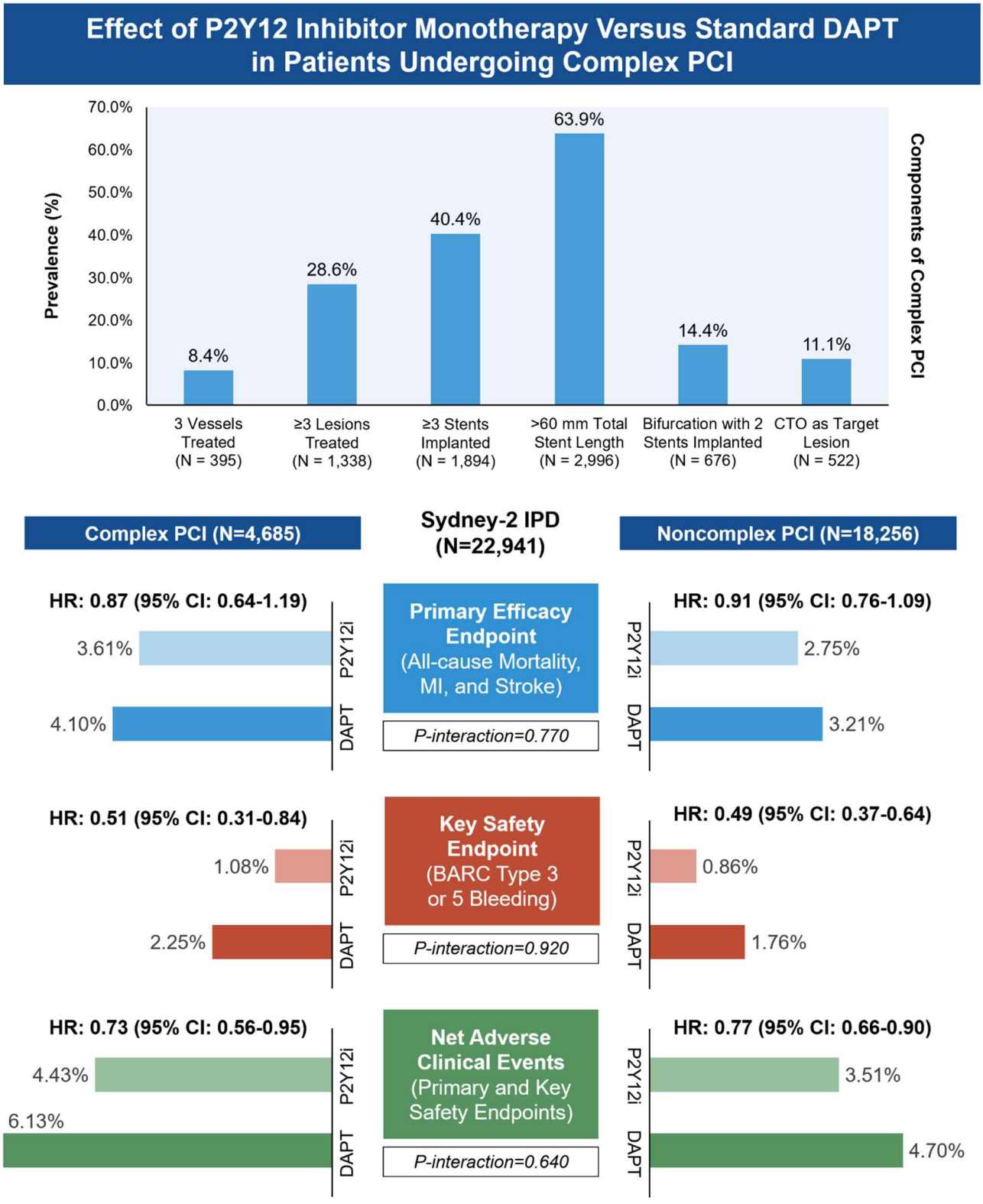


Figure 1

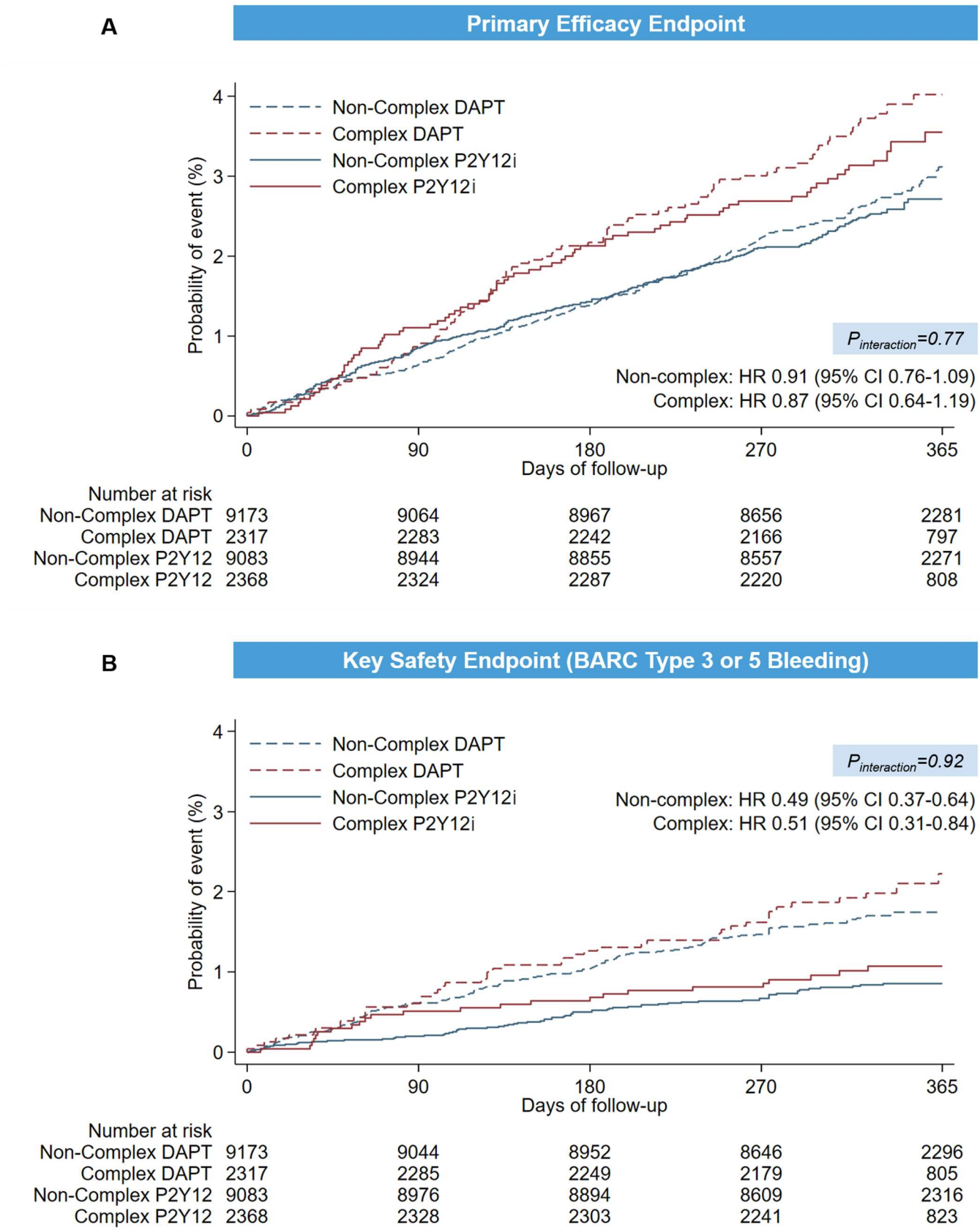

A
Primary Efficacy Endpoint
Non-Complex DAPT
Complex DAPT
Non-Complex P2Y12i
Complex P2Y12i
Probability of event (%)
0
1
2
3
4
$P_{interaction}$=0.77
Non-complex: HR 0.91 (95% CI 0.76-1.09)
Complex: HR 0.87 (95% CI 0.64-1.19)
0
90
180
270
365
Days of follow-up
Number at risk
Non-Complex DAPT 9173 9064 8967 8656 2281
Complex DAPT 2317 2283 2242 2166 797
Non-Complex P2Y12 9083 8944 8855 8557 2271
Complex P2Y12 2368 2324 2287 2220 808
B
Key Safety Endpoint (BARC Type 3 or 5 Bleeding)
Non-Complex DAPT
Complex DAPT
Non-Complex P2Y12i
Complex P2Y12i
Probability of event (%)
0
1
2
3
4
$P_{interaction}$=0.92
Non-complex: HR 0.49 (95% CI 0.37-0.64)
Complex: HR 0.51 (95% CI 0.31-0.84)
0
90
180
270
365
Days of follow-up
Number at risk
Non-Complex DAPT 9173 9044 8952 8646 2296
Complex DAPT 2317 2285 2249 2179 805
Non-Complex P2Y12 9083 8976 8894 8609 2316
Complex P2Y12 2368 2328 2303 2241 823

Figure 2

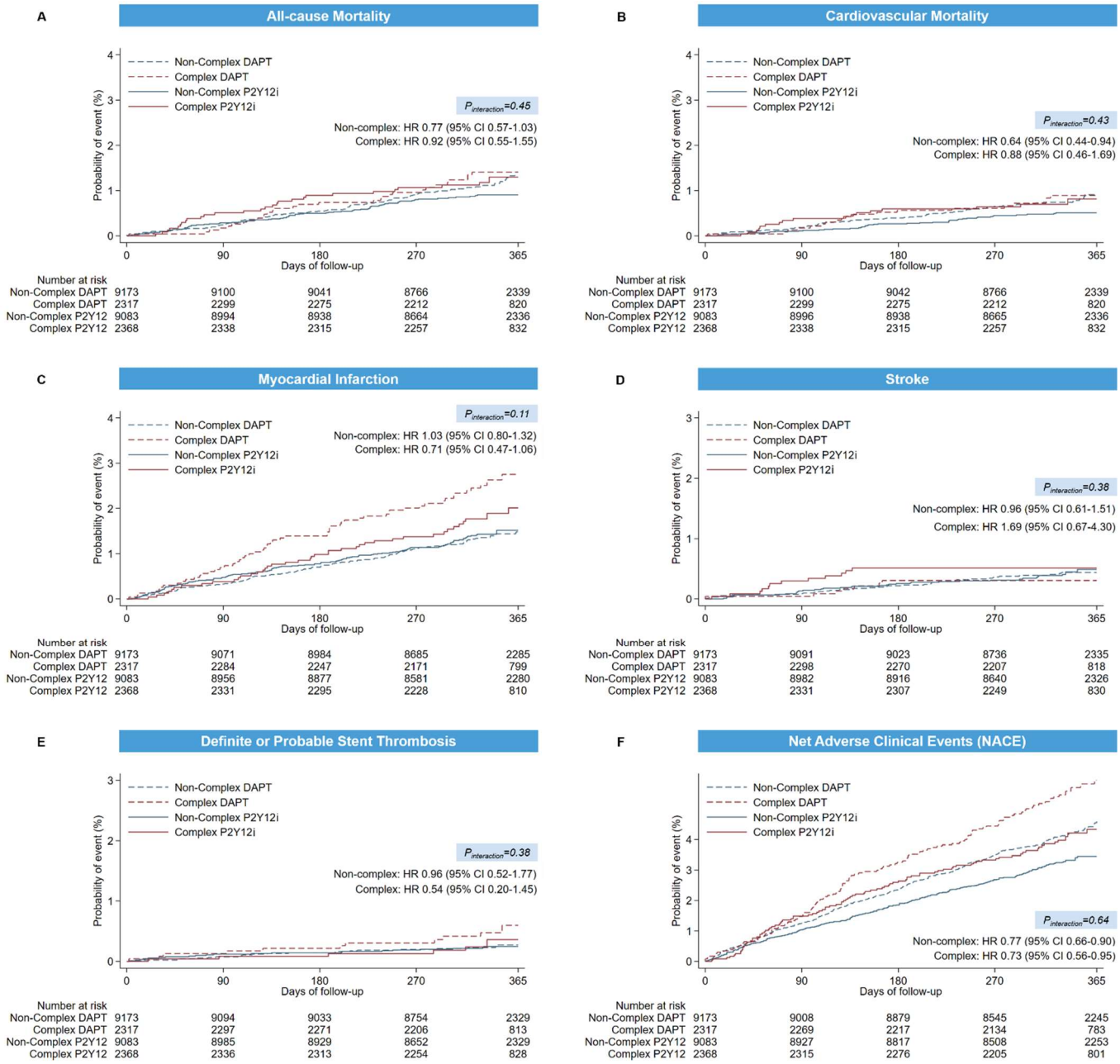
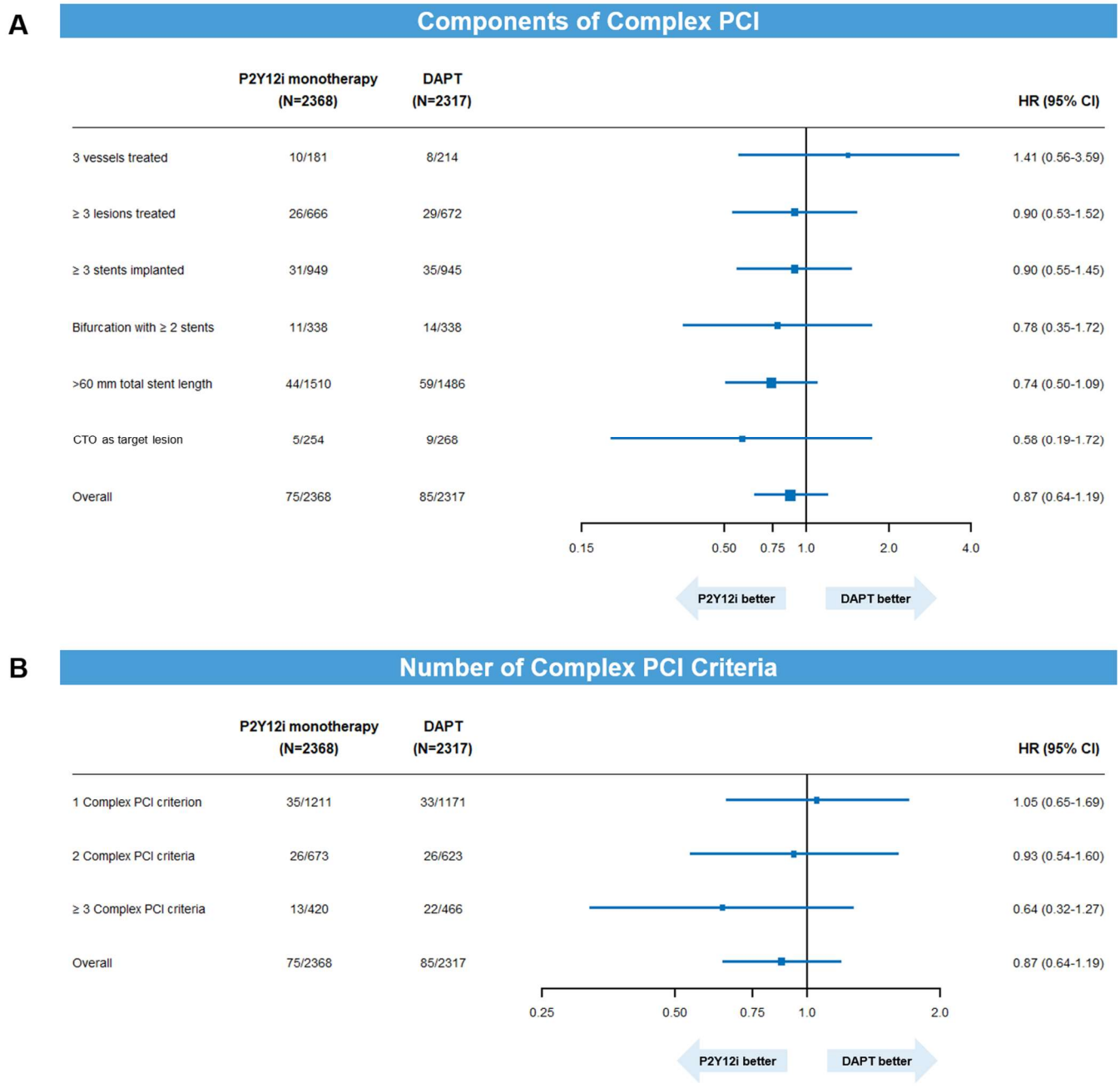

A
All-cause Mortality
Non-Complex DAPT
Complex DAPT
Non-Complex P2Y12i
Complex P2Y12i
$P_{interaction}$=0.45
Non-complex: HR 0.77 (95% CI 0.57-1.03)
Complex: HR 0.92 (95% CI 0.55-1.55)
Probability of event (%)
Days of follow-up
Number at risk
Non-Complex DAPT 9173 9100 9041 8766 2339
Complex DAPT 2317 2299 2275 2212 820
Non-Complex P2Y12 9083 8994 8938 8664 2336
Complex P2Y12 2368 2338 2315 2257 832
B
Cardiovascular Mortality
$P_{interaction}$=0.43
Non-complex: HR 0.64 (95% CI 0.44-0.94)
Complex: HR 0.88 (95% CI 0.46-1.69)
Number at risk
Non-Complex DAPT 9173 9100 9042 8766 2339
Complex DAPT 2317 2299 2275 2212 820
Non-Complex P2Y12 9083 8996 8938 8665 2336
Complex P2Y12 2368 2338 2315 2257 832
C
Myocardial Infarction
$P_{interaction}$=0.11
Non-complex: HR 1.03 (95% CI 0.80-1.32)
Complex: HR 0.71 (95% CI 0.47-1.06)
Number at risk
Non-Complex DAPT 9173 9071 8984 8685 2285
Complex DAPT 2317 2284 2247 2171 799
Non-Complex P2Y12 9083 8956 8877 8581 2280
Complex P2Y12 2368 2331 2295 2228 810
D
Stroke
$P_{interaction}$=0.38
Non-complex: HR 0.96 (95% CI 0.61-1.51)
Complex: HR 1.69 (95% CI 0.67-4.30)
Number at risk
Non-Complex DAPT 9173 9091 9023 8736 2335
Complex DAPT 2317 2298 2270 2207 818
Non-Complex P2Y12 9083 8982 8916 8640 2326
Complex P2Y12 2368 2331 2307 2249 830
E
Definite or Probable Stent Thrombosis
$P_{interaction}$=0.38
Non-complex: HR 0.96 (95% CI 0.52-1.77)
Complex: HR 0.54 (95% CI 0.20-1.45)
Number at risk
Non-Complex DAPT 9173 9094 9033 8754 2329
Complex DAPT 2317 2297 2271 2206 813
Non-Complex P2Y12 9083 8985 8929 8652 2329
Complex P2Y12 2368 2336 2313 2254 828
F
Net Adverse Clinical Events (NACE)
$P_{interaction}$=0.64
Non-complex: HR 0.77 (95% CI 0.66-0.90)
Complex: HR 0.73 (95% CI 0.56-0.95)
Number at risk
Non-Complex DAPT 9173 9008 8879 8545 2245
Complex DAPT 2317 2269 2217 2134 783
Non-Complex P2Y12 9083 8927 8817 8508 2253
Complex P2Y12 2368 2315 2276 2205 801

Figure 3


A
Components of Complex PCI
P2Y12i monotherapy (N=2368)
DAPT (N=2317)
HR (95% CI)
3 vessels treated 10/181 8/214 1.41 (0.56-3.59)
≥ 3 lesions treated 26/666 29/672 0.90 (0.53-1.52)
≥ 3 stents implanted 31/949 35/945 0.90 (0.55-1.45)
Bifurcation with ≥ 2 stents 11/338 14/338 0.78 (0.35-1.72)
>60 mm total stent length 44/1510 59/1486 0.74 (0.50-1.09)
CTO as target lesion 5/254 9/268 0.58 (0.19-1.72)
Overall 75/2368 85/2317 0.87 (0.64-1.19)
0.15 0.50 0.75 1.0 2.0 4.0
P2Y12i better
DAPT better
B
Number of Complex PCI Criteria
P2Y12i monotherapy (N=2368)
DAPT (N=2317)
HR (95% CI)
1 Complex PCI criterion 35/1211 33/1171 1.05 (0.65-1.69)
2 Complex PCI criteria 26/673 26/623 0.93 (0.54-1.60)
≥ 3 Complex PCI criteria 13/420 22/466 0.64 (0.32-1.27)
Overall 75/2368 85/2317 0.87 (0.64-1.19)
0.25 0.50 0.75 1.0 2.0
P2Y12i better
DAPT better