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Peer-reviewed author version

Gragnano, Felice; Mehran, Roxana; Branca, Mattia; Franzone, Anna; Baber, Usman; Jang, Yangsoo; Kimura, Takeshi; Hahn, Joo-Yong; Zhao, Qiang; Windecker, Stephan; Gibson, Charles M.; Kim, Byeong-Keuk; Watanabe, Hirotoshi; Bin Song, Young; Zhu, Yunpeng; VRANCKX, Pascal; Mehta, Shamir; Hong, Sung-Jin; Ando, Kenji; Gwon, Hyeon-Cheol; Calabro, Paolo; Serruys, Patrick W.; Dangas, George D.; McFadden, Eugene P.; Angiolillo, Dominick J.; Heg, Dik & Valgimigli, Marco (2023)
P2Y12 Inhibitor Monotherapy or Dual Antiplatelet Therapy After Complex Percutaneous Coronary Interventions. In: JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY, 81 (6) , p. 537 -552.

DOI: 10.1016/j.jacc.2022.11.041
Handle: http://hdl.handle.net/1942/39841

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

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On behalf of the Single Versus Dual Antiplatelet Therapy (Sidney-2) Collaboration

: Equally contributing

Running title: $P2Y_{12}$ inhibitor monotherapy after complex PCI

Total word count (main text, references, and figure legends): 4,641

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Funding: This study was funded by institutional support of the Cardiocentro Ticino Institute, Ente Ospedaliero Cantonale, which had no role in the data analysis, interpretation, or writing of the report. There was no industry involvement in the design, analysis or funding of this study.

Relationships with Industry and Other Entities:
Dr. Valgimigli reports personal fees from Astra Zeneca, grants and personal fees from Terumo, personal fees from Alvimedica/CID, personal fees from Abbott Vascular, personal fees from Daiichi Sankyo, personal fees from Bayer, personal fees from CoreFLOW, personal fees from IDORSIA PHARMACEUTICALS LTD, personal fees from Universität Basel | Dept. Klinische Forschung, personal fees from Bristol Myers Squib SA, personal fees from Medscape, personal fees from Biotronik, personal fees from Novartis, outside the submitted work.

Dr. Branca and Dr. Heg are affiliated with CTU Bern, University of Bern, which has a staff policy of not accepting honoraria or consultancy fees. However, CTU Bern is involved in design, conduct, or analysis of clinical studies funded by not-for-profit and for-profit organizations. In particular, pharmaceutical and medical device companies provide direct funding to some of these studies. For an up-to-date list of CTU Bern's conflicts of interest see http://www.ctu.unibe.ch/research/declaration_of_interest/index_eng.html.
Dr. Kimura reports grants and personal fees from Abbott Medical Japan, grants from Boston Scientific, and served as advisory board for Abbott Medical Japan and Terumo, outside the submitted work.
Dr. Hahn reports grants from Ministry of Health & Welfare, grants and personal fees from Abbott Vascular, grants and personal fees from Biotronik, grants and personal fees from Boston Scientific, grants and personal fees from Daiichi Sankyo, grants and personal fees from Medtronic, personal fees from Astra Zeneca, personal fees from Sanofi-Aventis, outside the submitted work.
Dr. Zhao reports grants and personal fees from AstraZeneca, personal fees from Novartis, personal fees from Sanofi, personal fees and non-financial support from Johnson & Johnson, personal fees and non-financial support from Medtronic, grants and personal fees from Chugaipharma, outside the submitted work.
Dr. Windecker reports research and educational grants to the institution from Abbott, Amgen, BMS, Bayer, Boston Scientific, Biotronik, Cardinal Health, CardioValve, CSL Behring, Daiichi Sankyo, Edwards Lifesciences, Johnson&Johnson, Medtronic, Querbet, Polares, Sanofi, Terumo, Sinomed. He serves as unpaid advisory board member and/or unpaid member of the steering/executive group of trials funded by Abbott, Abiomed, Amgen, Astra Zeneca, BMS, Boston Scientific, Biotronik, Cardiovalve, Edwards Lifesciences, MedAlliance, Medtronic, Novartis, Polares, Sinomed, V-Wave and Xeltis, but has not received personal payments by pharmaceutical companies or device manufacturers. He is also member of the steering/excecutive committee group of several investigated-initiated trials that receive funding by industry without impact on his personal remuneration. He is an unpaid member of the Pfizer Research Award selection committee in Switzerland.
Dr. Gibson reports personal fees from AstraZeneca, during the conduct of the study; personal fees from Angel Medical Corporation, Bayer Corp., grants and personal fees from CSL Behring, grants and personal fees from Janssen Pharmaceuticals, grants and personal fees from Johnson & Johnson Corporation, personal fees from The Medicines Company, personal fees from Boston Clinical Research Institute, personal fees from Cardiovascular Research Foundation, personal fees from Eli Lilly and Company, personal fees from Gilead Sciences, Inc., personal fees from Novo Nordisk, personal fees from Web MD, personal fees from UpToDate in Cardiovascular Medicine, personal fees from Amarin Pharma, personal fees from Amgen, personal fees from Boehringer Ingelheim , personal fees from Merck & Co, Inc., personal fees from PharmaMar, personal fees from Sanofi, personal fees from Somahlution, personal fees from Vereseon Corporation , personal fees from Boston Scientific, personal fees from Duke Clinical Research Institute, personal fees from Impact Bio, LTD, personal fees from MedImmune, personal fees from Medtelligence, personal fees from Microport, personal fees from PERT Consortium, other from nference, non-financial support from Baim Institute, grants from SCAD Alliance, personal fees from GE Healthcare, personal fees from Caladrius Bioscience, personal fees from CeleCor Therapeutics , personal fees from Thrombolytic Science , personal fees from Eidos Therapeutics, personal fees from Kiniksa Pharmaceuticals, personal fees from Micodrop, LLC, personal fees from MD Magazine, personal fees from MJHealth, personal fees from Samsung, personal fees from SCAI, personal fees from Revance Therapeutics, personal fees from Pfizer, personal fees from Gentech, other from Dyad Medical, outside the submitted work.
Dr. Watanabe reports personal fees from Abbott Medical Japan and Daiichi Sankyo, outside the submitted work.

Dr. Zhu reports grants and personal fees from AstraZeneca, personal fees from Novartis, personal fees from Sanofi, personal fees and non-financial support from Medtronic, grants and personal fees from Chugaipharma, outside the submitted work.
PWS reports personal fees from Sinomedical, personal fees from SMT, personal fees from Philips, personal fees from Xeltis, personal fees from Novartis, personal fees from Merillife, outside the submitted work.
Dr. Dangas reports grants from astrazeneca, during the conduct of the study; personal fees from biosensors, grants from abbott vascular, grants and personal fees from boston scientific, grants from medtronic, grants from daiichi-sankyo, grants from bayer, outside the submitted work.
Dr. Mc Fadden reports personal fees from Cardialysis BV, Rotterdam, Netherlands, outside the submitted work.
Dr. Angiolillo declares that he has received consulting fees or honoraria from Abbott, Amgen, Aralez, AstraZeneca, Bayer, Biosensors, Boehringer Ingelheim, Bristol-Myers Squibb, Chiesi, Daiichi-Sankyo, Eli Lilly, Haemonetics, Janssen, Merck, PhaseBio, PLx Pharma, Pfizer, Sanofi, and The Medicines Company and has received payments for participation in review activities from CeloNova and St Jude Medical, outside the present work. He declares that his institution has received research grants from Amgen, AstraZeneca, Bayer, Biosensors, CeloNova, CSL Behring, Daiichi-Sankyo, Eisai, Eli Lilly, Gilead, Janssen, Matsutani Chemical Industry Co., Merck, Novartis, Osprey Medical, Renal Guard Solutions and Scott R. MacKenzie Foundation.
Dr. Vranckx declares that he has received consulting fees or honoraria from AstraZeneca, Bayer AG, Daiichi-Sankyo, and The Medicines Company outside the present work. PV also declares that his institution has received research grants from Daiichi-Sankyo and Medtronic.
Dr. Mehran reports grants from Abbott Laboratories, AstraZeneca, Bayer, Beth Israel Deaconess, BMS, CSL Behring, DSI, Medtronic, Novartis Pharmaceuticals, OrbusNeich, personal fees from Abbott Laboratories, other financial relationships with Abbott Laboratories, Abiomed, The Medicines Company, personal fees from Boston Scientific, Medscape/WebMD, Siemens Medical Solutions, PLx Opco Inc/dba PLx Pharma Inc, non-financial support from and other relationships with Regeneron Pharmaceuticals, personal fees from Roivant Sciences, other financial relationships with Spectranetics/Philips/Volcano Corp, personal fees from Sanofi, Medtelligence (Janssen Scientific Affairs, personal fees from Janssen Scientific Affairs, other from Bristol Myers Squibb, and other financial relationships with Watermark Research Partners, outside the submitted work.
There are no other relationships that could appear to have influenced the submitted work.

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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

191 **INTRODUCTION**

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

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

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

216

217 **METHODS**

218 **Study design**

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

227

228 **Data extraction and quality assessment**

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

233

234 **Study population**

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

243 **Study endpoints**

244 The pre-specified primary efficacy endpoint was the composite of all-cause mortality, myocardial
245 infarction, and stroke throughout the duration of the randomized comparison of protocol-mandated
246 $P2Y_{12}$ inhibitor monotherapy versus DAPT. The pre-specified key safety endpoint was Bleeding
247 Academic Research Consortium (BARC) type 3 or 5 bleeding. Secondary endpoints included the
248 individual components of the primary endpoint, cardiovascular and non-cardiovascular mortality,
249 ischemic and hemorrhagic stroke, definite and/or probable stent thrombosis, bleeding according to
250 the BARC and Thrombolysis in Myocardial Infarction (TIMI) scales, and net adverse clinical events
251 (NACE) (a composite of the primary efficacy and key safety endpoints). All events were centrally
252 adjudicated. Outcome definitions were largely consistent across trials (**Supplemental Tables 1-3**).

253

254 **Statistical analysis**

255 We used a one-step approach to analyze the data from all trials simultaneously using a mixed-effect
256 Cox regression model with baseline hazards stratified by trial and a random intercept to account for
257 variation between trials in treatment effect. The primary analysis was performed in the intention-to-
258 treat population and included clinical events occurring after the time when the protocol specified the
259 change from DAPT to $P2Y_{12}$ inhibitor monotherapy in the experimental group. All events which
260 occurred during the initial DAPT phase, if present, common to both experimental and treatment
261 groups, were censored. Treatment effects were assessed as hazard ratios (HRs) and 95% confidence
262 intervals (CIs). Data were analyzed up to the longest available time-point with protocol-specified
263 $P2Y_{12}$ inhibitor monotherapy in the experimental group and DAPT in the control group. The
264 heterogeneity of the treatment effect between trials was quantified using the variance of the random
265 slope Tau^2. Pre-specified sensitivity analyses were based on a two-step approach using a
266 DerSimonian-Laird random-effects model to combine trial-level estimates. Between-trial
267 heterogeneity for the two-step model was estimated using I^2. The consistency of treatment effects of
268 $P2Y_{12}$ inhibitor monotherapy versus DAPT between the complex PCI and noncomplex PCI groups

269 was evaluated with formal interaction testing. Additional analyses were done by stratifying patients
270 according to the individual complex PCI components and number of criteria fulfilled. Per-protocol,
271 on-treatment, and sensitivity analyses were performed as secondary analyses. All tests were two-
272 sided, and a p-value of <0.05 was considered to be statistically significant. Analyses were done in
273 Stata Release 17.1 (StataCorp LP, College Station, Texas) and R version 4.0.3 (R Foundation,
274 Vienna, Austria). Further details on statistical analysis are described in the **Online Appendix**.
275
276 **RESULTS**
277 A total of 23,308 patients from six randomized controlled trials were included in this IPD meta-
278 analysis. We excluded 334 patients (1.4%) who underwent surgical revascularization in one trial (16)
279 and 33 patients (0.14%) who did not undergo PCI in one other trial (17) (**Supplemental Figure 1**).
280 Therefore, the study cohort consists of 22,941 patients from five studies, of whom 4,685 (20.4%)
281 underwent complex PCI and 18,256 (79.6%) noncomplex PCI. The prevalence of the complex PCI
282 criteria is shown in the **Central Illustration** and **Supplemental Table 5**.
283 Baseline clinical and angiographic characteristics for patients with complex and noncomplex PCI are
284 presented in **Tables 1 and 2**. Mean age was 64.9 years in both groups. Patients undergoing complex
285 PCI were more likely to be male or being affected by diabetes mellitus, presented more frequently
286 with a diagnosis of acute myocardial infarction without ST-segment elevation and less often with ST-
287 segment elevation myocardial infarction compared with noncomplex PCI patients. Procedural
288 characteristics were largely imbalanced between complex and noncomplex PCI groups. Patients with
289 complex PCI had a greater extent of coronary artery disease with a higher number of treated coronary
290 vessels and lesions; they received a greater number of coronary stents with a higher total stent length.
291 Baseline characteristics according to the randomized treatment and PCI complexity were well
292 balanced between groups (**Supplemental Tables 6 and 7**). The median treatment duration was 334
293 days (range: 9-12 months). The risk of bias assessment showed some concerns for four out of five

294 trials included in the present study related to the open-label treatment allocation (**Supplemental**
295 **Table 4**).
296
297 **Clinical outcomes according to PCI complexity**
298 The primary efficacy endpoint of all-cause death, myocardial infarction, and stroke occurred more
299 often in the complex PCI group compared with the noncomplex PCI group (3.86% vs. 2.98%; HR:
300 1.28; 95% CI: 1.04-1.59; p=0.02) (**Supplemental Table 8, Supplemental Figure 2**). The risk of the
301 key safety endpoint of BARC type 3 or 5 bleeding was numerically but not statistically significant
302 higher in complex PCI patients (1.66% vs. 1.31%; HR: 1.18; 95% CI: 0.87-1.59; p=0.292). The risk
303 of NACE was higher in patients with complex compared with noncomplex PCI (5.27% vs. 4.1%;
304 HR: 1.24; 95% CI: 1.01-1.52; p=0.041). The rates of secondary endpoints, including all-cause and
305 cardiovascular mortality, myocardial infarction, stroke, BARC type 2, 3 or 5 bleeding, and definite
306 or probable stent thrombosis, were numerically but not statistically significant higher in the complex
307 PCI group when assessed in isolation.
308
309 **Efficacy endpoints according to the randomized treatment and PCI complexity**
310 Efficacy endpoints according to the randomized treatment and PCI complexity are presented in **Table**
311 **3**. The composite endpoint of all-cause mortality, myocardial infarction, and stroke occurred in 75
312 (3.61%) and 222 (2.75%) patients on $P2Y_{12}$ inhibitor monotherapy and 85 (4.1%) and 247 (3.21%)
313 patients on DAPT in the complex PCI (HR: 0.87; 95% CI: 0.64-1.19; p=0.379) and noncomplex PCI
314 groups (HR: 0.91; 95% CI: 0.76-1.09; p=0.299), respectively, with no significant treatment-by-
315 subgroup interaction for PCI complexity (p-interaction=0.770) (**Central Illustration, Figure 1,**
316 **Supplemental Figure 3**). Among patients undergoing complex PCI and noncomplex PCI, the risks
317 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;
318 p-interaction=0.450), cardiovascular death (HR: 0.88; 95% CI: 0.46-1.69; p=0.703, and HR: 0.64;
319 95% CI: 0.44-0.94; p=0.022; p-interaction=0.430), myocardial infarction (HR: 0.71; 95% CI: 0.47-

320 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;
321 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
322 definite or probable stent thrombosis (HR: 0.54; 95% CI: 0.20-1.45; p=0.219, and HR: 0.96; 95% CI:
323 0.52-1.77; p=0.895; p-interaction=0.380) did not differ between the two treatment strategies, with no
324 evidence of treatment-by-subgroup interaction for any of the ischemic endpoints (**Table 3, Figure**
325 **2**). The effect of $P2Y_{12}$ inhibitor monotherapy versus DAPT for the primary endpoint was consistent
326 across the components of the complex PCI definition and the number of criteria fulfilled (**Figure 3**).
327 The treatment effect for the primary endpoint was consistent across predefined subgroups in the
328 complex PCI group (**Supplemental Figure 4**). There was a treatment-by-subgroup interaction for
329 sex in the noncomplex PCI group (p-interaction=0.010), suggesting that $P2Y_{12}$ inhibitor monotherapy
330 reduces the risk of the primary endpoint in females (HR: 0.59; 95% CI: 0.40-0.87) but not males (HR:
331 1.03; 95% CI: 0.84-1.27) with noncomplex PCI (**Supplemental Figure 5**). This corresponded to a
332 number-needed-to-treat-to-benefit (NNTB) of 66 (95% CI: 40-200) in female patients. When the
333 components of the primary endpoint were stratified by sex, no significant interaction was found for
334 individual outcomes (**Supplemental Figures 6 and 7**). In both complex and noncomplex PCI groups,
335 the effect of monotherapy on the primary endpoint or its components was consistent when stratified
336 by the use of clopidogrel or newer $P2Y_{12}$ inhibitors in the experimental arm (**Supplemental Figures**
337 **8 and 9**). In a secondary analysis restricted to studies with newer $P2Y_{12}$ inhibitors monotherapy, the
338 treatment effect was consistent across subgroups except for sex in the noncomplex PCI cohort (p-
339 interaction=0.027) (**Supplemental Figures 10 and 11**). In an analysis restricted to studies with
340 clopidogrel monotherapy, the treatment effect remained consistent across all subgroups
341 (**Supplemental Figures 12 and 13**).
342
343 **Safety endpoints according to the randomized treatment and PCI complexity**
344 $P2Y_{12}$ inhibitor monotherapy significantly reduced the risk of the key safety endpoint of BARC type
345 3 or 5 bleeding compared with DAPT in patients undergoing complex PCI (1.08% vs. 2.25%; HR:

346 0.51; 95% CI: 0.31-0.84; p=0.008; NNTB: 83; 95% CI: 50-250) and noncomplex PCI (0.86% vs.
347 1.76%; HR: 0.49; 95% CI 0.37-0.64; p<0.001; NNTB: 111; 95% CI: 76-200) with no evidence of
348 heterogeneity for the treatment effect in relation to PCI complexity (p-interaction=0.920) (**Central**
349 **Illustration, Figure 1, Supplemental Figure 14**). The benefits of $P2Y_{12}$ inhibitor monotherapy was
350 significant for other bleeding endpoints and NACE, with no evidence of interaction between complex
351 and noncomplex PCI patients (**Table 3, Figure 2**). The treatment effect on BARC type 3 or 5 bleeding
352 was consistent across pre-defined subgroups, with the exception of a treatment-by-subgroup
353 interaction for clinical presentation (acute coronary syndrome: HR: 0.38; 95% CI: 0.26-0.54; chronic
354 coronary syndrome: HR: 0.77; 95% CI: 0.49-1.21; p-interaction=0.048) and type of $P2Y_{12}$ inhibitor
355 in the control group (newer $P2Y_{12}$ inhibitors: HR: 0.37; 95% CI: 0.26-0.53; clopidogrel: HR: 0.82;
356 95% CI: 0.51-1.31; p-interaction=0.0050) in the noncomplex PCI group (**Supplemental Figures 15**
357 **and 16**).
358
359 **Sensitivity and secondary analyses**
360 Sensitivity analyses including the initial DAPT phase after randomization in four out of five trials,
361 showed consistent results for the primary efficacy endpoint, with no evidence for heterogeneity in the
362 treatment effect between complex and noncomplex PCI patients (**Supplemental Table 9**). In the
363 complex PCI group, all-cause death occurred in 35 (1.18%) patients on $P2Y_{12}$ inhibitor monotherapy
364 and 43 (1.38%) with DAPT (HR: 0.81; 95% CI: 0.52-1.27; p=0.355) when GLOBAL LEADERS
365 instead of GLASSY was pooled with the other trials. The corresponding figures in the noncomplex
366 PCI group were 109 (0.92%) with $P2Y_{12}$ inhibitor monotherapy and 128 (1.32%) with DAPT (HR:
367 0.86; 95% CI: 0.66-1.11; p=0.234), with no evidence of significant interaction between groups (p-
368 interaction=0.920). At per-protocol analysis and on-treatment analysis excluding one trial due to lack
369 of information (18), there was no excess of ischemic events and evidence for lower bleeding risk with
370 $P2Y_{12}$ inhibitor monotherapy in patients with and without complex PCI (**Supplemental Tables 10**
371 **and 11**). The hazard ratio of the primary endpoint censoring events that occurred nine months after

372 initiating the $P2Y_{12}$ inhibitor monotherapy in the experimental arm (to achieve a uniform length of
373 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;
374 p=0.428) in the complex PCI and noncomplex PCI groups, respectively, without significant
375 interaction (p-interaction=0.830) (**Supplemental Table 12**). The treatment effect was consistent
376 when patients presenting with acute or chronic coronary syndromes were appraised separately
377 (**Supplemental Tables 13 and 14**). In an additional sensitivity analysis, implementing an alternative
378 and more extended version of the complex PCI definition, the study results for the primary and all
379 secondary endpoints remained entirely consistent (**Supplemental Table 15**).
380

381 **DISCUSSION**

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

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

398 International guidelines currently endorse, with a class I recommendation, six to twelve months of
399 DAPT after PCI, irrespective of clinical presentation (1–3). This approach is grounded in the evidence
400 indicating the potential benefit of extended DAPT duration in reducing the risk of stent-related and
401 spontaneous ischemic events, which is anticipated to be higher in patients with extensive coronary
402 artery disease and complex stenting (1–4). The introduction of newer-generation drug-eluting stents
403 has greatly reduced the incidence of stent-related complications, which are currently responsible for
404 only a minority of ischemic recurrences after revascularization (19,20). Hence, the benefit of a long-
405 term DAPT mainly derives from preventing thrombotic events in non-stented coronary segments and
406 non-coronary vasculature (20). The intensification and/or prolongation of DAPT involve a trade-off
407 between decreasing ischemic risk and increasing bleeding risk (1–6), with both affecting subsequent
408 mortality (21,22). Patients necessitating complex PCI commonly have concomitant comorbidities,
409 which confer elevated bleeding risk and could act as a treatment modifier for DAPT duration (5,6).
410 More recent evidence suggests that PCI complexity does not justify *per se* a longer course of DAPT
411 and that the overall benefit-risk ratio should instead inform decision-making on DAPT selection (5,6).
412 In this context, implementation of antiplatelet strategies that maximize both efficacy and safety in
413 patients with complex PCI remains crucial.
414 The present study, including patient-level data from 5 randomized controlled trials reporting centrally
415 adjudicated outcomes, represents the largest analysis examining the effect of aspirin removal after 1
416 or 3 months of DAPT and continuation with $P2Y_{12}$ inhibitor monotherapy versus standard DAPT in
417 relation to PCI complexity. We found that monotherapy with an oral $P2Y_{12}$ inhibitor was not
418 associated with potential harm after complex or noncomplex PCI, showing similar rates of fatal and
419 ischemic events to DAPT and no signals of excess myocardial infarction or stent thrombosis. The
420 treatment effect was consistent across the individual components of the complex PCI definition and
421 the degrees of procedural complexity or when a modified and more comprehensive definition of
422 complex intervention was adopted (10). Confirmatory analyses were done in the per-protocol and on-
423 treatment populations and across subgroups of interest. The effect of monotherapy remained

424 consistent irrespective of the type of $P2Y_{12}$ inhibitor. However, newer $P2Y_{12}$ inhibitors ticagrelor and
425 prasugrel were over- and under-represented, respectively, in the study population, and clopidogrel
426 monotherapy was only tested in Asian cohorts compared with a clopidogrel-based DAPT. The
427 observation of a possible benefit on the primary endpoint with $P2Y_{12}$ inhibitor monotherapy in female
428 patients with noncomplex interventions extends our previous findings and suggests a possible sex
429 disparity (8) but remains hypothesis-generating.
430 In terms of bleeding endpoints, we observed a significant and sustained reduction in major bleeding
431 with $P2Y_{12}$ inhibitor monotherapy compared with standard DAPT, which was uniform in magnitude
432 between patients with and without complex PCI, and attained about 50% relative reduction in both
433 groups. The consistency of the effect was retained when an alternative bleeding scale was adopted
434 for grading severity. We ran several analyses, which suggested that the observed effect on bleeding
435 was robust and reproducible across subgroups and potentially more relevant in patients presenting
436 with acute coronary syndromes, which is in keeping with previous observations (23).
437 Our pooled analysis of five randomized trials expands on previous post-hoc analyses of individual
438 trials (9–13). The low number of patients included in prior studies resulted in substantial imprecisions
439 around the ischemic and bleeding endpoint estimates (10–13). Investigator-reported events without
440 central adjudication were analyzed in one study (9), introducing possible inaccuracy in outcome
441 classification. Heterogeneous definitions of PCI complexity were adopted across previous post-hoc
442 analyses, therefore producing study-specific results (9–13). Our IPD meta-analysis enabled us to
443 uniformly implement two sets of angiographic criteria (i.e., the original Giustino criteria (4) and an
444 alternative and more comprehensive version of these criteria) to consistently define complex PCI
445 across all study databases. In addition, previous analyses included events occurring during the initial
446 DAPT phase, which was identical in both experimental and control arms (9,11–13) and might have
447 biased treatment estimates toward the null (9,11–13). Both ischemic and bleeding complications have
448 been shown to cluster within the first months after complex interventions (4,9,11–13). In the current
449 analysis, we censored 35% of all primary endpoint events, 48% cardiovascular deaths, 63% definite

450 or probable stent thromboses, and 41% BARC type 3 or 5 bleedings in the complex PCI group. These
451 events had occurred during the initial DAPT phase and, therefore, should not be considered for
452 examining the risks and benefits associated with the removal of aspirin.
453
454 **Study Limitations**
455 The current study should be interpreted in view of several limitations. This is a sub-analysis of an
456 IPD meta-analysis; the study findings should be considered hypothesis-generating and require
457 confirmatory randomized investigations. The complex PCI group was not powered to draw definite
458 conclusions on the safety and efficacy of $P2Y_{12}$ inhibitor monotherapy compared with DAPT. Yet,
459 the magnitude and direction of treatment effects in patients with complex and noncomplex PCI were
460 largely consistent with the primary analysis (8). Chronic total occlusion procedures were not available
461 for two trials (13,17), and the use of atherectomy devices was available in one trial only (10).
462 Although the lack of these items might have interacted with the treatment effect, individual
463 components had limited power to detect heterogeneity due to the small size of each subgroup. The
464 effect of the type of $P2Y_{12}$ inhibitor according to PCI complexity requires further investigation. In an
465 open-label and underpowered trial, monotherapy with clopidogrel after 1 to 2 months of DAPT failed
466 to attest noninferiority to standard DAPT for the net clinical benefit in acute coronary syndrome
467 patients (24). This trial was not included in the Sidney-2 meta-analysis because it was completed after
468 the preparation of the IPD dataset. The present analysis is subject to the limitations of the original
469 studies, including the open-label design in four of five trials (9,11–13,17). Noteworthy, all studies
470 implemented central event adjudication, and endpoint definitions were largely consistent across trials.
471
472
473
474
475

476 **CONCLUSIONS**

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

482 **PERSPECTIVES**

483

484 **Competency in Patient Care and Procedural Skills:**

485 $P2Y_{12}$ inhibitor monotherapy after 1 or 3 months of DAPT was associated with a similar risk of
486 fatal and ischemic events and lower incidence of major bleeding compared with standard DAPT,
487 irrespective of PCI complexity.

488

489 **Translational Outlook:**

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

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573 **FIGURE TITLES AND LEGEND**

574

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

582

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

590

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

598 **Figure 3. Treatment effect of $P2Y_{12}$ inhibitor monotherapy versus DAPT across the components**
599 **of the complex PCI definition and the number of complex PCI criteria fulfilled.**
600 Risk of the primary efficacy endpoint of (A) all-cause mortality, myocardial infarction, and stroke
601 across the individual components of the complex PCI definition and (B) according to the number of
602 complex PCI criteria fulfilled.
603

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.

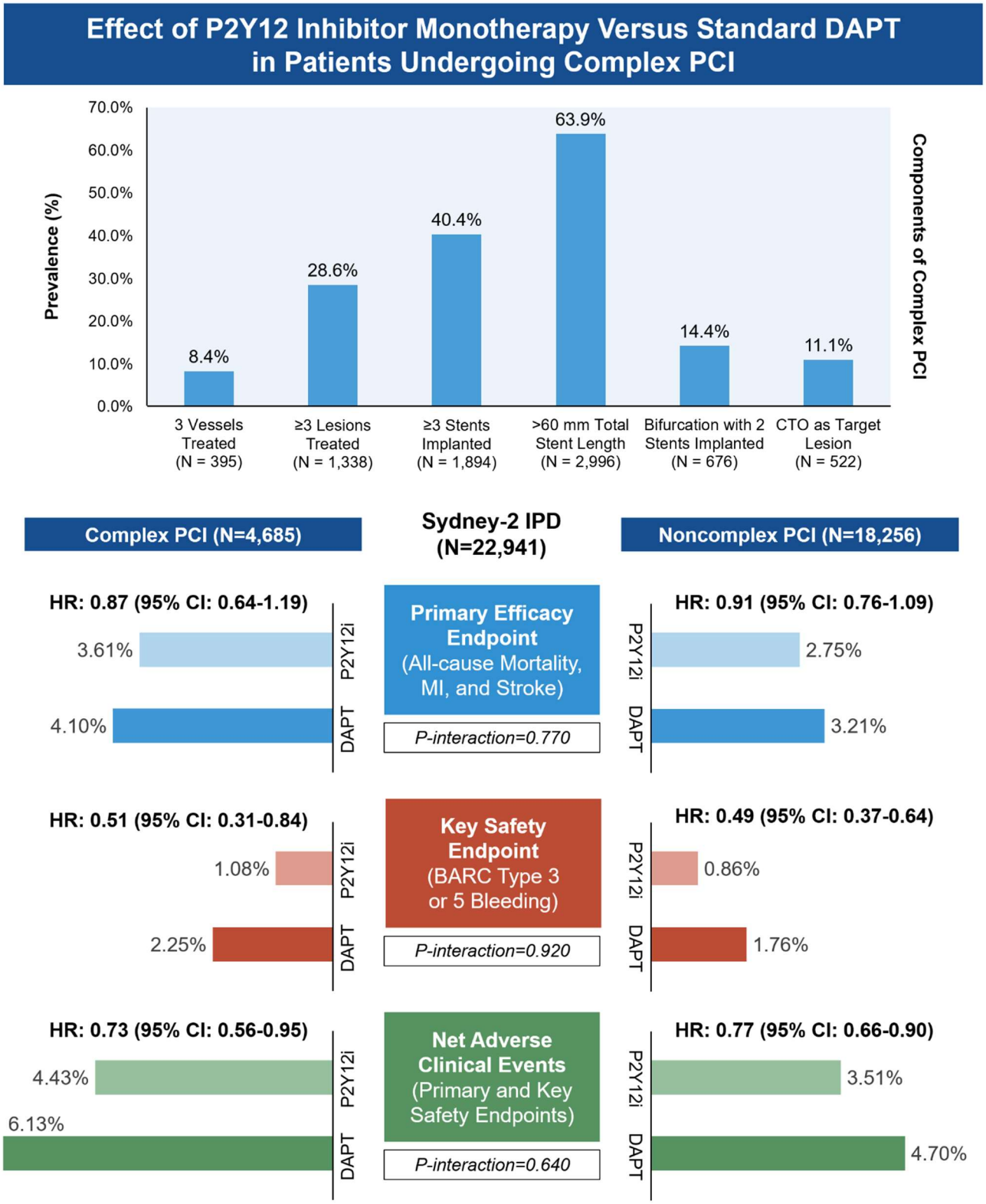
620 **Table 3.** Clinical outcomes according to PCI complexity and randomized treatment group.

	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.

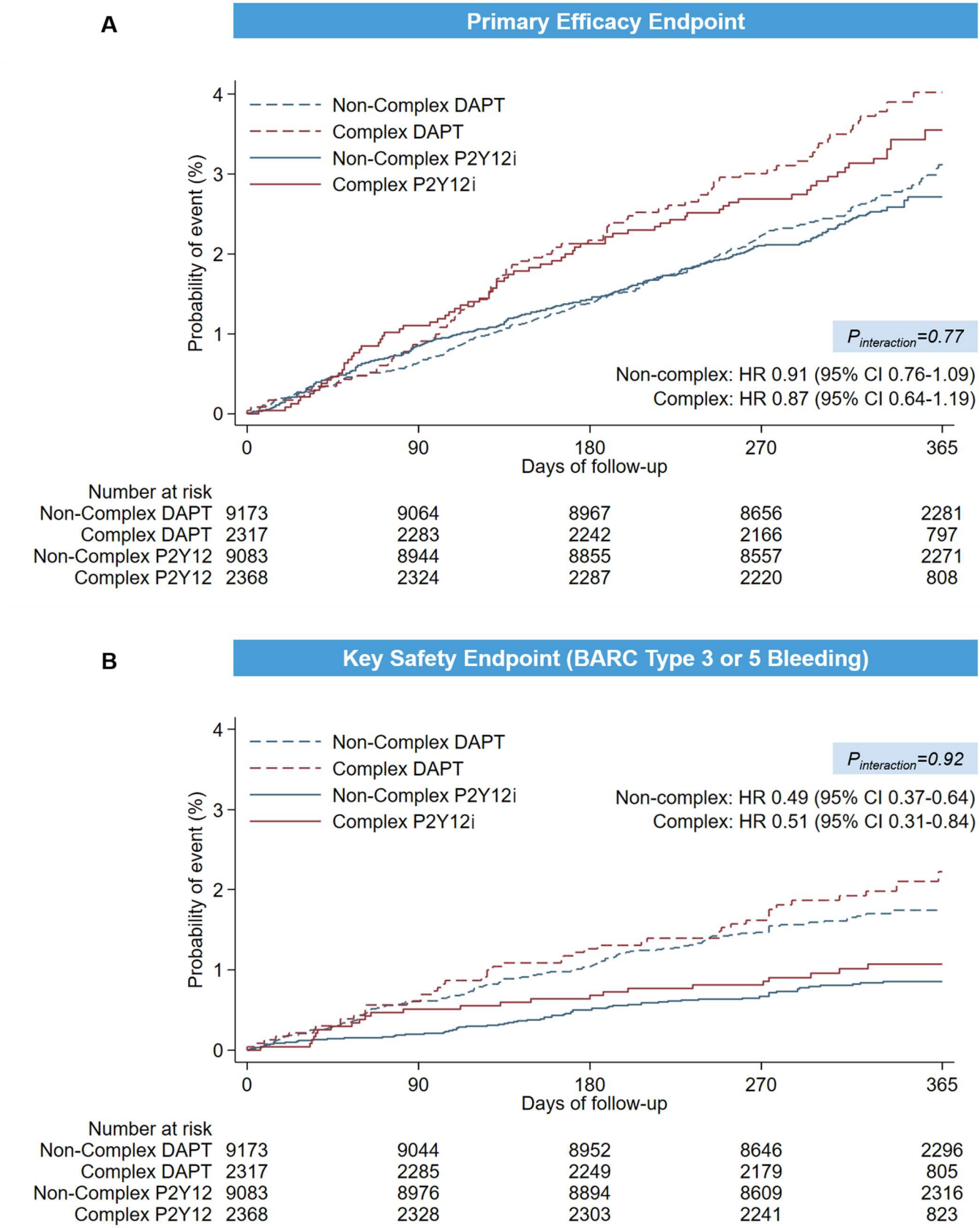
625 **Central Illustration**
626



627

628 **Figure 1**

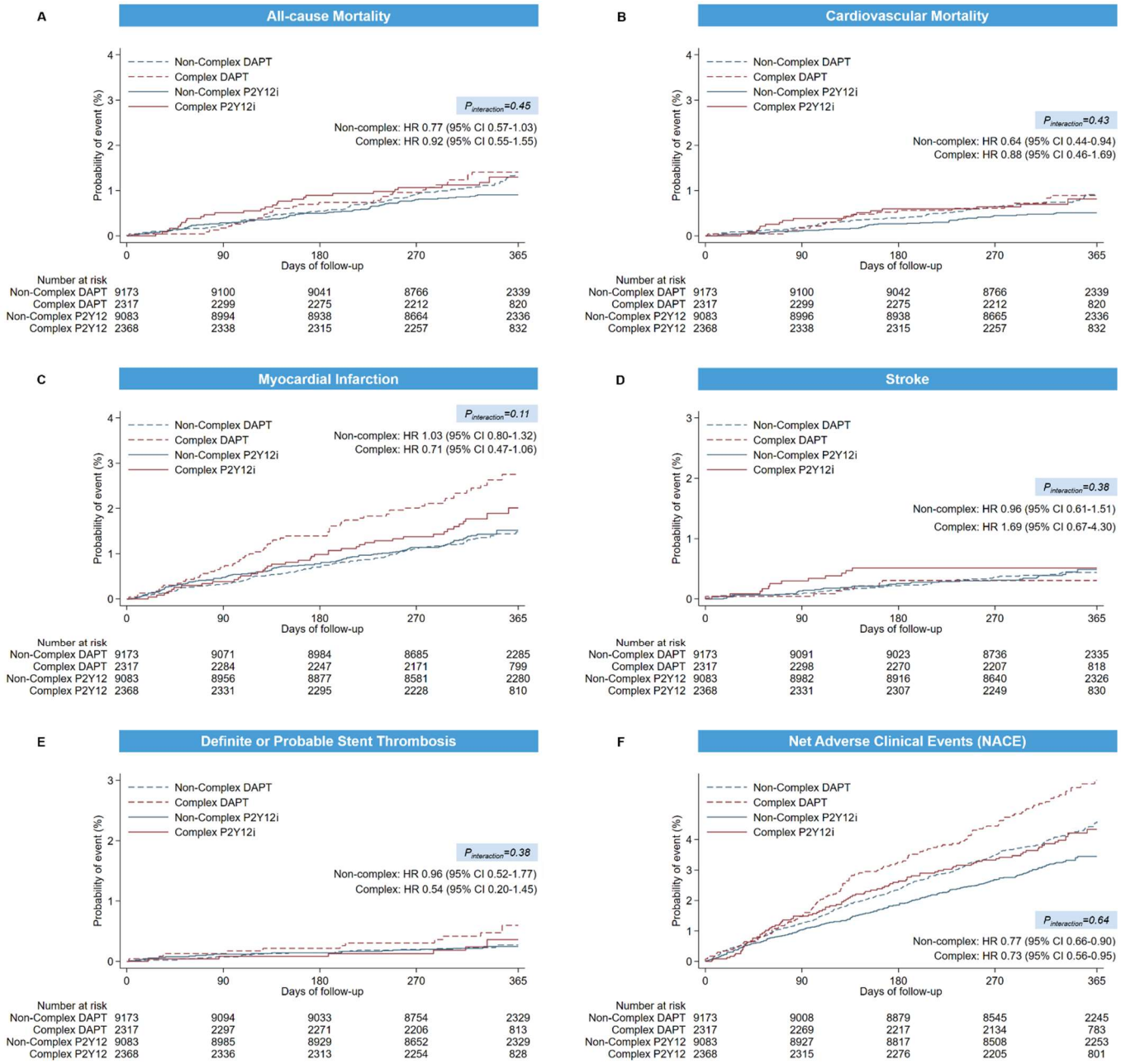
629



630

631 **Figure 2**

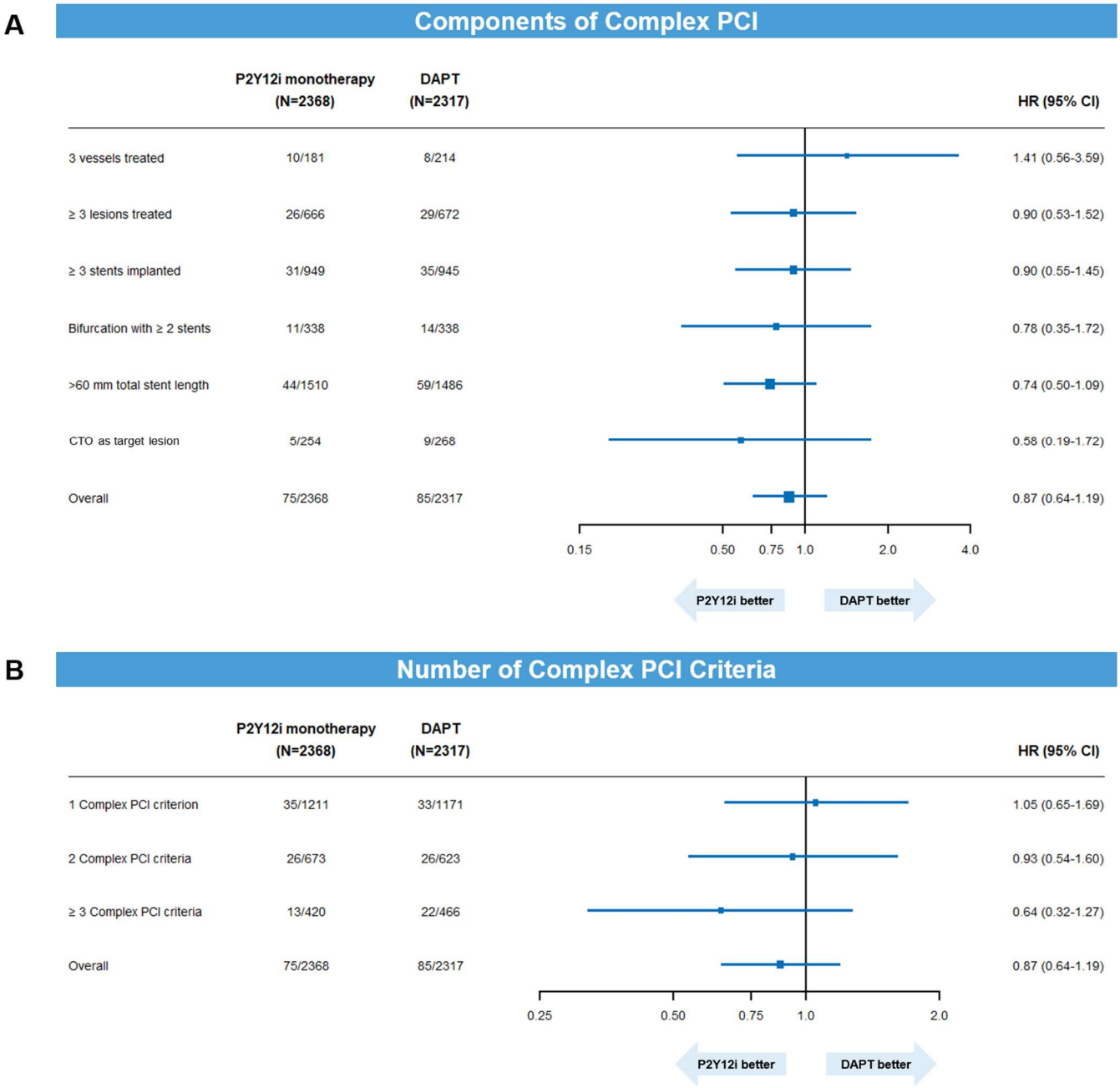
632



633

634 **Figure 3**

635



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