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Appraising the counter-balancing ischemia and bleeding risks for dual antiplatelet therapy duration after coronary stenting

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Introduction

The PRECISE-DAPT score is a 5-item bleeding risk prediction model developed to estimate the bleeding risk in patients receiving dual antiplatelet therapy (DAPT) after stent implantation (1). This score has been validated in two large, independent acute coronary syndrome (ACS) patient populations (2) and in a contemporary real world registry.(3) The categorization of patients based on the PRECISE-DAPT score was shown useful to inform the decision making for DAPT duration in stented patients (1), which drove its endorsement by international guidelines (4,5). In particular, patients with a score of 25 or greater derived net clinical harm if treated with a DAPT regimen in excess of 3 to 6 instead of at least 12 months after stenting (1).Yet, this prediction tool deserves further validation in order to extend its application in multiple patient subgroups, including those at higher ischemic risk.

Extensive coronary artery disease necessitating complex percutaneous revascularization techniques frequently drives a longer than average DAPT duration among practitioners (6). This is currently supported by two retrospective analyses of a single large or multiple small to medium sized combined studies showing an absolute greater ischemic risk reduction in patients receiving a long, instead of a short, DAPT duration after complex intervention (7,8). Nonetheless,

patients undergoing complex intervention carry at the same time features that significantly increase their bleeding hazard, such as multiple comorbidities, renal disease, or prior bleeding. The mutual role of ischemic and bleeding risks on outcomes and whether a long or a short DAPT duration should be prioritized in the setting of patients carrying both high bleeding and ischemic risk features remains unclear and constitutes the focus of the current analysis.

Methods

Study Design and population

The study population consisting of a total of 14,963 patients treated with percutaneous coronary intervention (PCI) and subsequent DAPT has been previously described.(1) In brief, patients treated with coronary stenting in an elective, urgent or emergent setting, were pooled at individual level from 8 randomized controlled trials (**Figure 1**).(9-16) The duration of DAPT with aspirin and a $P2Y_{12}$ inhibitor was randomly assigned to short (three or six months) or long (12 or 24 months) treatment duration in 10,081 patients among 5 of the 8 included studies(11-15) whereas it was according international guidelines in two (9,10), and ranging from 1 to 12 months based on patient characteristics in one study (16) (**Figure 1**). The terminology used for short or long DAPT duration throughout the manuscript is based on the aforementioned randomization scheme and refer to the short (i.e. 3 or 6 months) or long (i.e. 12 or 24 months) duration of the assigned DAPT treatment.

All clinical trials were approved by the ethics committees at each study center, and all patients provided written informed consent. For the purpose of the present analysis, we stratified the population based on quantifiable bleeding versus ischemic risks and analyzed outcomes in terms of both safety and efficacy

endpoints in the overall cohort whereas the impact of DAPT duration, further stratified by ischemic and bleeding risks, was restricted to studies which randomly allocated patients to a short or long DAPT regimen.

Bleeding risk assessment

The PRECISE-DAPT score was calculated as previously described based on age, creatinine clearance, hemoglobin, white-blood cell count, and prior spontaneous bleeding (1). Validation of the PRECISE-DAPT score and instruction for its calculation are discussed elsewhere (1,4). Patients were considered at high bleeding risk (HBR) for scores ≥25 and non-HBR for scores<25. Sensitivity analysis taking into account quartiles of bleeding risk (i.e. very low risk: score ≤10; low risk: score 11–17; moderate risk: score 18–24; and high risk: score ≥25) have been performed.

Ischemic risk assessment

The predicted ischemic risk after PCI was quantified using previously validated and guidelines-endorsed criteria of PCI complexity (4,7) as follows: PCI with ≥3 stents implanted and/or ≥3 lesions treated and/or 3 coronary vessels treated and/or bifurcation with 2 stents implanted and/or total stent length > 60 mm and/or treatment of a chronic total occlusion. The presence of at least one element of

complexity qualified the patient into the complex PCI group. Occurrence of more than one element of complexity in the same patient was also accounted (i.e., complex PCI score). We also analyzed the impact of an alternative high ischemic risk definition accounting for both the clinical and anatomical/procedural features (i.e. complex patient), by accounting ACS at presentation as an additional criterion to the previously established anatomical/procedural complex PCI features. Both high ischemic risk assessment methods have been pre-specified in the study plan.

Outcomes

All clinical and laboratory variables included in the current analysis were prospectively collected (1). Major and minor bleeding according to the Thrombosis in Myocardial Infarction (12) definition (17), and the composite of myocardial infarction (MI), definite stent thrombosis (ST) (18), stroke or target vessel revascularization (TVR) were appraised at up to two years follow-up and pre-specified as primary safety and efficacy endpoints, respectively. Net adverse clinical events (NACE), obtained after pooling ischemic and bleeding events, and other ischemic and bleeding secondary endpoints were also explored. All clinical events were adjudicated by a blinded independent Clinical Events Committee for each of the included study.

Statistical Analysis

The patient population was stratified according to the presence or absence of a high PRECISE-DAPT score and/or the presence or absence of at least one or more complex PCI criteria. Categorical variables are reported as percentages, continuous variables are reported as median and interquartile range and in-between-group differences were assessed using $\chi 2$ test and Wilcoxon rank sum test respectively. Event rates in the four explored groups have been evaluated using Kaplan-Meier estimates at 24 months and compared with log-rank test. The impact of a randomized DAPT duration among the PRECISE-DAPT bleeding risk strata was evaluated in a large sub-group of patients (n= 10,081) (**Figure 1**). In this analysis. events were counted after the landmark point of treatment divergence in the two study arms. For instance, if in one of the DAPT trials envisioned a 3 vs. 12 months treatment duration, events occurring in the first three months, where treatment was identical in the two study arms, were censored. The absolute risk difference (ARD) and its 95% confidence interval are calculated according to Newcombe & Altman (2000). The method for the calculation of the risk difference, which is a difference between proportions, requires the calculation of the confidence intervals of the two proportions separately. With l_1 to u_1 being the 95% confidence interval of the first proportion (p_1) and l_2 to u_2 being the 95% confidence interval of the second proportion (p_2), the 95% confidence interval for

the difference is given by $95\%CI = RD - \sqrt{(p_1 - l_1)^2 + (u_2 - p_2)^2}\ to\ RD + \sqrt{(p_2 - l_2)^2 + (u_1 - p_1)^2}$.

The ARD was calculated to evaluate the difference in event incidence after a long vs. short DAPT duration in each stratum for primary and secondary ischemic and bleeding endpoints. We tested the null hypothesis of a homogeneous ARD (long vs. short DAPT treatment) within complex-PCI vs. non-complex PCI patients. A p-value below 0.05 was used to detect significant heterogeneity across subgroups. ARD for bleeding and ischemia after a long treatment, and their confidence intervals were plotted for the four groups of PRECISE-DAPT high/non-high vs. complex/non-complex PCI (19). All analyses were performed with R package version 3.3.2 (2016).

Results

Among 14,963 patients undergoing PCI in the study-pooled cohort, 11,845 (79.2%) underwent non-complex PCI, of whom 8,982 (60.0%) were not at HBR and 2,863 (19.1%) were at HBR. Complex PCI was performed in 3,118 (20.8%) patients, of whom 2,273 (15.2%) were not at HBR and 845 (5.6%) were at HBR. Among those undergoing complex PCI, 1,668 (53.5%) had one single element qualifying for complexity and 1,450 (46.5%) had two or more (**Figure 2**). Patients with complex PCI were older and more commonly had a history of diabetes mellitus and peripheral vascular disease, reduced ejection fraction, and were more commonly treated with 2nd generation drug-eluting stents (DES) as well as ticagrelor or prasugrel at discharge (**Table 1**). The distribution of the PRECISE-DAPT score in the complex PCI population and further stratified according to each complex PCI criterion is presented in **Figure 3**. Median PRECISE-DAPT score was slightly lower in patients with as compared to those without complex PCI features (16.2 vs.17.0 score points; p=0.001) but increased modestly with the increasing number of elements of complexity (non-complex: 16.2 points vs. 1 element: 16.0 points vs. ≥2 elements: 18.2 points; p<0.0001).

Clinical events based on ischemic and bleeding risks

The occurrence of the primary composite endpoint of MI, definite ST, stroke

or TVR was higher among patients in the complex, compared to the non-complex, PCI group both with and without HBR features (**Table 2 and Figure 4A**). The presence of more than 1 element of complexity was associated with greater risk of the primary endpoint (**Table 3**). HBR was also associated with a greater rate of ischemic events (**Table 2 and Figure 4A**). Major or minor bleeding events were roughly three-fold greater in the HBR groups, both with (5.8% vs. 1.8%, P<0.001) and without (4.8% vs. 1.4%, P<0.001) complex PCI features. Fulfillment of complex PCI criteria alone was not instead associated with a significant increase in bleeding risk for TIMI major or TIMI major or minor bleeding (**Table 2 and Figure 4B**). Results were consistent when considering the four quartiles of bleeding risk (**Figure 5**) and when the analysis was limited at the first 12 months of follow-up (**Table 4**). Multivariable models including the PRECISE-DAPT score variables and the complex PCI criteria are presented in **Table 5 and Table 6**.

Impact of randomized DAPT duration according to ischemic and bleeding risks

Kaplan-Meier curves for the composite endpoint of MI, definite ST, stroke or TVR and TIMI major or minor bleeding in high and non-high bleeding and ischemic risk groups based on randomized long vs. short DAPT treatment are provided in **Figure 6 and 7**.

A long-term DAPT duration was associated with a reduction of ischemic

events in patients without HBR in both complex and non-complex PCI strata (ARD for long vs. short DAPT: non-complex PCI = –1.14% [–2.26 to –0.02] vs. complex PCI = –3.86% [–7.71 to +0.06]; p_{int}= 0.19) (**Figure 8** and **Table 7**). In contrast, no benefit of long-term treatment with DAPT was observed among HBR patients, irrespective of complex PCI features (ARD for long vs. short DAPT: non-complex PCI = +1.45% [–1.84 to +4.72) vs. complex PCI = +1.30% [–6.99 to +9.57); p_{int}= 0.97) (**Figure 8** and **Table 7**).

A long-term DAPT duration was associated with an excess of bleeding in patients with HBR irrespective of PCI complexity, with a significant increase of TIMI major or minor bleeding among non-complex PCI treated patients (ARD for long vs. short DAPT= +2.61% [95%CI +0.89 to +4.31) and a numerical but not statistically significant increase in the complex PCI stratum (ARD for long vs. short DAPT = +3.04% [95%CI –2.97 to +8.82]) (p_{int}= 0.89) (**Figure 8** and **Table 7**). In contrast, among patients without HBR, longer DAPT duration was not associated with higher bleeding liability, irrespective of PCI complexity (ARD for long vs. short DAPT: non-complex PCI = +0.12% [95%CI –0.25 to +0.50) vs. complex PCI = +0.28% [95%CI –0.46 to +1.26); p_{int}= 0.73) (**Figure 8** and **Table 7**).

Results remained consistent when both ischemic and bleeding events were evaluated in the composite net adverse clinical events endpoint (**Figure 8** and

Table 7). The net clinical benefit from long DAPT among non-HBR patients was numerically higher among complex PCI patients, albeit the interaction term did not reach statistical significance (ARD for long vs. short DAPT: non-complex PCI = -0.91% [–2.07 to +0.25) vs. complex PCI = –4.05% [–7.96 to –0.07); p_{int}= 0.14). Results in terms of ischemic, bleeding or combined ischemic and bleeding endpoints were corroborated when only ACS patients were analyzed (**Table 8**) or when the number of complex PCI criteria were further accounted for (**Figure 9**). Further stratification according to the four bleeding risk quartiles showed consistent ischemic benefits in patients at very low, low or moderate bleeding risks, but not for those with PRECISE DAPT≥25 (**Table 9**).

When the study population was stratified according to either ACS presentation and/or procedural patient complexity (i.e. ACS at presentation ± complex PCI criteria), significant interactions were noted with respect to ischemic and net adverse events for treatment duration and patient complexity among non-HBR individuals, but not among HBR. (**Figure 8 and Table 10**).

Discussion

The main findings of this study are as follows:

1. In univariate analysis, patients undergoing complex compared with non-complex PCI had higher ischemic and mortality risks, which were further increased in those with more than 1 element of complexity criteria. The fulfillment of complex PCI criteria did not significantly affect the bleeding risk. Patients with HBR had a higher incidence of both bleeding and ischemic events, including mortality, compared with non-HBR patients.
2. Patients not fulfilling HBR criteria had a consistent benefit from long compared with short DAPT duration, with no apparent trade-off in bleeding. The absolute magnitude of the ischemic risk benefit offered by a long DAPT regimen trended greater in patients who underwent complex as compared to non-complex PCI, albeit the interaction was not significant (p_{int}= 0.14). Such difference became statistically significant when ACS was also factored in as an additional element of ischemic risk (p_{int}< 0.001).
3. HBR patients did not derive ischemic or mortality benefit from long DAPT, irrespective of the complexity of the undertaken intervention or the acute presentation at the time of PCI, and experienced an excess of bleeding events compared with a short duration of treatment.

DAPT reduces coronary ischemic events after PCI, and its action is two-fold: prevention of MI and ST arising from previously stented segments and prevention of MI in non-culprit segments (20,21). Stent-related ischemic events mainly occur due to stent underexpansion during the early phase after implantation, and by restenosis or neoatherosclerosis in a later phase and appear to be critically dependent on the degree of $P2Y_{12}$ pathway residual activation (22). The introduction of current generation DES greatly reduced the risk of early, late, and very late stent thrombosis (23,24), and warranted the investigation of a short DAPT for six, three,(12,14) or even one month only after stenting (16,25). With contemporary devices, ST is rare and is responsible for a minority of recurrent ischemic events: in the DAPT trial, among patients treated with second generation DES, ST was responsible for only 15% of recurrent ischemic events in the placebo arm (26). Hence, a long course with DAPT achieves its benefit by mainly preventing ischemic events in the untreated coronary vasculature, thereby reducing the global risk of non-stent-related MI with marginal effects of stroke and venous thromboembolism (27). The benefit provided by the institution and continuation of DAPT is however counterbalanced by an increase in major bleeding risk (20), which accrues over time and affects morbidity, mortality, quality of life, and costs (28,29). This sets the rationale for an individualized approach in the decision

making for DAPT duration, taking into account the anticipated risks and benefits (4,5,30).

Multiple studies have investigated individual patient or procedural features enhancing, diminishing or not affecting the anticipated risk/benefit trade-off of a long DAPT regimen (31). PCI complexity, defined according to six anatomical/procedural criteria, has been recently proposed as a marker of ischemic risk, and a driver for DAPT duration selection (7). By applying this definition, it was noted that patients fulfilling at least one of those criteria had higher risk of recurrent ischemic events. Most importantly, the authors showed that patients undergoing complex PCI had a significant 44% reduction of MACE with a ≥12 month DAPT compared with a 3-6 months course, a difference that was not observed in the non-complex PCI subgroup. However, an excess of bleeding events was consistently noted in both complex and non-complex PCI patients treated with long DAPT (7). It was therefore speculated that complex PCI might be a marker of more extensive coronary disease, justifying, at least in part, the potential benefit offered by a longer DAPT regimen in this patient category. Similarly, in a sub-analysis of the I-LOVE-IT 2 trial, patients who were randomized to 6 or 12 months of DAPT have been further stratified according to the residual SYNTAX score after index intervention (32). A higher residual SYNTAX score was associated with an increased risk of recurrent ischemic events,

and to greater potential benefit from the treatment with long vs. short DAPT (32). In a consistent manner, an analysis from the PRODIGY trial showed that patients with left main (LM) or proximal left anterior descending coronary artery disease are an increased risk of adverse ischemic events and derived a 55% reduction of definite, probable, or possible stent thrombosis after twenty-four, compared with six, months of DAPT (33).

Yet none of these previous studies assessed the mutual and possibly competing role of high ischemic risk *and* bleeding risk features, and whether which one should preferentially affect the decision-making on DAPT duration in patients at concomitantly high ischemic and bleeding status.

Our current analysis shows that, among patients *not* showing HBR features, the presence of complex PCI might further increase the absolute ischemic risk reduction achieved by a long course of treatment, identifying this specific population as the one with the highest achievable benefit from a longer DAPT treatment. No signal of increased bleeding liability was noted in non-HBR patients despite long-term DAPT duration.

By contrast, HBR features portend an elevated risk of both ischemic and bleeding events, and long DAPT regimen does not mitigate the former but only increases the latter, irrespective to the baseline ischemic risk. There are multiple possible explanations for these novel and clinically important findings.

The occurrence of bleeding in HBR patients may trigger ischemic events by the abrupt cessation of all antiplatelet agents, by transfusion and subsequent inflammation, or by non-adherence to medical therapy.

Alternatively, HBR features may be associated with an inherent higher ischemic risk, which is not or only minimally modifiable by antiplatelet therapy duration/intensity modification. In a prior mediation analysis from the ADAPT-DES study, HBR features as anemia and CKD, were associated to an excess of ischemic risk, which was not mediated, or only marginally mediated, by residual platelet reactivity (34). Hence, the implementation of an intensified and prolonged DAPT regimen may be ineffective in preventing and limiting that risk. Direct effects of HBR features on thrombosis have been previously proposed: the anemic state stimulates the bone marrow to release immature platelets that are hyperreactive, less responsive to anti-platelet agents and more thrombogenic (35); similarly the presence of uremic solutes in patients with terminal CKD has been associated to a higher thrombotic milieu (36).

Against previous evidence that ACS at presentation is a major treatment modifier with respect to DAPT duration,(31,37) we have also analyzed the acuity of presentation (i.e. ACS versus non-ACS) as an additional high ischemic risk feature, with or without complex PCI criteria. We have consistently observed no

evidence that HBR patients, even if undergoing complex intervention due to an ACS derive benefit from long DAPT duration.

Our findings should also be placed in context of a recent analysis by Yeh et al, which explored the impact of lesion complexity, in terms of unprotected left main, >2 lesions per vessel, lesion length ≥30 mm, bifurcation lesion with side branch ≥ 2.5 mm, vein bypass graft (segment or anastomosis), or thrombus-containing lesion, in the DAPT trial dataset (8). The authors observed that the benefits and risks of extending DAPT beyond 12 months were consistent irrespective of concomitant lesion complexity criteria, and patients with higher DAPT scores (i.e. a decision making tool for DAPT duration based on the calculation of the net benefit from 12 vs. 30 months DAPT), derived the greatest absolute benefit from prolonged treatment with thienopyridines irrespective of anatomical complexity (8).

The management of HBR patients post bioresorbable polymer coated stent implantation with a short versus long DAPT regimen (MASTER DAPT) study is currently assessing whether the presence of at least one HBR feature, including PRECISE DAPT score ≥25 justifies a shorter than average DAPT duration both in patients with or without complex PCI (clinicaltrial.gov NCT03023020).

Our study should be interpreted in light of several limitations: First, this is a post hoc retrospective analysis and as such hypothesis generating, requiring further

prospective validation. Second, as a pooled-analysis of randomized clinical trials, this study is subject to the original limitations of the included trials. Yet, the high quality of the studies, with consistent external adjudication of clinical events, and the patient-level design, reassure about the robustness of our dataset. Third, elements for complex PCI criteria were prospectively collected in each of the included study by investigators and have not been reviewed by a central core laboratory. This is of minor importance for some of the complex PCI features (e.g., number of stents implanted, number of lesions treated, or overall stent lenght) , yet a more granular description of the bifurcation stenting technique (e.g., culotte stenting vs. mini-crush) or chronic total occlusion characteristics would have been desirable. Fourth, due to the retrospective design of the analysis we couldn't explore the value of other potentially important elements of complexity not available in the dataset. Yet, the main aim of the analysis was to benchmark the PRECISE-DAPT score on a solid and widely accepted definition of complex PCI. Fifth, the study power was limited to explore heterogeneity for rare events or smaller subgroups. Similarly, each individual element of intervention complexity may act as treatment modifier DAPT duration at different degrees. Finally, patients on oral anticoagulation were not included in the study.

Conclusions

Patients who undergo complex PCI are at further increased risk of ischemic events. However, such patients do not appear to derive any additional benefit from a long course of DAPT if HBR features according to the PRECISE-DAPT score are also present, ultimately presenting an unfavorable net clinical outcome. Our analysis suggests that when concordant, bleeding more than ischemic risk should inform decision-making on DAPT duration. Ongoing prospective studies are investigating whether HBR patients derive greater net clinical benefit from a short as compared to a long DAPT regimen, irrespective of PCI complexity.

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Figure Legends

Figure 1: Flow-chart describing the PRECISE-DAPT pooled dataset population.

Figure 2: Venn's Diagram for complex PCI elements interrelation in the PRECISE-DAPT population (2 groups with 4 elements). Taking two groups as a reference (i.e. ≥3 stents implanted and >60mm total stent length) we explored their relation with the pair bifurcation with 2 stents and the pair ≥3 lesions treated and 3 vessels treated respectively. The relation between bifurcation, CTO, lesions treated and 3 vessel disease was not explored in the figure as it was not possible to draw a figure taking into account the relation of the 6 groups at the same time. CTO: chronic total occlusion.

Figure 3: PRECISE-DAPT score quartiles distribution among single complex PCI definition parameters. PCI: percutaneous coronary intervention.

Figure 4: Ischemic (A) and bleeding (B) events overtime for patients with/without high bleeding risk (HBR) and with/without complex percutaneous coronary intervention (PCI). Kaplan-Meier estimates for myocardial infarction (MI), definite stent thrombosis (def ST), stroke or target

vessel revascularization (TVR)(A), and TIMI major or minor bleeding (B) during the 24 months follow-up are presented. Log-rank test was used for comparison. The occurrence of MI, def ST, stroke or TVR was higher among patients with complex PCI or HBR and highest in the group where both characteristics were present (A). The occurrence of TIMI major or minor bleeding was higher among patients with HBR but not among those with complex PCI alone (B).

Figure 5: Ischemic (A) and bleeding (B) events overtime for patients at very-low, low, moderate and high bleeding risk (BR) and with/without complex PCI.

Figure 6: Ischemic events among patients randomized to a long or short treatment with DAPT with/without high bleeding risk and PCI complexity. Twenty-four month Kaplan-Meier estimates of myocardial infarction (MI), definite stent thrombosis (def ST), stroke or target vessel revascularization (TVR) for patients randomly assigned to long (12–24 months) or short (3–6 months) dual antiplatelet therapy (DAPT) in the four explored groups with/without high bleeding risk and with/without complex percutaneous coronary intervention (PCI). Long DAPT was associated with a reduction of MI, def ST, stroke or TVR in patients without high bleeding risk and non-complex PCI and with a borderline reduction in patients in the complex PCI stratum (upper panels). In contrast, long

DAPT provided no benefit among patients with high bleeding risk (lower panels) irrespective of complex PCI features.

Figure 7: Bleeding events among patients randomized to a long or short treatment with DAPT with/without high bleeding risk and PCI complexity. Twenty-four month Kaplan-Meier estimates of TIMI major or minor bleeding for patients randomly assigned to long (12–24 months) or short (3–6 months) dual antiplatelet therapy (DAPT) in the four explored groups with/without high bleeding risk and with/without complex percutaneous coronary intervention (PCI). Long DAPT was not associated with an increase of TIMI major or minor bleeding in patients without high bleeding risk (upper panels) irrespective of PCI complexity. In contrast, long DAPT was associated with an increase of TIMI major or minor bleeding among patients with high bleeding risk and non-complex PCI features (lower panels).

Figure 8: Risk difference for long vs. short DAPT duration for bleeding*, ischemic† and net adverse clinical events‡ in patients stratified according to the PRECISE-DAPT score and with/without complex PCI (A) or with/without complex patient criteria (B). *Bleeding endpoint defined according the TIMI major/minor bleeding definition. † Ischemic endpoint defined according to the

composite of myocardial infarction, definite stent thrombosis, stroke or target vessel revascularization. ‡ Net adverse clinical events defined according to the composite of myocardial infarction, definite stent thrombosis, stroke, target vessel revascularization or TIMI major/minor bleeding. Complex PCI is defined as the presence of a PCI with ≥3 stents implanted and/or ≥3 lesions treated and/or 3 coronary vessels treated and/or bifurcation with 2 stents implanted and/or total stent length > 60 mm and/or treatment of a chronic total occlusion. Complex patient is defined as the presence of at least one element of the prior mentioned complex PCI definition and/or the presence of acute coronary syndrome at presentation. DAPT: dual antiplatelet therapy. NACE: Net adverse clinical events.

Figure 9: Risk difference for long vs. short DAPT duration for bleeding and ischemic events in the overall patient population and in patients with high/non-high PRECISE-DAPT score, stratified according to the number of elements qualifying for complex PCI. DAPT: dual antiplatelet therapy. MI: myocardial infarction. Def ST: definite stent thrombosis. TVR: target vessel revascularization.

Table 1: Baseline characteristics in the four explored groups by bleeding risk and intervention complexity

	PRECISE-DAPT<25 (non-HBR) Non-Complex PCI (N=8,982)	PRECISE-DAPT<25 (non-HBR) Complex PCI (N=2,273)	PRECISE-DAPT ≥25 (HBR) Non-Complex PCI (N=2,863)	PRECISE-DAPT ≥25 (HBR) Complex PCI (N=845)	P value PRECISE-DAPT<25 (non-HBR) Non-Complex PCI Vs. Complex PCI	P value PRECISE-DAPT≥25 (HBR) Non-Complex PCI Vs. Complex PCI
Age (years)	61 (54-68)	62 (55-68.6)	76.4 (71.8-81)	77.2 (72.9-82)	0.04	0.008
Women (vs. Man)	25.8%	23.6%	42.6%	40.6%	0.03	0.30
Hypertension	69.4%	68.7%	79.0%	80.9%	0.49	0.23
Dyslipidemia	62.2%	65.7%	56.0%	57.3%	0.002	0.50
Current smoking	29.0%	31.1%	12.7%	12.1%	0.06	0.61
Diabetes	26.7%	28.5%	29.4%	34.6%	0.06	0.003
Insulin dependent	5.2%	5.6%	4.9%	7.6%	0.41	0.002
PVD	6.1%	8.1%	17.3%	21.5%	0.02	0.03
Prior MI	19.2%	19.5%	20.7%	23.0%	0.76	0.15
Prior PCI	15.0%	17.0%	17.7%	18.1%	0.02	0.78
Prior CABG	5.1%	5.9%	8.4%	7.6%	0.13	0.43

Weight (Kg)	75 (66-85)	75 (66-85)	68.4 (60-78)	70 (61-80)	0.94	0.03
Creatinine clearance (ml/min)	89.3 (76-106.6)	89.4 (76.7-103.9)	52.3 (40.5-62.2)	51.9 (41.1-62.7)	0.99	0.41
White blood cells count (10^3 units/μL)	7.7 (6.2-10.1)	7.8 (6.4-9.7)	8.2 (6.7-10.6)	8.0 (6.7-10.4)	0.42	0.39
Hemoglobin (g/dL)	14.0 (13.1-15)	14.2 (13.2-15.1)	12.7 (11.4-14.1)	12.4 (11.1-13.7)	0.05	0.03
Left ventricle ejection fraction (%)	55.0 (50.0-61)	55.0 (45.0-64.4)	55.0 (45.0-60.0)	54.0 (40.0-60.4)	<0.001	0.94
Left ventricle ejection fraction less than 35%	6.7%	8.9%	13.2%	15.7%	0.001	0.08
Clinical presentation						
SCAD	45.7%	48.4%	40.1%	35.0%		

UA	23.2%	20.1%	23.5%	21.4%	<0.0001	<0.0001
NSTEMI	11.3%	13.8%	18.3%	28.2%		
STEMI	19.8%	17.7%	18.1%	15.5%		
Single vessel disease	64.9%	38.2%	48.4%	23.8%	<0.0001	<0.0001
Number of vessel treated						
1	87.0%	60.8%	81.3%	41.4%		
2	12.8%	31.7%	18.5%	44.9%	<0.0001	<0.0001
3	0.2%	7.5%	0.2%	13.7%		
More than one lesions treated	18.0%	50.5%	20.6%	67.4%		
Overall stent length (mm)	24.0 (18.0-33.0)	58.0 (36.0-78.0)	24.0 (18.0-33.0)	63.0 (43.0-81.0)	<0.0001	<0.0001
Type of stent implanted						
BMS	11.5%	8.5%	19.4%	16.3%		
1st generation DES	7.5%	8.5%	9.4%	6.8%	<0.0001	0.004
2nd generation DES	81.0%	83.0%	71.2%	76.9%		

Therapy at discharge						
Aspirin	99.1%	99.1%	97.3%	97.0%	0.92	0.70
Clopidogrel	87.6%	78.0%	90.2%	83.5%	<0.0001	<0.0001
Prasugrel	8.1%	12.1%	3.2%	4.4%	<0.0001	0.10
Ticagrelor	2.8%	8.5%	2.3%	8.5%	<0.0001	<0.0001
Statin	90.8%	90.7%	84.6%	87.4%	0.95	0.05
Beta blocker	74.4%	76.9%	71.9%	73.9%	0.02	0.27
ACE/ARB	65.8%	70.8%	66.0%	66.5%	<0.0001	0.80
PPI	34.2%	29.6%	51.3%	51.3%	0.004	0.99

HBR= high bleeding risk. PVD= peripheral vascular disease. MI= myocardial infarction. PCI= percutaneous coronary intervention. CABG= coronary artery bypass graft. SCAD= stable coronary artery disease. UA= unstable angina. NSTEMI= non-ST segment elevated myocardial infarction. STEMI= ST segment elevated myocardial infarction. ACE/ARB: ACE inhibitor or angiotensin-II receptor blocker. PPI= proton pump inhibitor.

Table 2: Ischemic and bleeding events according to bleeding (PRECISE-DAPT) and intervention complexity risk profiles.

	PRECISE-DAPT <25 (non-HBR) Non-Complex PCI	PRECISE-DAPT <25 (non-HBR) Complex PCI	PRECISE-DAPT ≥25 (HBR) Non-Complex PCI	PRECISE-DAPT ≥25 (HBR) Complex PCI	P value PRECISE-DAPT <25 (non-HBR) Vs. PRECISE-DAPT ≥25 (HBR)	P value Non-Complex PCI Vs. Complex PCI
MI, Def ST, Stroke or TVR	7.6%	13.9%	12.5%	20.5%	<0.0001	<0.0001
MI, Def ST, Stroke	3.5%	6.8%	8.6%	13.3%	<0.0001	<0.0001
Definite Stent Thrombosis	0.7%	1.6%	1.3%	0.8%	0.03	0.009
Death for all Causes	2.4%	2.8%	12.2%	14.7%	<0.0001	0.008
Cardiovascular Death	1.4%	1.7%	8.3%	9.9%	<0.0001	0.01
Non Cardiovascular Death	0.9%	1.1%	4.3%	5.2%	<0.0001	0.22
TIMI Major or Minor	1.4%	1.8%	4.8%	5.8%	<0.0001	0.06
TIMI Major	0.7%	1.1%	2.5%	2.9%	<0.0001	0.08
Fatal Bleeding	0.07	0.3%	0.8%	1.3%	<0.0001	0.05

Twenty-four months Kaplan Meier estimates are presented. Log-rank test was used for comparison.

HBR= high bleeding risk. MI= myocardial infarction. ST= stent thrombosis. TVR= target vessel revascularization. Def/Prob= definite or probable. TIMI= thrombosis in myocardial infarction.

Table 3: Ischemic and bleeding events according to the number of complex PCI features (complex PCI score)

	Non-Complex PCI	Complex PCI 1 element	Complex PCI ≥2 elements	P value
MI, Def ST, stroke or TVR	7.4% (875/11845)	10.5% (176/1668)	16.3% (237/1450)	<0.0001
MI, Def ST, stroke	4.0% (473/11845)	6.1% (102/1668)	8.7% (127/1450)	<0.0001
Definite Stent Thrombosis	0.8% (90/11845)	1.0% (18/1668)	1.4% (21/1450)	0.02
Def/Prob Stent Thrombosis	1.6% (185/11845)	2.8% (47/1668)	3.8% (56/1450)	<0.0001
Death for all causes	4.1% (489/11845)	4.5% (75/1668)	6.1% (87/1450)	0.003
Cardiovascular Death	2.7% (318/11845)	2.7% (45/1668)	4.4% (63/1450)	0.001
Non Cardiovascular Death	1.4% (166/11845)	1.8% (30/1668)	1.7% (24/1450)	0.37
TIMI Major or minor	2.0% (236/11845)	2.8% (46/1668)	2.3% (33/1450)	0.11
TIMI Major	1.0% (120/11845)	1.4% (24/1668)	1.4% (20/1450)	0.23
Fatal Bleeding	0.2% (26/11845)	0.4% (6/1668)	0.5% (7/1450)	0.12

MI= myocardial infarction. ST= stent thrombosis. TVR= target vessel revascularization. Def/Prob= definite or probable. TIMI= thrombosis in myocardial infarction.

Table 4: Ischemic and bleeding events at 12 months according to bleeding (PRECISE-DAPT) and intervention complexity risk profiles

	PRECISE-DAPT <25 (non-HBR) Non-Complex PCI	PRECISE-DAPT <25 (non-HBR) Complex PCI	PRECISE-DAPT ≥25 (HBR) Non-Complex PCI	PRECISE-DAPT ≥25 (HBR) Complex PCI	P value PRECISE-DAPT <25 (non-HBR) Vs. PRECISE-DAPT ≥25 (HBR)	P value Non-Complex PCI Vs. Complex PCI
MI, Def ST, Stroke or TVR	5.4%	10.1%	8.7%	14.5%	<0.0001	<0.0001
MI, Def ST, Stroke	2.6%	4.9%	5.9%	9.3%	<0.0001	<0.0001
Definite Stent Thrombosis	0.5%	1.1%	1.1%	0.8%	0.009	0.02
Death for all Causes	1.6%	2.0%	8.9%	10.2%	<0.0001	0.02
Cardiovascular Death	1.0%	1.4%	6.4%	7.6%	<0.0001	0.01
Non Cardiovascular Death	0.5%	0.6%	2.7%	2.8%	<0.0001	0.54
TIMI Major or Minor	1.1%	1.6%	3.9%	3.9%	<0.0001	0.06
TIMI Major	0.5%	1.0%	1.8%	1.8%	<0.0001	0.06
Fatal Bleeding	0.03%	0.2%	0.7%	0.5%	<0.0001	0.24

Twelve months Kaplan Meier estimates are presented. Log-rank test was used for comparison.
HBR= high bleeding risk. MI= myocardial infarction. ST= stent thrombosis. TVR= target vessel revascularization. Def/Prob= definite or probable. TIMI= thrombosis

Table 5: Multivariable models exploring events' predictors*

Events	MI, Definite ST, stroke or TVR		TIMI major or Minor		All cause death	
	Hazard Ratio	**P**	**Hazard Ratio**	**P**	**Hazard Ratio**	**P**
Model 1						
PRECISE-DAPT score						
Age	1,00 (0.99-1.01)	0,57	1,02 (1.01-1.04)	0,0004	1,05 (1.03-1.06)	<0,0001
Hemoglobin	0,83 (0.75-0.91)	0,0003	0,71 (0.60-0.85)	0,0002	0,65 (0.58-0.73)	<0,0001
White blood cell count	0,97 (0.95-1.00)	0,05	1,05 (1.01-1.09)	0,025	1,05 (1.02-1.07)	0,0001
Creatinine clearance	0,99 (0.99-0.99)	0,0004	0,98 (0.98-0.99)	0,0003	0,98 (0.98-0.99)	<0,0001
Prior Bleeding	1,86 (1.13-3.07)	0,01	2,72 (0.88-8.36)	0,08	1,08 (0.59-1.99)	0,79
Complex PCI						
>60 mm total stent length	1,32 (1.02-1.70)	0,03	1,14 (0.64-2.01)	0,66	1,13 (0.73-1.76)	0,56
≥ 3 lesions treated	1,23 (0.95-1.61)	0,11	0,75 (0.35-1.58)	0,44	0,91 (0.61-1.36)	0,66
≥ 3 stents implanted	1,31 (1.03-1.65)	0,025	1,17 (0.71-1.93)	0,55	1,02 (0.68-1.54)	0,91
3 vessel treated	1,15 (0.79-1.69)	0,45	0,95 (0.33-2.73)	0,92	0,81 (0.45-1.44)	0,48
Bifurcation with 2 stents	1,05 (0.88-1.24)	0,61	1,20 (0.79-1.79)	0,38	1,02 (0.64-1.63)	0,92
Chronic total occlusion	1,41 (1.05-1.90)	0,023	0,77 (0.39-1.55)	0,47	1,09 (0.61-1.96)	0,76

Model 2						
Complex PCI score†	1,25 (1.20-1.32)	<0.0001	1,09 (0.96-1.23)	0.18	1,04 (0.95 -1.15)	0.34
+ Age	1,01 (1.00-1.02)	<0.0001	1,04 (1.02-1.05)	<0.0001	1,07 (1.06-1.08)	<0.0001
Model 3						
Complex PCI score†	1,25 (1.19-1.31)	<0.0001	1,09 (0.96-1.23)	0.18	1,06 (0.96-1.17)	0.24
+ Prior bleeding	1,88 (1.16-3.07)	0.01	2,87 (1.08-7.60)	0.03	1,16 (0.62-2.18)	0.64
Model 4						
Complex PCI score†	1,25 (1.19-1.31)	<0.0001	1,09 (0.97-1.24)	0.16	1,06 (0.96-1.17)	0.24
+ White blood cell count	0,97 (0.95-0.99)	0.01	1,04 (0.99-1.09)	0.16	1,02 (1.00-1.05)	0.09
Model 5						
Complex PCI score†	1,25 (1.19-1.31)	<0.0001	1,08 (0.95-1.22)	0.22	1,03 (0.92-1.14)	0.58
+ Hemoglobin	0,91 (0.87-0.94)	<0.0001	0,82 (0.75-0.88)	<0.0001	0,67 (0.63-0.71)	<0.0001
Model 6						

Complex PCI score†	1,25 (1.19-1.31)	<0.0001	1,08 (0.96-1.22)	0.20	1,04 (0.94-1.15)	0.45
+ Creatinine clearance	0,99 (0.99-1.00)	<0.0001	0,98 (0.98-0.99)	<0.0001	0,97 (0.97-0.98)	<0.0001
Model 7						
Complex PCI score†	1,25 (1.19-1.31)	<0.0001	1,07 (0.95-1.21)	0.25	1,04 (0.94-1.15)	0.44
+ PRECISE-DAPT score	1,02 (1.01-1.02)	<0.0001	1,08 (1.07-1.10)	<0.0001	1,10 (1.09-1.11)	<0.0001

*: All events accounted from study inclusion. †: Complex PCI score represent the discrete number of elements qualifying for PCI complexity (e.g. presence of a total stent length >60 mm and three lesions treated = 2 points).

MI= myocardial infarction. ST= stent thrombosis. TVR= target vessel revascularization. TIMI= thrombosis in myocardial infarction.

Table 6: Multivariable model exploring predictors of events among the components of the PRECISE-DAPT score and complex PCI features. Analysis restricted to out-of-hospital events.

Events	MI, Definite ST, stroke or TVR		TIMI major or Minor		All cause death	
	Hazard Ratio	**P**	**Hazard Ratio**	**P**	**Hazard Ratio**	**P**
PRECISE-DAPT score						
Age	1,00 (0.99-1.01)	0,67	1,02 (1.01-1.04)	0,003	1,04 (1.03-1.05)	<0,0001
Hemoglobin	0,84 (0.76-0.94)	0,002	0,65 (0.53-0.80)	0,0001	0,64 (0.57-0.72)	<0,0001
White blood cell count	0,97 (0.93-1.00)	0,03	1,04 (0.98-1.11)	0,20	1,04 (1.02-1.07)	0,0007
Creatinine clearance	0,99 (0.99-1.00)	0,0001	0,99 (0.98-0.99)	0,0005	0,98 (0.98-0.99)	<0,0001
Prior Bleeding	2,02 (1.15-3.55)	0,01	2,88 (0.63-13.2)	0,17	1,10 (0.59-2.07)	0,75
Complex PCI						
>60 mm total stent length	1,28 (0.97-1.71)	0,08	0,93 (0.50-1.75)	0,84	0,93 (0.60-1.43)	0,75
≥ 3 lesions treated	1,32 (0.98-1.77)	0,06	0,64 (0.26-1.56)	0,33	0,96 (0.62-1.46)	0,85
≥ 3 stents implanted	1,22 (0.93-1.60)	0,14	1,15 (0.65-2.03)	0,63	1,11 (0.74-1.67)	0,59
3 vessel treated	1,16 (0.77-1.74)	0,47	1,58 (0.49-5.07)	0,44	0,83 (0.45-1.53)	0,54
Bifurcation with 2 stents	1,03 (0.85-1.26)	0,75	1,21 (0.75-1.95)	0,42	1,00 (0.63-1.57)	0,99
Chronic total occlusion	1,57 (1.15-2.14)	0,004	0,88 (0.37-2.07)	0,77	1,09 (0.55-2.14)	0,79

MI= myocardial infarction. ST= stent thrombosis. TVR= target vessel revascularization. Def/Prob= definite or probable. TIMI= thrombosis in myocardial infarction.

Table 7: Clinical events according to the PRECISE-DAPT score and the PCI complexity among patients randomized to short vs. long DAPT duration

	PRECISE-DAPT <25 (non-HBR)					PRECISE-DAPT ≥25 (HBR)				
	Short DAPT	Long DAPT	ARD	P	P_{int}	Short DAPT	Long DAPT	ARD	P	P_{int}
MI, definite ST, stroke or TVR										
Non-Complex PCI	4.52%	3.38%	–1.14% (–2.26 to –0.02)	0.04	0.19	6.76%	8.21%	+1.45% (–1.84 to +4.72)	0.39	0.97
Complex PCI	10.18%	6.32%	–3.86% (–7.71 to +0.06)	0.05		10.3%	11.6%	+1.30% (–6.99 to +9.57)	0.76	
Death, MI, definite ST, stroke or TVR										
Non-Complex PCI	5.33%	4.37%	–0.96% (–2.21 to +0.30)	0.13	0.38	10.66%	11.05%	+0.39% (–3.46 to +4.24)	0.84	0.75
Complex PCI	11.26%	8.33%	–2.93% (–7.21 to +1.30)	0.17		15.9%	18.0%	+2.14% (–8.05 to +12.48)	0.68	
Definite stent thrombosis										
Non-Complex PCI	0.25%	0.15%	-0.10% (–0.34 to +0.14)	0.43	0.18	0.41%	0.67%	+0.26% (–0.46 to +1.11)	0.51	n.a.

Complex PCI	0.67%	0.00%	-0.67% (–1.33 to +0.25)	n.a.		0.00%	0.00%	0.00% (0.00 to 0.00)	n.a.	
Death for all causes										
Non-Complex PCI	0.98%	1.28%	+0.30% (–0.36 to +0.96)	0.37	0.54	6.12%	4.67%	-1.45% (–4.15 to +1.24)	0.29	0.93
Complex PCI	1.36%	2.29%	+0.93% (–0.99 to +2.86)	0.34		10.01%	8.89%	-1.12% (–8.55 to +6.29)	0.77	
TIMI major or minor										
Non-Complex PCI	0.37%	0.49%	+0.12% (–0.25 to +0.50)	0.53	0.73	1.03%	3.64%	+2.61% (+0.89 to +4.31)	0.003	0.89
Complex PCI	0.32%	0.60%	+0.28% (–0.46 to +1.26)	0.57		3.30%	6.34%	+3.04% (–2.97 to +8.82)	0.30	
MI, definite ST, stroke TVR or TIMI major/minor bleeding										
Non-Complex PCI	4.73%	3.82%	–0.91% (–2.07 to +0.25)	0.12	0.14	7.65%	10.46%	+2.81% (–0.72 to +6.33)	0.11	0.83
Complex PCI	10.58%	6.54%	–4.05% (–7.96 to –0.07)	0.04		12.52%	14.20%	+1.68% (–7.85 to +11.15)	0.73	

Twenty-four months Kaplan Meier estimates are presented for long vs. short DAPT treatment. The absolute risk difference (ARD) and its 95% confidence interval are calculated according to Newcombe & Altman (2000).
HBR= high bleeding risk. ARD= Absolute risk difference. MI= myocardial infarction. ST= stent thrombosis. TVR= target vessel revascularization. Def/Prob= definite or probable. TIMI= thrombosis in myocardial infarction.

Table 8: Clinical events according to the PRECISE-DAPT score and the PCI complexity among patients randomized to short vs. long DAPT duration and presenting with acute coronary syndrome.

	PRECISE-DAPT <25 (Non-HBR)					PRECISE-DAPT ≥25 (HBR)				
	Short DAPT	**Long DAPT**	**ARD**	**P**	**P_{int}**	**Short DAPT**	**Long DAPT**	**ARD**	**P**	**P_{int}**
MI, definite ST, stroke or TVR										
Non-Complex PCI	6.15%	2.76%	–3.39% (–5.37 to –1.44)	<0.001	0.19	8.83%	9.70%	+0.86% (–4.34 to +6.08)	0.75	0.54
Complex PCI	14.26%	6.19%	–8.08% (–14.86 to –1.52)	0.017		11.3%	16.3%	+4.96% (–6.86 to +17.22)	0.42	
Death, MI, definite ST, stroke or TVR										
Non-Complex PCI	6.85%	3.89%	–2.95% (–5.15 to –0.77)	0.008	0.40	13.41%	14.57%	+1.16% (–4.86 to +7.19)	0.71	0.18
Complex PCI	15.91%	9.64%	–6.26% (–13.75 to +1.05)	0.09		14.9%	26.8%	+11.9% (–2.04 to +26.9)	0.11	
MI, definite ST, stroke										
Non-Complex PCI	1.73%	1.11%	–0.61% (–1.74 to +0.51)	0.29	0.16	4.87%	6.88%	+2.02% (–2.20 to +6.26)	0.35	0.69
Complex PCI	4.24%	0.93%	–3.30% (–7.07 to +0.03)	0.06		6.11%	6.36%	+0.25% (–7.52 to +7.94)	0.95	

Death, MI, definite ST, stroke										
Non-Complex PCI	2.41%	2.41%	+0.00% (–1.52 to +1.53)	0.99	0.56	9.97%	11.7%	+1.76% (–3.60 to +7.13)	0.52	0.79
Complex PCI	5.90%	4.34%	–1.56% (–6.60 to +3.44)	0.54		13.6%	17.2%	+3.57% (–8.91 to +16.4)	0.58	
Stent thrombosis										
Non-Complex PCI	0.52%	0.29%	-0.23% (–0.78 to +0.29)	0.40	0.18	0.72%	0.87%	+0.14% (–1.09 to +1.50)	0.83	n.a.
Complex PCI	1.54%	0.00%	-1.54% (–3.08 to +0.55)	n.a.		0.00%	0.00%	0.00% (0.00 to 0.00)	n.a.	
Death for all causes										
Non-Complex PCI	0.89%	1.32%	+0.42% (–0.64 to +1.49)	0.44	0.63	7.20%	6.57%	-0.63% (–4.65 to +3.38)	0.76	0.58
Complex PCI	1.89%	3.14%	+1.24% (–1.88 to +4.47)	0.44		10.6%	13.1%	+2.53% (–7.79 to +13.1)	0.63	
TIMI major or minor										
Non-Complex PCI	0.67%	0.59%	–0.08% (–0.84 to +0.67)	0.83	n.a.	1.19%	2.59%	+1.41% (–0.69 to +3.54)	0.19	0.13
Complex PCI	0%	0%	n.a.	n.a.		2.41%	10.43%	+8.02% (+0.26 to +16.75)	0.05	
MI, definite ST, stroke TVR or TIMI major/minor bleeding										

Non-Complex PCI	6.47%	3.25%	–3.22% (–5.28 to –1.19)	0.002	0.17	9.71%	11.0%	+1.26% (–4.13 to +6.65)	0.65	0.29
Complex PCI	14.3%	6.24%	–8.07% (–14.9 to –1.49)	0.018		12.5%	21.6%	+9.03% (–4.05 to +22.9)	0.19	

HBR= high bleeding risk. ARD= Absolute risk difference. MI= myocardial infarction. ST= stent thrombosis. TVR= target vessel revascularization. Def/Prob= definite or probable. TIMI= thrombosis in myocardial infarction.

The absolute risk difference (ARD) and its 95% confidence interval are calculated according to Newcombe & Altman (2000).

Table 9: Clinical events according to the PRECISE-DAPT score quartiles (i.e. very low, low, moderate and high bleeding risk) and the PCI complexity among patients randomized to short vs. long DAPT duration

	Very low Bleeding Risk			Low Bleeding Risk			Moderate Bleeding Risk			High Bleeding Risk		
	ARD (95%CI)	P	P_{int}	ARD (95%CI)	P	P_{int}	ARD (95%CI)	P	P_{int}	ARD (95%CI)	P	P_{int}
MI, definite ST, stroke or TVR												
Non-Complex PCI	–0.82% (–2.67 to +1.02)	0.38	0.54	–1.21% (–3.04 to +0.63)	0.19	0.92	–1.46% (–3.60 to +0.68)	0.18	0.14	+1.45% (–1.84 to +4.72)	0.39	0.97
Complex PCI	–3.13% (–10.3 to +3.99)	0.39		–1.55% (–8.05 to +4.86)	0.64		–6.46% (–12.9 to –0.26)	0.04		+1.30% (–6.99 to +9.57)	0.76	
Death, MI, definite ST, stroke or TVR												
Non-Complex PCI	–0.89% (–2.82 to +1.03)	0.37	0.73	–0.96% (–2.94 to +1.03)	0.34	0.79	–1.10% (–3.72 to +1.50)	0.41	0.28	+0.39% (–3.46 to +4.24)	0.84	0.79
Complex PCI	–2.20% (–9.47 to +5.01)	0.55		–0.05% (–6.71 to +6.55)	0.99		–5.72% (–13.8 to +2.11)	0.16		+2.14% (–8.05 to +12.48)	0.68	

Definite stent thrombosis												
Non-Complex PCI	–0.18%	0.27		0.00%	0.99		–0.12%	0.59		+0.26%	0.51	
	(–0.50 to +0.14)		0.14	(–0.32 to +0.32)		n.a.	(–0.57 to +0.34)		n.a.	(–0.46 to +1.11)		n.a.
Complex PCI	–1.82%	n.a.		0.00%	n.a.		0.00%	n.a.		0.00%	n.a.	
	(–3.64 to +0.65)			(0.00 to 0.00)			(0.00 to 0.00)			(0.00 to 0.00)		
Death for all causes												
Non-Complex PCI	–0.07%	0.84		+0.16%	0.70		+0.73%	0.41		-1.45%	0.29	
	(–0.71 to +0.58)		0.13	(–0.66 to +0.98)		0.09	(–1.00 to +2.46)		0.61	(–4.15 to +1.24)		0.93
Complex PCI	+0.90%	n.a.		+2.81%	n.a.		–0.52%	0.82		-1.12%	0.77	
	(–0.34 to +1.81)			(–0.19 to +5.62)			(–5.14 to +3.90)			(–8.55 to +6.29)		
TIMI major or minor												
Non-Complex PCI	–0.24%	0.46		+0.20%	0.45		+0.43%	0.22		+2.61%	0.003	
	(–0.84 to +0.41)		n.a.	(–0.30 to +0.72)		0.27	(–0.23 to +1.17)		0.22	(+0.89 to +4.31)		0.89
Complex PCI	0.00%	n.a.		+1.33%	n.a.		–0.47%	0.46		+3.04%	0.30	
	(0.00 to 0.00)			(–1.23 to +2.67)			(–1.70 to +0.84)			(–2.97 to +8.82)		
MI, definite ST, stroke TVR or TIMI												

major/minor bleeding												
Non-Complex PCI	–0.79%	0.41		–0.83%	0.39		–1.17%	0.31		+2.81%	0.11	
												0.83
	(–2.69 to +1.10)			(–2.73 to +1.07)			(–3.43 to +1.08)			(–0.72 to +6.33)		
			0.53			0.84			0.10			
Complex PCI	–3.19%	0.38		–1.51%	0.65		–6.97%	0.04		+1.68%	0.73	
	(–10.4 to +3.94)			(–8.10 to +4.99)			(–13.7 to –0.58)			(–7.85 to +11.15)		

HBR= high bleeding risk. ARD= Absolute risk difference. MI= myocardial infarction. ST= stent thrombosis. TVR= target vessel revascularization. Def/Prob= definite or probable. TIMI= thrombosis in myocardial infarction.

The absolute risk difference (ARD) and its 95% confidence interval are calculated according to Newcombe & Altman (2000).

Table 10: Clinical events according to the PRECISE-DAPT score and the complex patient criteria* among patients randomized to short vs. long DAPT duration

	PRECISE-DAPT <25 (Non-HBR)					PRECISE-DAPT ≥25 (HBR)				
	Short DAPT	Long DAPT	ARD	P	P_{int}	Short DAPT	Long DAPT	ARD	P	P_{int}
MI, definite ST, stroke or TVR										
Non-Complex Patient	3.38%	3.82%	+0.43% (–0.87 to –1.73)	0.51	<0.001	4.29%	6.57%	+2.28% (–1.33 to +5.92)	0.22	0.68
Complex Patient	7.38%	3.89%	–3.50% (–5.31 to –1.70)	<0.001		9.33%	10.4%	+1.06% (–3.37 to +5.50)	0.64	
Death, MI, definite ST, stroke or TVR										
Non-Complex Patient	4.28%	4.69%	+0.41% (–1.05 to +1.88)	0.58	0.008	7.56%	7.41%	–0.15% (–4.73 to +4.41)	0.95	0.67
Complex Patient	8.20%	5.28%	–2.92% (–4.93 to –0.93)	0.004		14.2%	15.5%	+1.35% (–3.84 to +6.55)	0.61	
MI, definite ST, stroke										
Non-Complex Patient	0.80%	0.87%	+0.07% (–0.60 to +0.73)	0.85	0.11	1.06%	3.58%	+2.52% (+0.10 to +4.98)	0.04	0.73
Complex Patient	1.94%	1.04%	–0.90% (–1.90 to +0.09)	0.075		4.93%	6.70%	+1.76% (–1.69 to +5.22)	0.32	

Death, MI, definite ST, stroke										
Non-Complex Patient	1.70%	2.02%	+0.31% (–0.72 to +1.35)	0.55	0.55	5.07%	4.44%	–0.63% (–4.51 to +3.22)	0.75	0.62
Complex Patient	2.76%	2.55%	–0.21% (–1.55 to +1.13)	0.76		10.9%	11.8%	+0.88% (–3.71 to +5.48)	0.71	
Stent thrombosis										
Non-Complex Patient	0.05%	0.05%	0.00% (–0.12 to +0.12)	0.99	0.14	0.00%	0.49%	+0.49% (–0.18 to +0.97)	n.a.	0.48
Complex Patient	0.56%	0.20%	-0.36% (–0.83 to +0.10)	0.13		0.50%	0.60%	+0.10% (–0.76 to +1.04)	0.83	
Death for all causes										
Non-Complex Patient	1.04%	1.24%	+0.19% (–0.62 to +1.01)	0.64	0.55	5.05%	2.56%	–2.49% (–6.14 to +1.09)	0.18	0.53
Complex Patient	1.05%	1.61%	+0.57% (–0.38 to +1.51)	0.24		8.06%	7.21%	–0.85% (–4.43 to +2.71)	0.64	
TIMI major or minor										
Non-Complex Patient	0.16%	0.42%	+0.25% (–0.10 to +0.62)	0.16	0.49	0.80%	4.75%	+3.95% (+1.33 to +6.66)	0.004	0.22
Complex Patient	0.57%	0.58%	+0.01% (–0.60 to +0.61)	0.98		1.82%	3.60%	+1.78% (–0.47 to +4.05)	0.12	
MI, definite ST, stroke TVR or TIMI major/minor bleeding										

Non-Complex Patient	3.53%	4.22%	+0.70% (–0.65 to +2.05)	0.31	<0.001	5.18%	9.76%	+4.58% (+0.38 to +8.86)	0.03	0.32
Complex Patient	7.73%	4.28%	–3.45% (–5.31 to –1.59)	<0.001		10.6%	11.9%	+1.37% (–3.33 to +6.08)	0.56	

* Complex Patient criteria: including both anatomical/procedural characteristics of complex PCI definition and/or a clinical presentation with acute coronary syndrome as an additional element

HBR= high bleeding risk. ARD= Absolute risk difference. MI= myocardial infarction. ST= stent thrombosis. TVR= target vessel revascularization. Def/Prob= definite or probable. TIMI= thrombosis in myocardial infarction.

The absolute risk difference (ARD) and its 95% confidence interval are calculated according to Newcombe & Altman (2000).

Figure 1:

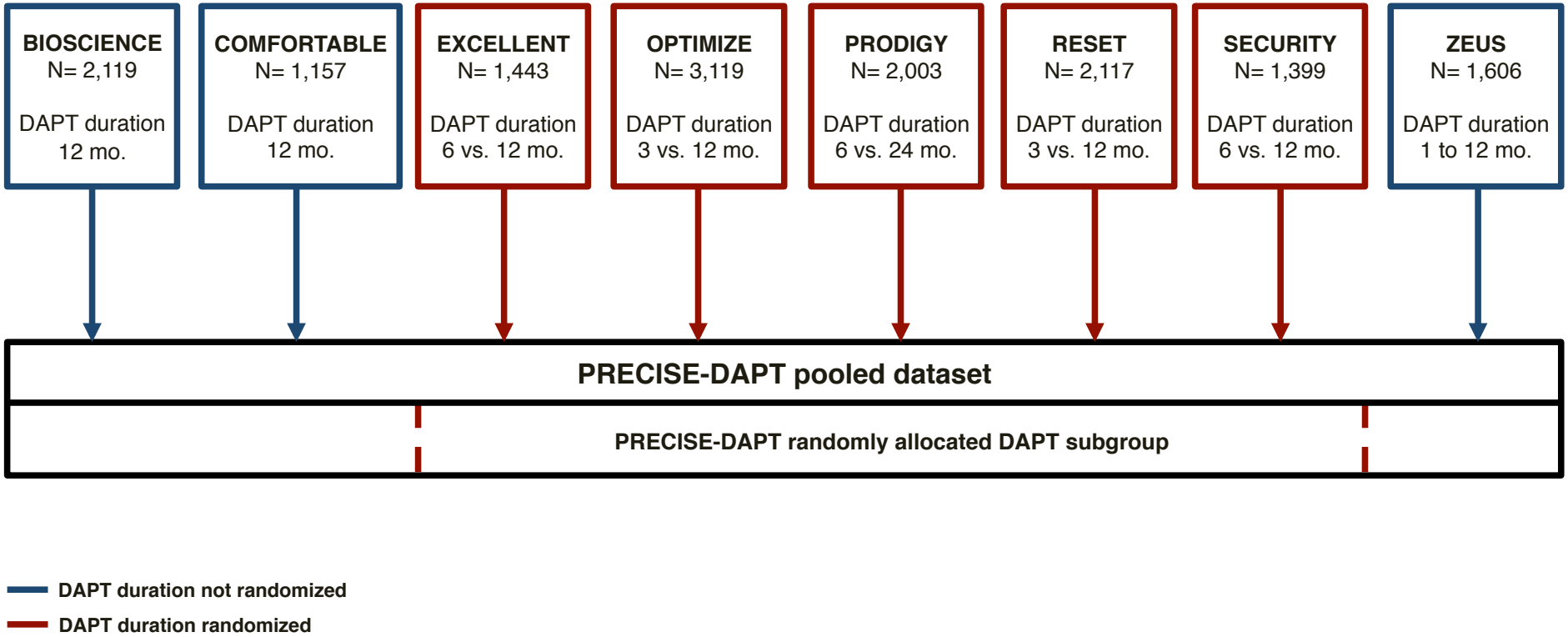

BIOSCIENCE
N= 2,119
DAPT duration
12 mo.
COMFORTABLE
N= 1,157
DAPT duration
12 mo.
EXCELLENT
N= 1,443
DAPT duration
6 vs. 12 mo.
OPTIMIZE
N= 3,119
DAPT duration
3 vs. 12 mo.
PRODIGY
N= 2,003
DAPT duration
6 vs. 24 mo.
RESET
N= 2,117
DAPT duration
3 vs. 12 mo.
SECURITY
N= 1,399
DAPT duration
6 vs. 12 mo.
ZEUS
N= 1,606
DAPT duration
1 to 12 mo.
PRECISE-DAPT pooled dataset
PRECISE-DAPT randomly allocated DAPT subgroup
DAPT duration not randomized
DAPT duration randomized

Figure 2:

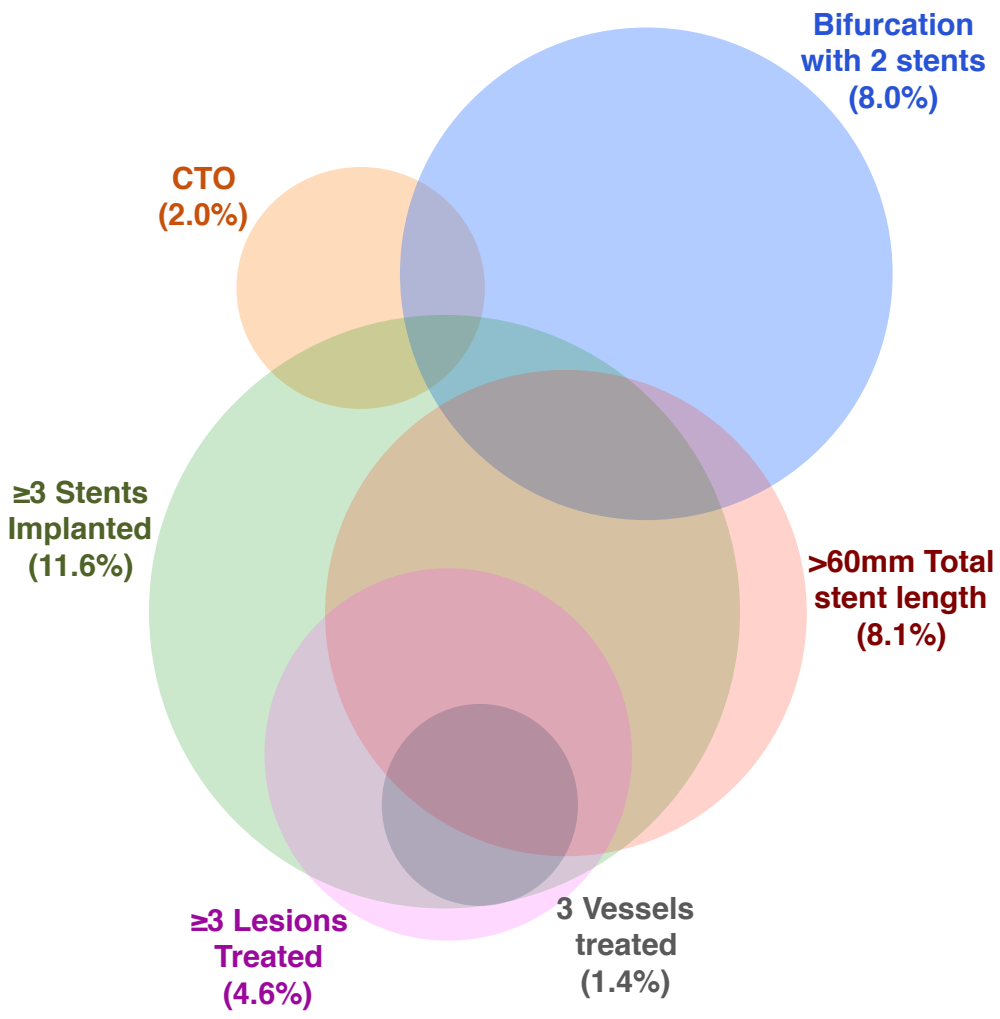

Bifurcation
with 2 stents
(8.0%)
CTO
(2.0%)
≥3 Stents
Implanted
(11.6%)
>60mm Total
stent length
(8.1%)
≥3 Lesions
Treated
(4.6%)
3 Vessels
treated
(1.4%)

Figure 3:

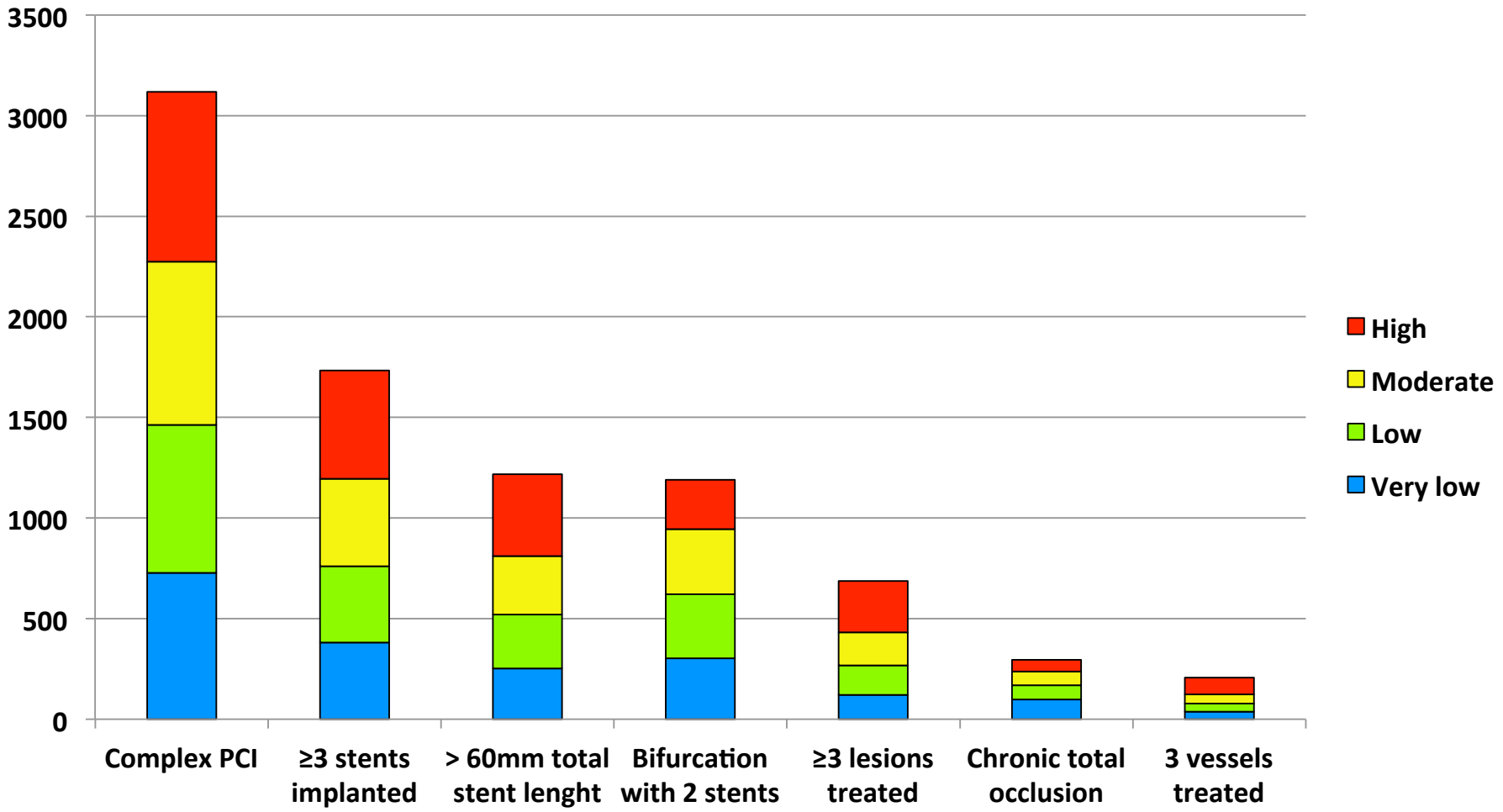
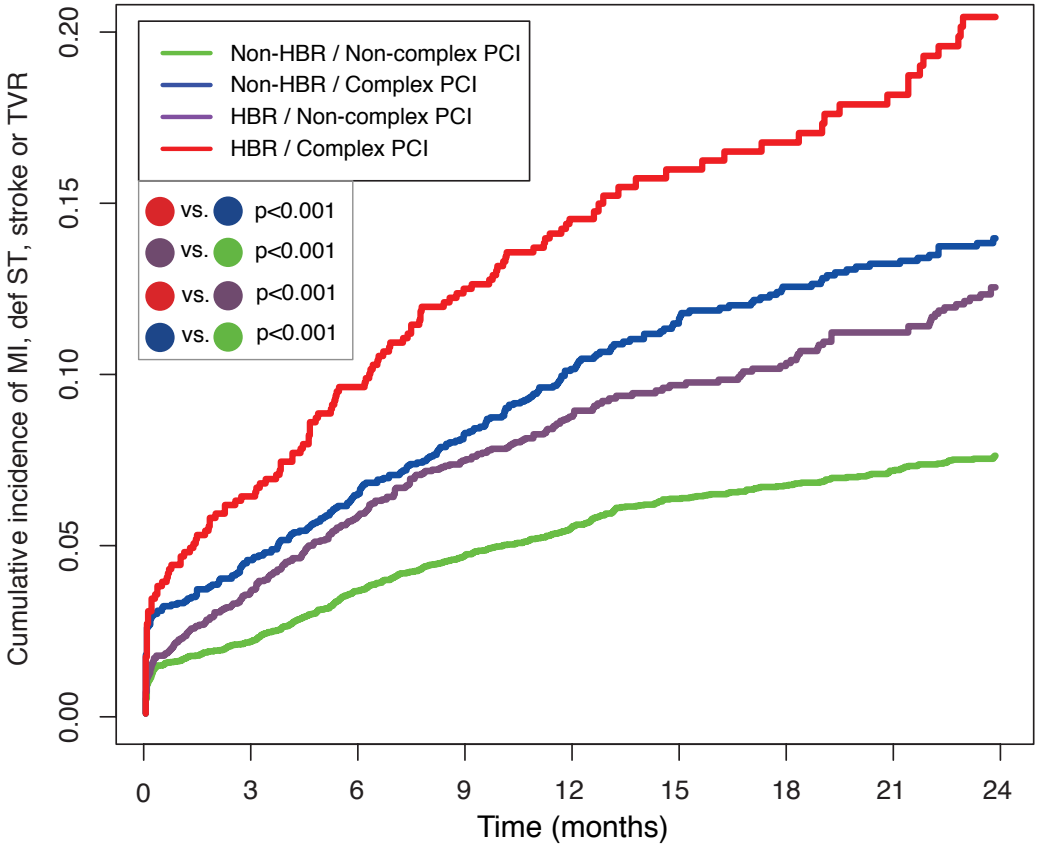

3500
3000
2500
2000
1500
1000
500
0
Complex PCI
≥3 stents implanted
> 60mm total stent lenght
Bifurcation with 2 stents
≥3 lesions treated
Chronic total occlusion
3 vessels treated
High
Moderate
Low
Very low

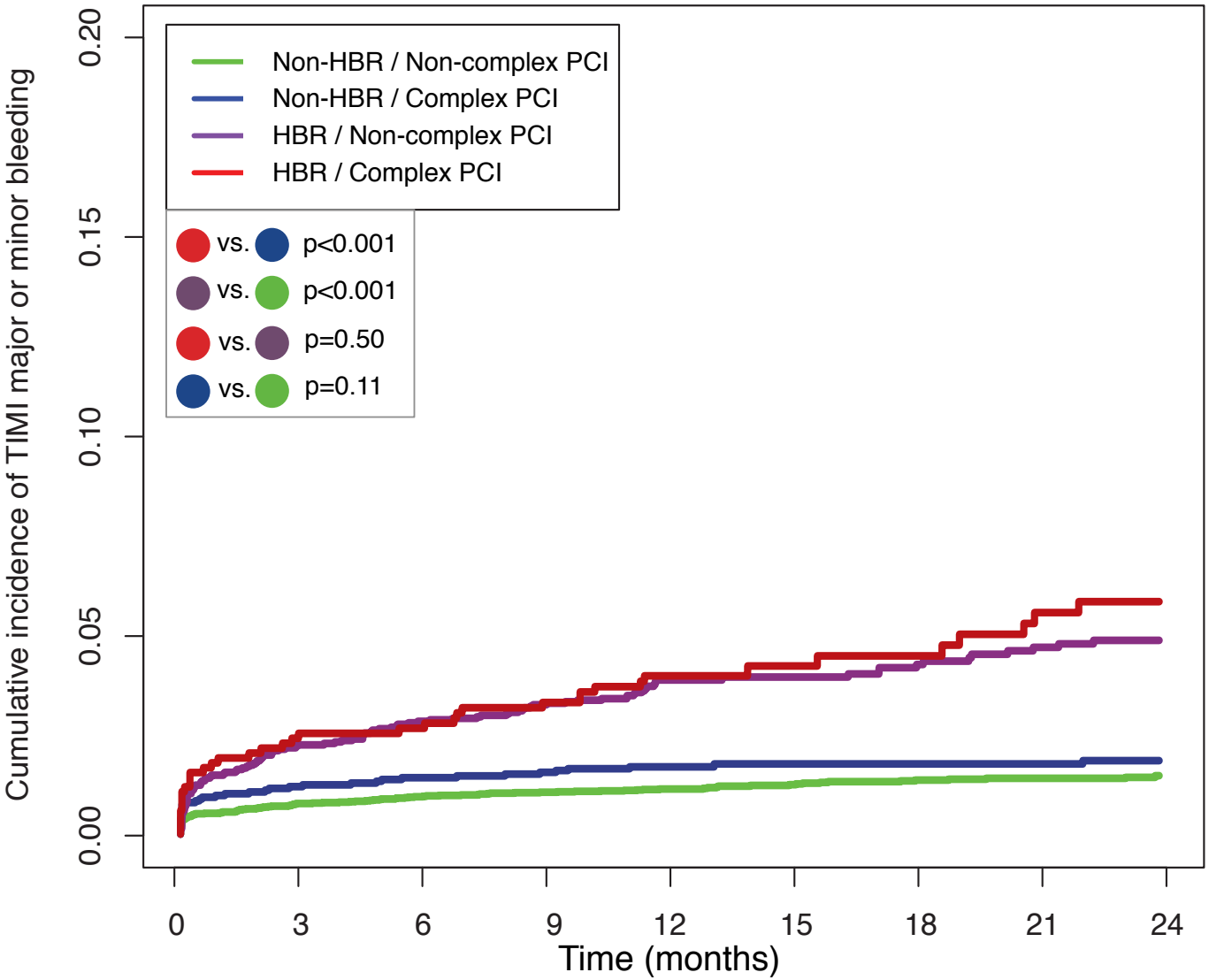
Figure 4:

A



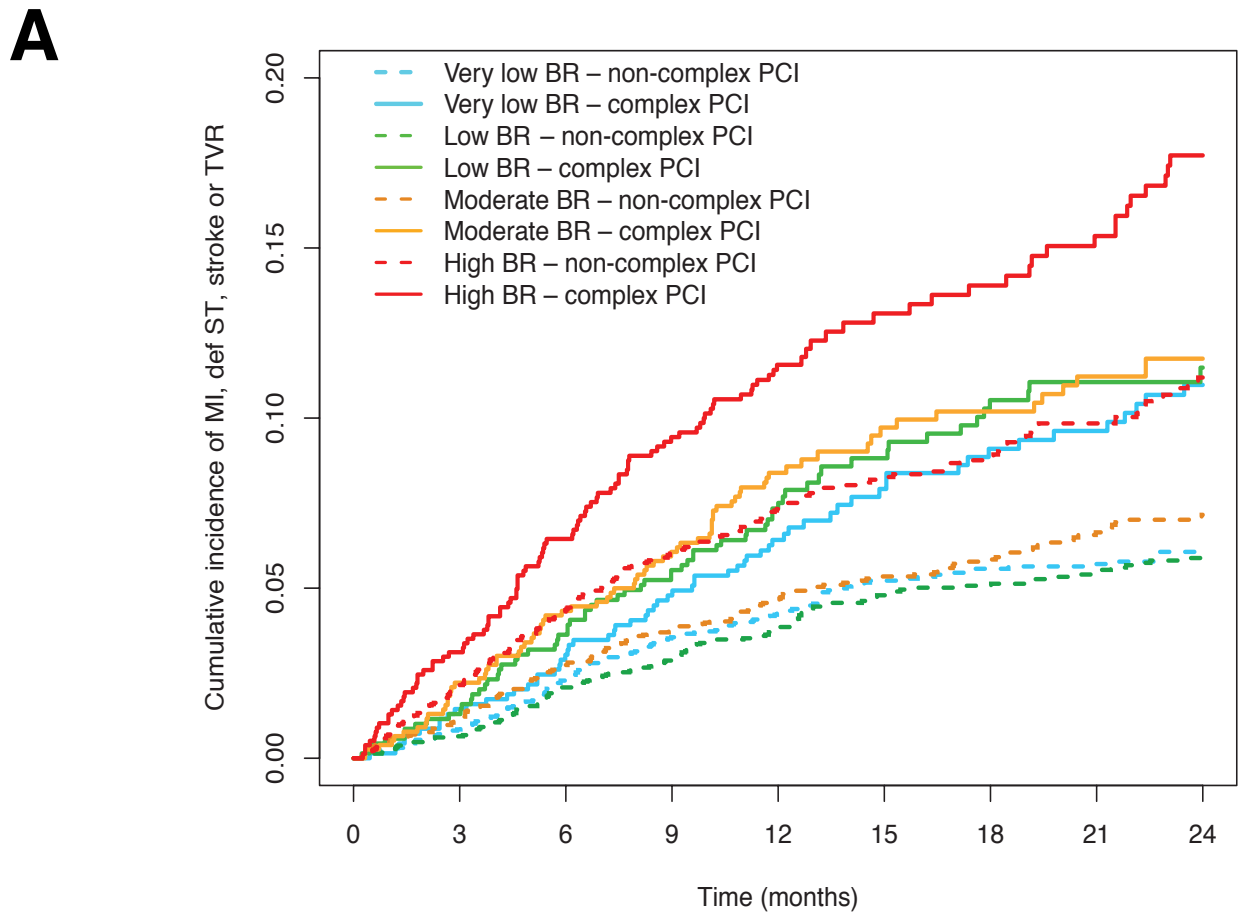
Non-HBR / Non-complex PCI	8981	8645	8446	8314	7571	4889	4593	3968	2032
Non-HBR / Complex PCI	2273	2105	2050	2000	1738	1156	1105	1017	582
HBR / Non-complex PCI	2863	2605	2495	2409	2191	1139	1066	968	381
HBR / Complex PCI	845	737	697	658	584	321	312	287	134

B



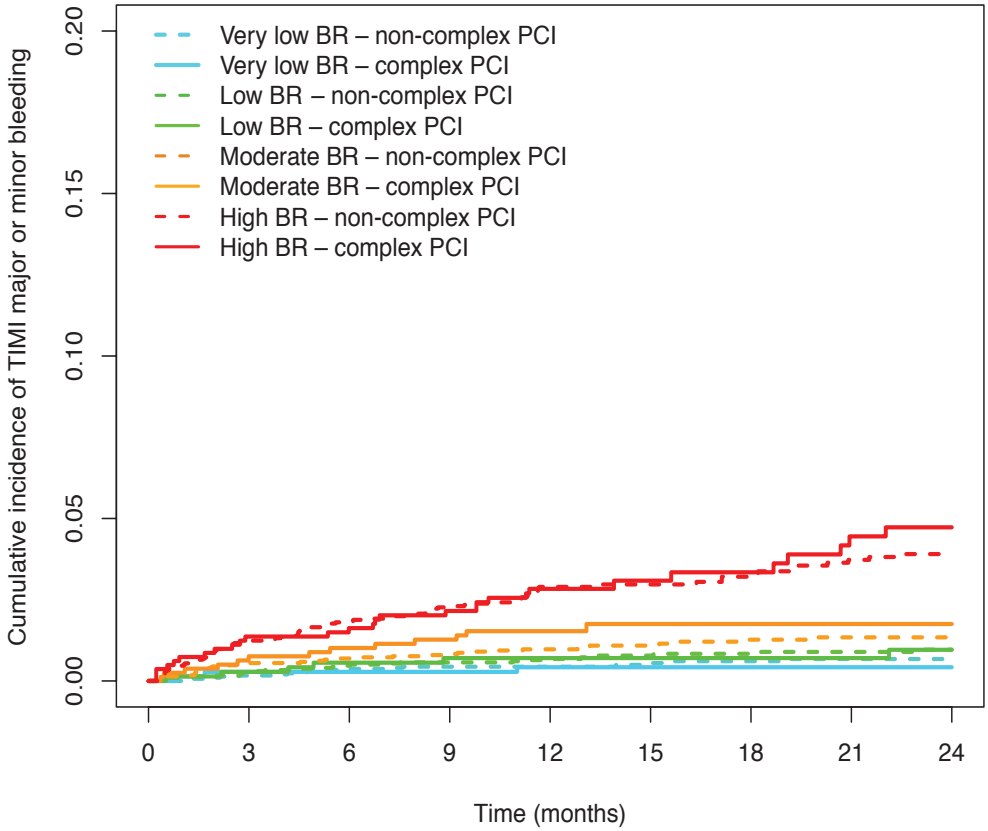
Non-HBR / Non-complex PCI	8981	8805	8711	8653	7949	5212	4921	4290	2156
Non-HBR / Complex PCI	2273	2200	2181	2166	1926	1307	1264	1181	646
HBR / Non-complex PCI	2863	2663	2592	2528	2325	1250	1182	1089	392
HBR / Complex PCI	845	782	757	733	668	378	368	344	162

Figure 5:



Very low BR/ Non-complex PCI	3013	2917	2846	2793	2556	1647	1550	1325	689
Very low BR/ Complex PCI	727	681	668	654	572	394	372	341	189
Low BR/ Non-complex PCI	3021	2918	2855	2822	2563	1705	1603	1387	715
Low BR/ Complex PCI	735	679	660	645	564	378	358	334	197
Moderate BR/ Non-complex PCI	2947	2810	2745	2699	2452	1537	1440	1256	628
Moderate BR/ Complex PCI	811	745	722	701	602	384	375	342	196
High BR/ Non-complex PCI	2863	2605	2495	2409	2191	1139	1066	968	381
High BR/ Complex PCI	845	737	697	658	584	321	312	287	134

B



Very low BR/ Non-complex PCI	3013	2970	2934	2914	2688	1761	1664	1432	738
Very low BR/ Complex PCI	727	711	709	707	629	443	425	394	210
Low BR/ Non-complex PCI	3021	2968	2939	2924	2681	1808	1705	1486	753
Low BR/ Complex PCI	735	708	702	699	626	427	412	389	218
Moderate BR/ Non-complex PCI	2947	2867	2838	2815	2580	1643	1552	1372	665
Moderate BR/ Complex PCI	811	781	770	760	671	437	427	398	218
High BR/ Non-complex PCI	2863	2663	2592	2528	2325	1250	1182	1089	392
High BR/ Complex PCI	845	782	757	733	668	378	368	344	162

Figure 6:

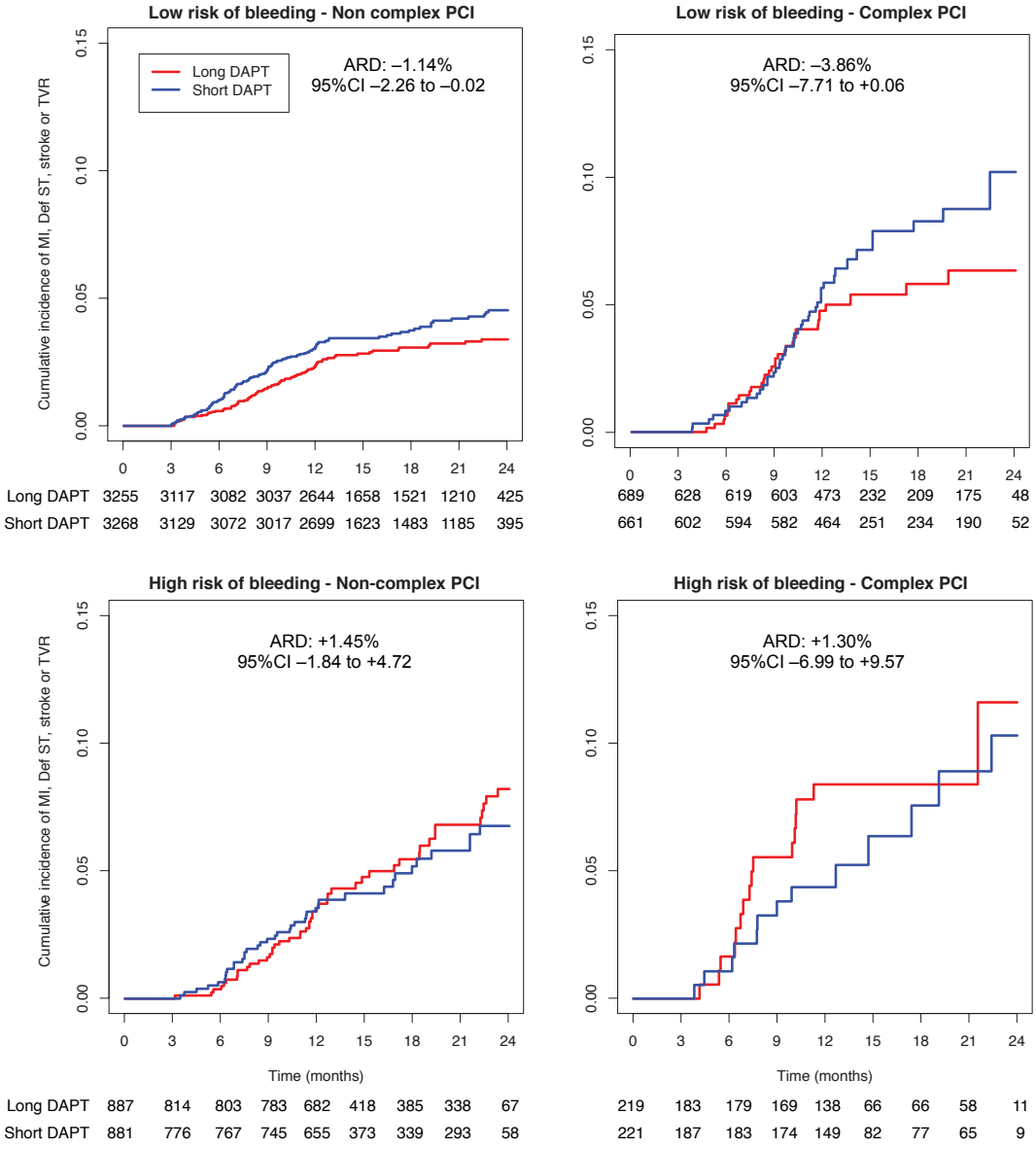

Low risk of bleeding - Non complex PCI
Long DAPT
Short DAPT
ARD: –1.14%
95%CI –2.26 to –0.02
Cumulative incidence of MI, Def ST, stroke or TVR
0.00
0.05
0.10
0.15
0 3 6 9 12 15 18 21 24
Long DAPT 3255 3117 3082 3037 2644 1658 1521 1210 425
Short DAPT 3268 3129 3072 3017 2699 1623 1483 1185 395
Low risk of bleeding - Complex PCI
ARD: –3.86%
95%CI –7.71 to +0.06
0 3 6 9 12 15 18 21 24
689 628 619 603 473 232 209 175 48
661 602 594 582 464 251 234 190 52
High risk of bleeding - Non-complex PCI
ARD: +1.45%
95%CI –1.84 to +4.72
Time (months)
Long DAPT 887 814 803 783 682 418 385 338 67
Short DAPT 881 776 767 745 655 373 339 293 58
High risk of bleeding - Complex PCI
ARD: +1.30%
95%CI –6.99 to +9.57
Time (months)
219 183 179 169 138 66 66 58 11
221 187 183 174 149 82 77 65 9

Figure 7:

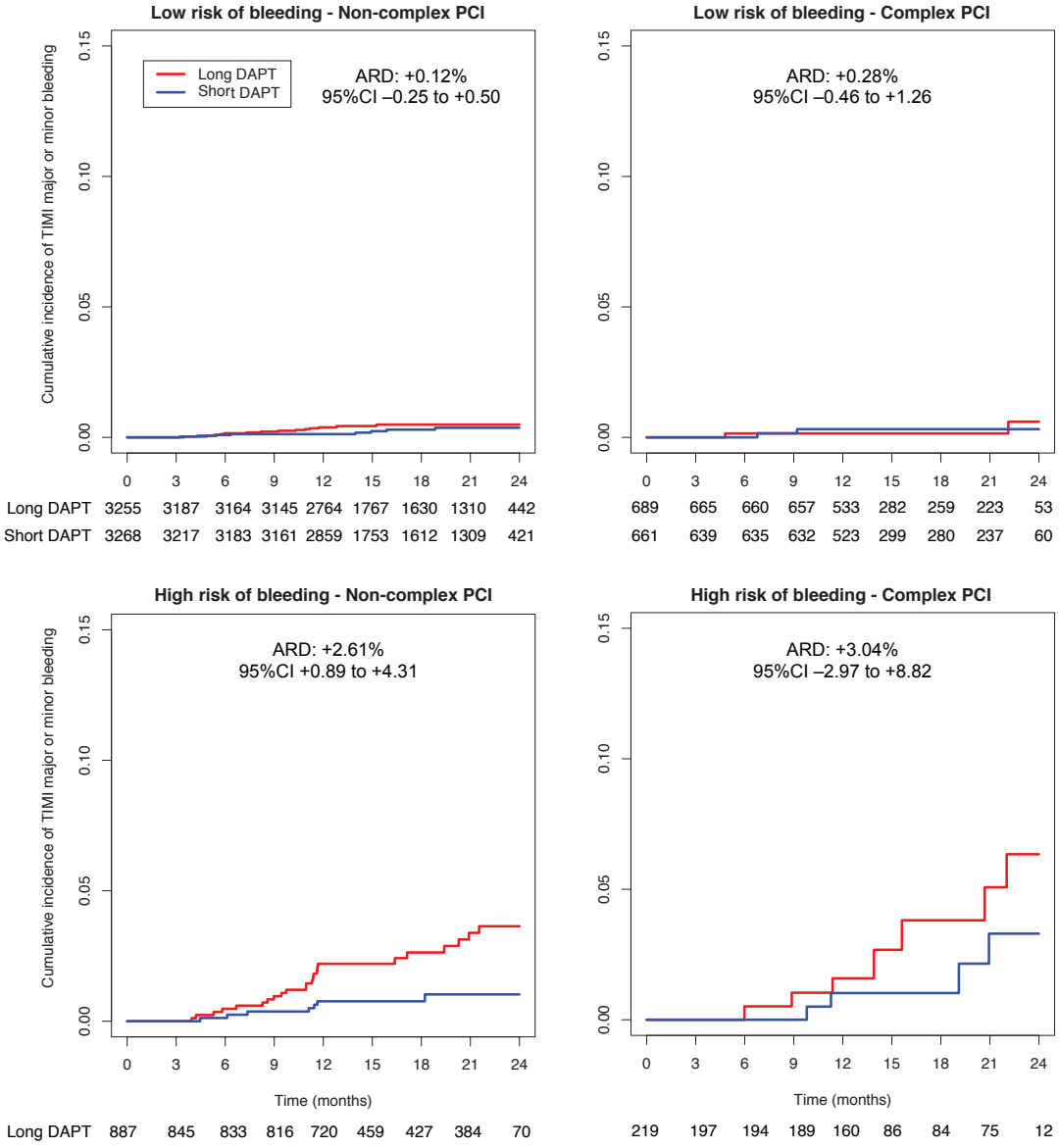
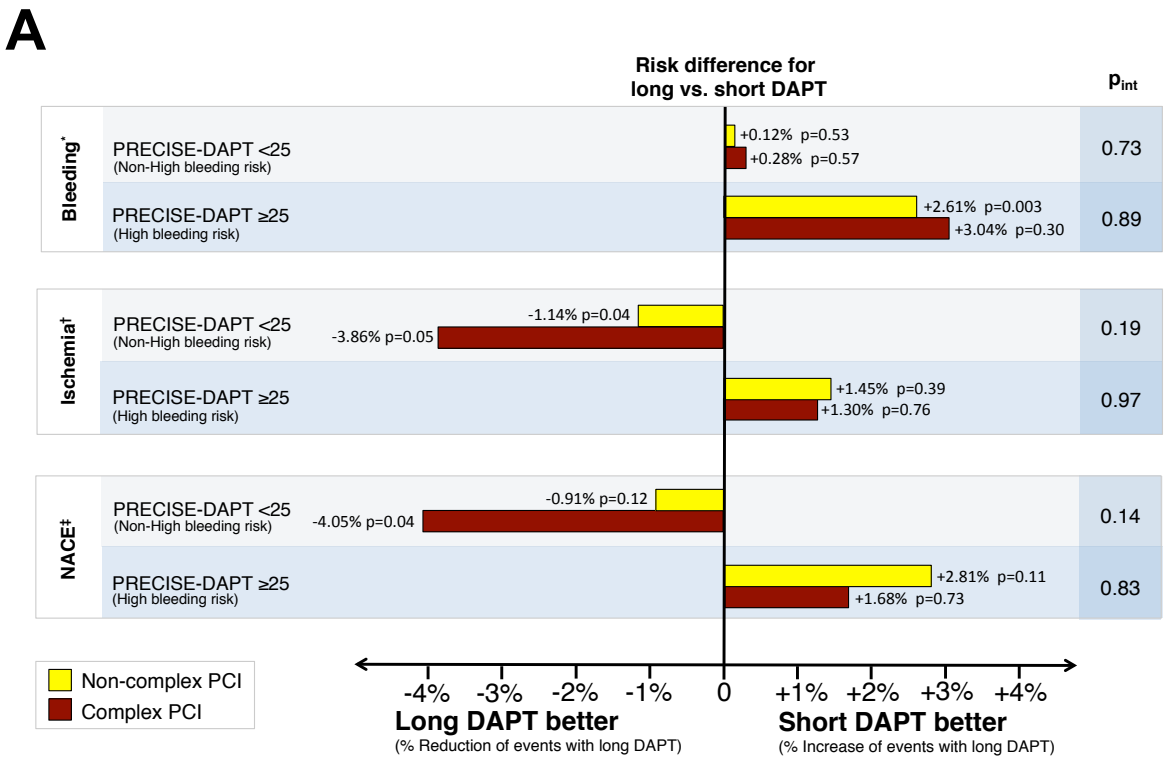

Low risk of bleeding - Non-complex PCI
Long DAPT
Short DAPT
ARD: +0.12%
95%CI –0.25 to +0.50
Cumulative incidence of TIMI major or minor bleeding
0.00
0.05
0.10
0.15
0 3 6 9 12 15 18 21 24
Long DAPT 3255 3187 3164 3145 2764 1767 1630 1310 442
Short DAPT 3268 3217 3183 3161 2859 1753 1612 1309 421
Low risk of bleeding - Complex PCI
ARD: +0.28%
95%CI –0.46 to +1.26
0 3 6 9 12 15 18 21 24
689 665 660 657 533 282 259 223 53
661 639 635 632 523 299 280 237 60
High risk of bleeding - Non-complex PCI
ARD: +2.61%
95%CI +0.89 to +4.31
Cumulative incidence of TIMI major or minor bleeding
0 3 6 9 12 15 18 21 24
Time (months)
Long DAPT 887 845 833 816 720 459 427 384 70
High risk of bleeding - Complex PCI
ARD: +3.04%
95%CI –2.97 to +8.82
0 3 6 9 12 15 18 21 24
Time (months)
219 197 194 189 160 86 84 75 12

Figure 8:


A
Risk difference for long vs. short DAPT
p_{int}
Bleeding*
PRECISE-DAPT <25
(Non-High bleeding risk)
+0.12% p=0.53
+0.28% p=0.57
0.73
PRECISE-DAPT ≥25
(High bleeding risk)
+2.61% p=0.003
+3.04% p=0.30
0.89
Ischemia†
PRECISE-DAPT <25
(Non-High bleeding risk)
-1.14% p=0.04
-3.86% p=0.05
0.19
PRECISE-DAPT ≥25
(High bleeding risk)
+1.45% p=0.39
+1.30% p=0.76
0.97
NACE‡
PRECISE-DAPT <25
(Non-High bleeding risk)
-0.91% p=0.12
-4.05% p=0.04
0.14
PRECISE-DAPT ≥25
(High bleeding risk)
+2.81% p=0.11
+1.68% p=0.73
0.83
Non-complex PCI
Complex PCI
-4% -3% -2% -1% 0 +1% +2% +3% +4%
Long DAPT better
(% Reduction of events with long DAPT)
Short DAPT better
(% Increase of events with long DAPT)

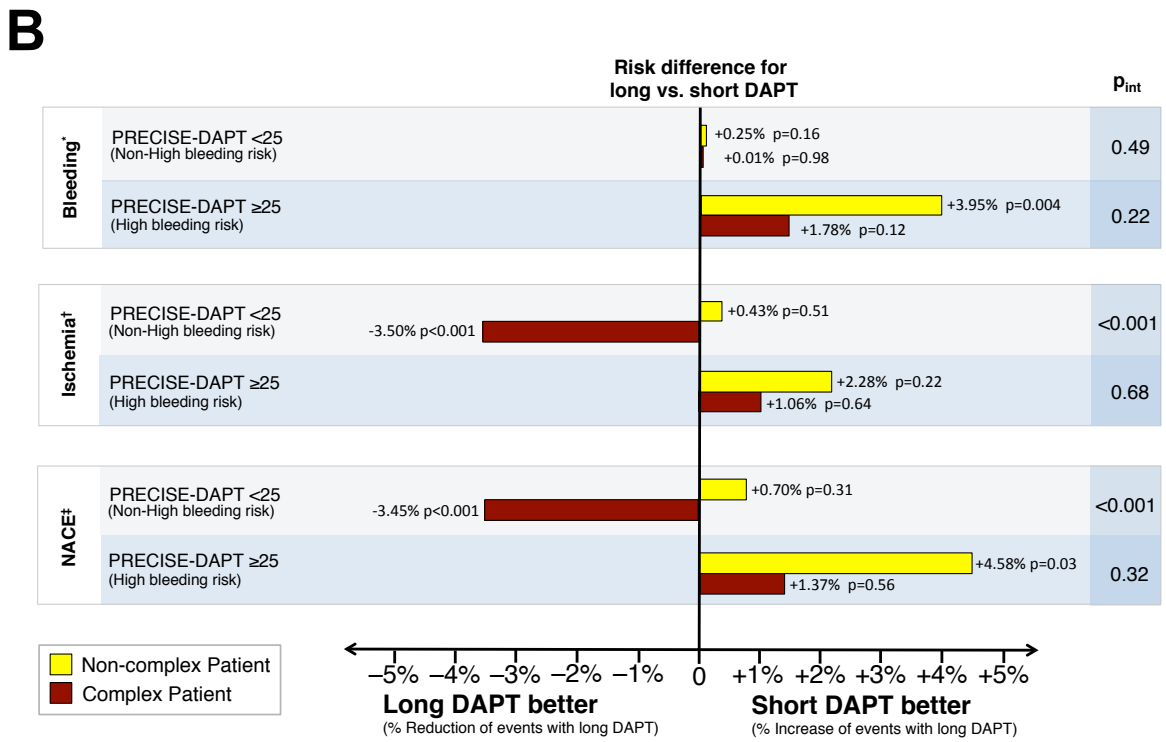
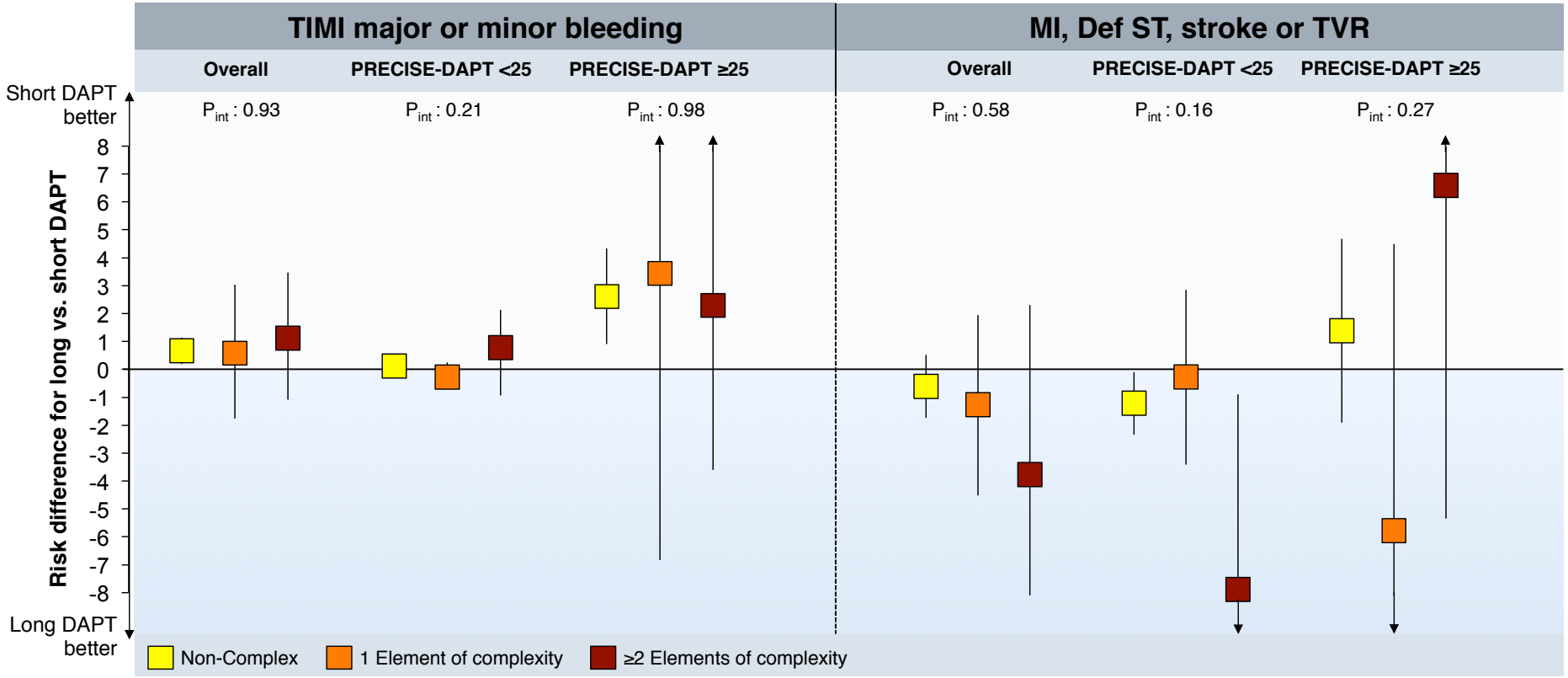

B
Risk difference for long vs. short DAPT
p_{int}
Bleeding*
PRECISE-DAPT <25
(Non-High bleeding risk)
+0.25% p=0.16
+0.01% p=0.98
0.49
PRECISE-DAPT ≥25
(High bleeding risk)
+3.95% p=0.004
+1.78% p=0.12
0.22
Ischemia†
PRECISE-DAPT <25
(Non-High bleeding risk)
+0.43% p=0.51
-3.50% p<0.001
<0.001
PRECISE-DAPT ≥25
(High bleeding risk)
+2.28% p=0.22
+1.06% p=0.64
0.68
NACE‡
PRECISE-DAPT <25
(Non-High bleeding risk)
+0.70% p=0.31
-3.45% p<0.001
<0.001
PRECISE-DAPT ≥25
(High bleeding risk)
+4.58% p=0.03
+1.37% p=0.56
0.32
Non-complex Patient
Complex Patient
–5% –4% –3% –2% –1% 0 +1% +2% +3% +4% +5%
Long DAPT better
(% Reduction of events with long DAPT)
Short DAPT better
(% Increase of events with long DAPT)

Figure 9:


TIMI major or minor bleeding
MI, Def ST, stroke or TVR
Overall
PRECISE-DAPT <25
PRECISE-DAPT ≥25
Overall
PRECISE-DAPT <25
PRECISE-DAPT ≥25
Short DAPT better
Long DAPT better
Risk difference for long vs. short DAPT
8
7
6
5
4
3
2
1
0
-1
-2
-3
-4
-5
-6
-7
-8
P int : 0.93
P int : 0.21
P int : 0.98
P int : 0.58
P int : 0.16
P int : 0.27
Non-Complex
1 Element of complexity
≥2 Elements of complexity