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Antithrombotic therapy according to baseline bleeding risk in patients with atrial fibrillation undergoing percutaneous coronary intervention: applying the PRECISE-DAPT score in RE-DUAL PCI

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Abstract: AIMS Patients with atrial fibrillation undergoing coronary intervention are at higher bleeding risk due to the concomitant need for oral anticoagulation and antiplatelet therapy. The RE-DUAL PCI trial demonstrated better safety with dual antithrombotic therapy (DAT: dabigatran 110 or 150 mg bid, clopidogrel or ticagrelor) compared to triple antithrombotic therapy (TAT: warfarin, clopidogrel or ticagrelor, and aspirin). We explored the impact of baseline bleeding risk based on the PRECISE-DAPT score for decision-making regarding DAT vs. TAT. **METHODS AND RESULTS** A score ≥ 25 points qualified high bleeding-risk (HBR). Comparisons were made for the primary safety endpoint ISTH major or clinically relevant non-major bleeding, and the composite efficacy endpoint of death, thromboembolic events, or unplanned revascularization, analyzed by time-to-event analysis. PRECISE-DAPT was available in 2,336/2,725 patients, and 37.9% were HBR. Compared to TAT, DAT with dabigatran 110 mg reduced bleeding risk both in non-HBR (HR 0.42, 95%CI, 0.31-0.57) and HBR (HR 0.70, 95%CI, 0.52-0.94), with a greater magnitude of benefit among non-HBR (Pint=0.02). DAT with dabigatran 150 mg vs. TAT reduced bleeding in non-HBR (HR 0.60, 95%CI, 0.45-0.80), with a trend toward less benefit in HBR patients (HR 0.92, 95%CI, 0.63-1.34, Pint=0.08). Risk of ischaemic events was similar on DAT with dabigatran (both 110 and 150 mg) vs. TAT in non-HBR and HBR patients (Pint=0.45 and Pint=0.56, respectively). **CONCLUSIONS** PRECISE-DAPT score appeared useful to identify AF patients undergoing PCI at further increased risk of bleeding complications, and may help clinicians identifying the antithrombotic regimen intensity with the best benefit-risk ratio in an individual patient.

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Antithrombotic therapy according to baseline bleeding risk in patients with atrial fibrillation undergoing percutaneous coronary intervention: applying the PRECISE-DAPT score in RE-DUAL PCI

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Brief Title: PRECISE-DAPT score and dual or triple therapy after stenting

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Abstract

Aims: Patients with atrial fibrillation undergoing coronary intervention are at higher bleeding risk due to the concomitant need for oral anticoagulation and antiplatelet therapy. The RE-DUAL PCI trial demonstrated better safety with dual antithrombotic therapy (DAT: dabigatran 110 or 150mg bid, clopidogrel or ticagrelor) compared to triple antithrombotic therapy (TAT: warfarin, clopidogrel or ticagrelor, and aspirin). We explored the impact of baseline bleeding risk based on the PRECISE-DAPT score for decision-making regarding DAT vs. TAT.

Methods and Results: A score ≥ 25 points qualified high bleeding-risk (HBR). Comparisons were made for the primary safety endpoint ISTH major or clinically relevant non-major bleeding, and the composite efficacy endpoint of death, thromboembolic events, or unplanned revascularization, analyzed by time-to-event analysis. PRECISE-DAPT was available in 2,336/2,725 patients, and 37.9% were HBR. Compared to TAT, DAT with dabigatran 110mg reduced bleeding risk both in non-HBR (HR 0.42, 95%CI, 0.31–0.57) and HBR (HR 0.70, 95%CI, 0.52–0.94), with a greater magnitude of benefit among non-HBR ($P_{\text{int}}=0.02$). DAT with dabigatran 150mg vs. TAT reduced bleeding in non-HBR (HR 0.60, 95%CI, 0.45–0.80), with a trend toward less benefit in HBR patients (HR 0.92, 95%CI, 0.63–1.34, $P_{\text{int}}=0.08$). Risk of ischemic events was similar on DAT with dabigatran (both 110 and 150mg) vs. TAT in non-HBR and HBR patients ($P_{\text{int}}=0.45$ and $P_{\text{int}}=0.56$, respectively).

Conclusions: PRECISE-DAPT score appeared useful to identify AF patients undergoing PCI at further increased risk of bleeding complications, and may help clinicians identifying the antithrombotic regimen intensity with the best benefit-risk ratio in an individual patient.

Introduction:

Coronary stenting in patients with the need for long term oral anticoagulation (OAC) poses special challenges regarding the best antithrombotic strategy.¹ Coronary stenting requires an initial period of dual antiplatelet therapy (DAPT) with aspirin and a P2Y12 inhibitor to prevent stent thrombosis and other coronary thrombotic events.² Yet, high-risk patients with atrial fibrillation (AF) need OAC to mitigate the risk of stroke or systemic embolism, further amplifying the bleeding risk of DAPT.³ In fact, this combination, also called triple antithrombotic therapy, has been associated to a >3-fold increased risk of major bleeding.⁴ Considering that indefinite OAC therapy is mandatory in this setting, reducing DAPT duration has been widely explored in multiple clinical trials to enhance safety, testing the hypothesis of removing one antiplatelet agent early after stenting, hence downgrading TAT to a dual antithrombotic therapy (DAT).⁵ The latter has ultimately proved useful to limit the risk of major bleeding and has been endorsed by clinical guidelines, which now suggest adjusting antiplatelet therapy duration, and eventually OAC dosage, based on the preponderant ischemic or bleeding risk.⁶ Given that bleeding risk is a major determinant for DAPT duration after stenting, standardized bleeding risk scores such as the PRECISE-DAPT may be useful to identify patients at high bleeding risk (HBR) whom may be indicated for shorter courses of treatment; however this score has never been tested in the context of AF-PCI.⁷ For this reason we aimed to explore the impact of a treatment with dabigatran DAT vs. warfarin TAT, among patients included in the RE-DUAL PCI trial at different baseline bleeding risk based on the PRECISE-DAPT score.

Methods:

This is a post hoc analysis of the RE-DUAL PCI trial, a randomized, open-label study. Study design and main results have been previously reported.^{8,9} A total of 2,725 AF-PCI patients

were randomly assigned to DAT comprising dabigatran 110 mg or 150 mg twice daily and a P2Y12 inhibitor (either clopidogrel or ticagrelor) or TAT with warfarin, adjusted to achieve an international normalized ratio of 2.0 to 3.0, in association with aspirin and a P2Y12 inhibitor. According to the study protocol, patients in the United States or younger patients in the rest of the world could be randomized to both doses of dabigatran (i.e. 110 and 150mg twice-daily) or to warfarin plus aspirin in a 1:1:1 ratio. Whereas elderly patients outside the United States (i.e. ≥ 80 years of age worldwide, ≥ 70 years of age in Japan) were randomized only to the 110-mg dabigatran dose versus warfarin plus aspirin comparison in a 1:1 ratio. All patients were to receive clopidogrel (75 mg daily) or ticagrelor (90 mg twice daily) for at least 12 months after randomization. Aspirin in the triple therapy arm was prescribed for 1 or 3 months after PCI in case of bare-metal or drug-eluting stent implantation respectively, whereas in the dual therapy arm was maintained during the periprocedural phase in all patients and discontinued at the time of randomization which occurred after PCI.

In the current analysis the baseline bleeding risk was estimated by the PRECISE-DAPT score as previously reported.⁷ The PRECISE-DAPT score is calculated through five clinical and laboratory variables: age, creatinine clearance, haemoglobin, white-blood cell count and a history of prior bleeding (**Supplementary Figure 1**). Patients with a score ≥ 25 points were deemed HBR. Patients in which the PRECISE-DAPT score was not available owing to missing values were excluded (N=389/2725). Details regarding excluded patients and the distribution of score missing variables are presented in the appendix (**Supplementary Table 1 and 2**). The modified HAS-BLED (Hypertension, Abnormal renal and liver function, Stroke, Bleeding tendency/predisposition, Elderly, Drugs, or alcohol excess), omitting the labile INR component, was also computed.^{10, 11}

The primary safety endpoint of the study was International Society of Thrombosis and Haemostasis (ISTH) major bleeding events or clinically relevant non-major bleeding events (CRNMBE). The main efficacy endpoint was a composite of death or thromboembolic events (DTE: death for all causes, myocardial infarction, stroke, or systemic embolism) or

unplanned revascularization. A list of other safety and efficacy endpoints have also been explored as pre-specified in the study protocol.⁸

Statistical Analysis: Baseline patients' characteristics were presented by HBR status.

Categorical variables were reported as frequencies and percentages, and continuous variables as means and standard deviations. Discrimination and calibration of the PRECISE-DAPT score and the modified HAS-BLED score were calculated in the RE-DUAL PCI population based on C-statistics and Hosmer-Lemeshow goodness-of-fit test. For the comparison of dabigatran 110mg DAT vs. warfarin Cox proportional hazard regression models stratified by age (elderly vs. non-elderly) were computed, whereas unstratified Cox proportional hazard regression models were computed for the comparison of dabigatran 150mg DAT vs. warfarin, among HBR and non-HBR patients. Treatment by subgroup interaction P-values for dabigatran 110mg DAT vs. warfarin TAT and dabigatran 150mg DAT vs. warfarin TAT were provided. Additionally, Cox proportional hazard regression models including the score as a continuous variable, the treatment and the interaction between the treatment and the score were also computed. Treatment-independent Cox proportional hazard regression models were computed to evaluate the impact of HBR vs. non-HBR at baseline on the efficacy and safety outcomes.

Results:

Population: PRECISE-DAPT score was available in 2336 of 2725 patients in the RE-DUAL PCI trial. Median PRECISE-DAPT score was 21 (IQR 13-29) and 37.9% (N=885) were deemed at HBR. Patients at HBR were older, more frequently women, with a higher prevalence of prior TIA or stroke and major bleeding (**Table 1**). These patients had worse renal function and higher CHA₂DS₂-VASc and HAS-BLED scores. Drug-eluting stents have been used in a similar proportion irrespectively of bleeding risk status. Patients assigned to

DAT with dabigatran 110mg therapy were 842 (502 non-HBR and 340 HBR), those assigned to DAT with dabigatran 150mg were 659 (474 non-HBR and 185 HBR), whereas patients assigned to warfarin TAT were 835 (475 non-HBR and 360 HBR). Details regarding baseline characteristics for HBR status and randomized treatment are presented in **Supplementary Table 3 and 4.**

Score performance: PRECISE-DAPT score distribution in the RE-DUAL PCI population is presented in **Supplementary Figure 1**. Discrimination and calibration of the bleeding risk scores is presented in **Table 2**. PRECISE-DAPT score and HAS-BLED score showed modest discrimination in the RE-DUAL PCI population except for TIMI major bleed and ICH. PRECISE-DAPT showed numerically higher discrimination compared to HAS-BLED score for the primary safety endpoint, and higher discrimination for ISTH Major bleeding. Similar results were observed with multiple definitions for bleeding. At difference with HAS-BLED score, PRECISE-DAPT appeared well calibrated for the primary safety endpoint and for multiple definition of bleeding explored (**Table 2**).

Impact of bleeding risk status on clinical events: Compared to non-HBR, HBR patients were associated to higher risks of bleeding (**Table 3**). This was confirmed irrespective of the bleeding definition used (**Supplementary Table 5**) except for TIMI major bleed and ICH. HBR status was also associated with a higher risk of ischemic events and death for all causes (**Table 3**).

Safety of the randomized treatment on bleeding risk subgroups: The impact of DAT vs. TAT on the primary safety endpoint by PRECISE-DAPT score as a continuous variable is presented in **Figure 1**. There was no statistically significant interaction between the continuous PRECISE-DAPT score and the treatment comparing DAT with dabigatran 110mg

vs. TAT for the primary safety endpoint ($P_{\text{int}} = 0.10$). Yet, a trend could be observed for a greater magnitude of the benefit of DAT compared to TAT with decreasing PRECISE-DAPT scores (**Figure 1A**). For the comparison of DAT with dabigatran 150 mg vs. TAT, a statistically significant interaction in the treatment effect for varying PRECISE-DAPT scores was observed ($P_{\text{int}} = <0.01$), suggesting a benefit of DAT vs. TAT in patients with lower PRECISE-DAPT values (**Figure 1B**). However, due to a low number of patients with a very high PRECISE-DAPT scores, the confidence intervals remain wide.

When the study population was stratified in two groups according to the HBR status (i.e. HBR and non-HBR according to the standard bleeding risk cut-off ≥ 25 points of the PRECISE-DAPT score), DAT with dabigatran 110 mg compared to TAT with warfarin was associated with lower bleeding risks in non-HBR patients (HR 0.42, 95% CI, 0.31–0.57) and in HBR patients (HR 0.70, 95% CI, 0.52–0.94), with a statistically significant interaction ($P_{\text{int}} = 0.02$), suggesting a similar direction, but a greater magnitude of the benefit, among non-HBR patients (**Central Figure and Table 3**). DAT with dabigatran 150 mg vs. TAT was associated with reduced bleeding risk among non-HBR patients (HR 0.60, 95% CI, 0.45–0.80), but no clear benefit among HBR patients (HR 0.92, 95% CI, 0.63–1.34) with a borderline interaction p-value suggesting a trend towards less benefit among HBR patients ($P_{\text{int}} = 0.08$) (**Central Figure and Figure 3**). Results remained largely consistent when other definition for bleeding were explored (**Figure 3 and Supplementary Table 6**).

At sensitivity analysis using an alternative score cut-off for HBR (i.e. ≥ 30 points) (**Supplementary Figure 2**) and higher vs. lower haemoglobin values (**Supplementary Appendix**) consistent results were obtained.

Efficacy of the treatment on bleeding risk subgroups: For the main secondary composite endpoint of DTE or unplanned revascularization, DAT with dabigatran (at both dosages of 110 and 150 mg twice daily) showed similar risks of events compared to TAT in non-HBR and HBR patients' ($P_{\text{int}} = 0.45$ and $P_{\text{int}} = 0.56$, respectively) (**Figure 2**). The impact of DAT vs.

TAT according to the bleeding risk of the PRECISE-DAPT score managed as a continuous variable is presented in **Supplementary Figure 3**. Stent thrombosis rates are presented in **Supplementary Table 7**. DAT with dabigatran showed similar risks for definite stent thrombosis compared to TAT in non-HBR and HBR patients' at both dosages of 110 and 150 mg twice daily ($P_{\text{int}} = 0.55$ and $P_{\text{int}} = 0.99$ respectively) (**Supplementary Table 7**).

No interaction between baseline bleeding risk subgroup and the treatment was observed for other secondary ischemic endpoints (**Figure 3**).

Discussion:

The main findings of the current analysis of the RE-DUAL PCI trial can be summarized as follows: first, HBR patients selected according to the PRECISE-DAPT score had a 38% higher risk of major or clinically relevant non-major bleeding and 71% higher risk of ISTH major bleeding; second, DAT with dabigatran 110mg reduced bleeding among both non-HBR and HBR patients compared to warfarin TAT and the magnitude of the benefit conferred by DAT with dabigatran 110 mg appeared higher among non-HBR than HBR patients; third, DAT with dabigatran 150mg, compared to warfarin TAT, reduced bleeding among non-HBR patients, while a trend towards less benefit among HBR patients was observed.

European and North American guidelines suggest that bleeding risk should be taken into account to select the optimal antithrombotic strategy in AF-PCI patients.^{1, 2, 6} Hence, decisions for DAT or TAT, and eventually OAC dose, should be based on individual patients' risk. Given the higher prevalence of bleeding complications in this setting, DAT or very short courses of TAT should be the primary choice in most of the cases.⁵ In fact, DAT appeared safer across multiple strata of bleeding risk, especially when dabigatran 110mg was selected.

Importantly, OAC dose selection in AF-PCI patients should be based on the approved dose effective for stroke prevention, tested in adequately powered clinical trials. Pivotal trials demonstrated that both approved doses of dabigatran (i.e. 110 and 150 mg bid) proved effective for stroke prevention,¹² and real-world data confirmed that also among patients with no formal elements for dose reduction according to drug labeling, dabigatran at lower dose remains effective.^{13, 14} Hence, international guidelines suggest to select dabigatran 150-mg for AF-PCI patients considered at higher thrombotic risk, while the 110-mg dose should be considered in elderly patients and those with higher bleeding risk.⁶ Our study is the first to give support to guidelines for treatment selection according to patients baseline bleeding risk in AF-PCI patients. We found that the PRECISE-DAPT score, assessed by age, prior bleeding history, creatinine clearance, haemoglobin and white-blood cell count, could identify higher risk of bleeding among AF-PCI patients.

Recently, a risk model was generated from AF patients included in the RELY trial, to highlight ischemic and bleeding risk factors and guide optimal dose selection of dabigatran.¹⁵ Also in this report, older age, lower haemoglobin and creatinine clearance, together with additional use of antiplatelet therapy were found to be major predictors for bleeding, and higher bleeding risk patients had better safety with dabigatran 110mg dose, whereas those not qualifying as HBR could get additional ischemic advantage from dabigatran 150mg without an excessive bleeding liability. DAT with dabigatran 110mg, showed the most favourable net outcome among patients with the expected higher clinical impact from a bleeding, and appeared to be the best choice when bleeding risk was a concern.¹⁶ Our results align with current international drug labeling, as many patients with higher bleeding risk according to PRECISE-DAPT score would already qualify for dose reduction owing to age or renal function. Yet, at difference with single elements, the use of a score, taking into account multiple features with different weights at the same time, is more effective in estimating risk and taking decisions.

An interesting observation from the current study was that the relative benefit for DAT

compared to TAT was actually *greater* in those at *lower* bleeding risk than among those at higher bleeding risk at baseline. This is unexpected, as one would predict that a reduction of the number of antithrombotic agents would lower bleeding especially among individuals with a higher risk at baseline. While this result is counterintuitive several possible explanations could be proposed. HBR patients are often older and with a worse renal function. Direct oral anticoagulants are excreted through renal clearance, and dabigatran have 80% renal elimination. Higher blood concentrations and accumulation of dabigatran are expected in this subgroup, justifying the smaller advantage of a dabigatran DAT strategy, especially when higher doses of the drug are used.¹⁷ In fact, as observed in the current analysis, a relatively lower benefit of DAT compared to TAT was also observed among elderly patients, whereas the benefit of DAT in terms of reduction of bleeding appeared larger among young patients.¹⁸ Yet, renal function alone does not appear to fully justify our findings. Hohnloser et al. showed that DAT reduced bleeding compared to TAT irrespective of baseline renal function.¹⁹ In addition, in the current study, when in a sensitivity analysis bleeding risk was gauged by levels of haemoglobin alone, a similar pattern arose as when analysed by bleeding risk groups. Hence, HBR status might broadly represent a marker of frailty, and in the context of AF-PCI, the exaggerated bleeding risk conveyed by baseline clinical features added to the multiple antithrombotic therapies might plateau the risk of bleeding and mask the benefit of aspirin withdrawal. Nevertheless, among HBR patients with AF-PCI, the association of dabigatran 110mg DAT was safer than warfarin TAT and appear the best choice to limit the risk of bleeding, while maintaining adequate stroke protection.⁶ Plus, the availability of a reversing agent might be convenient in case of overt major bleeding would occur in this high risk population.²⁰

Limitations:

This is a post hoc analysis of the RE-DUAL PCI trial and as such, results should be

considered hypothesis generating. Nevertheless, this is the first study exploring the role of baseline bleeding risk according to the PRECISE-DAPT score and its implications towards treatment decision-making within AF patients undergoing coronary interventions. Further validation of this tool in other cohorts of patients with AF-PCI is warranted. RE-DUAL PCI trial was neither powered to explore the effect of treatment with respect to ischemic endpoints in the overall population nor to explore any safety or efficacy endpoint in subgroups. Hence, the interaction p values presented can only be regarded as exploratory. In particular, the group of patients at HBR assigned to DAT with dabigatran 150mg was very small, hence more data are needed to inform the nuances of treatment with various dosages of oral anticoagulation in the PCI population. Nonetheless, sensitivity analysis and prior subanalysis from the same population support the findings of the current study. Recent studies reported an excess of stent thrombosis with DAT compared to TAT,²¹ especially during the first 30 days after PCI.²² In RE-DUAL PCI rates of stent thrombosis were very low, and while the occurrence of these events was similar in the subgroups explored, the study was not powered to evaluate treatment impact with respect to this rare event. Further studies in larger populations are needed to explore factors associated with an increased risk of stent thrombosis favouring a prolonged use of aspirin. The use of potent P2Y12 inhibitors such as ticagrelor in combination with oral anticoagulation was reported elsewhere.²³ Since this treatment was not randomized and administered in a relatively small group of patients, the potential to draw conclusions regarding its impact among bleeding risk categories is limited.

Conclusions:

The PRECISE-DAPT score appeared useful for risk stratification in patients with AF receiving anticoagulation in addition to antiplatelet therapy post PCI, helping to identify patients with an additional higher risk for bleeding complications. In this setting, DAT with dabigatran 110mg, compared to warfarin TAT, reduced bleeding among non-HBR and HBR

patients, with a higher magnitude of the benefit among non-HBR patients. DAT with dabigatran 150mg, compared to warfarin TAT, reduced bleeding among non-HBR patients, with a trend towards less benefit among HBR patients. In line with guideline recommendations, bleeding risk evaluation may be useful to inform the intensity of the antithrombotic treatment (DAT and dabigatran dose) and select the combination with the best benefit-risk ratio in an individual patient.

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Data availability statement: To ensure independent interpretation of clinical study results, Boehringer Ingelheim grants all external authors access to all relevant material, including participant-level clinical study data, and relevant material as needed by them to fulfill their role and obligations as authors under the ICMJE criteria. Furthermore, clinical study documents (e.g. study report, study protocol, statistical analysis plan) and participant clinical study data are available to be shared after publication of the primary manuscript in a peer-reviewed journal and if regulatory activities are complete and other criteria met per the BI Policy on Transparency and Publication of Clinical Study Data: <https://trials.boehringer-ingelheim.com/>. Prior to providing access, documents will be examined, and, if necessary, redacted and the data will be de-identified, to protect the personal data of study participants and personnel, and to respect the boundaries of the informed consent of the study participants. Clinical Study Reports and Related Clinical Documents can also be requested via the link <https://trials.boehringer-ingelheim.com/>. All requests will be governed by a Document Sharing Agreement. Bona fide, qualified scientific and medical researchers may request access to de-identified, analysable participant clinical study data with corresponding documentation describing the structure and content of the datasets. Upon approval, and

governed by a Data Sharing Agreement, data are shared in a secured data-access system for a limited period of 1 year, which may be extended upon request. Researchers should use the <https://trials.boehringer-ingelheim.com/> link to request access to study data.

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Figure Legends:

Central Figure: Impact of triple antithrombotic therapy with warfarin or dual antithrombotic therapy with dabigatran according to the baseline bleeding risk.

Results for the primary endpoint. Hazard ratios (HRs) and 95% CIs from Cox proportional hazard model; stratified by age (elderly vs nonelderly) for dabigatran 110 mg dual therapy vs warfarin triple therapy; unstratified for dabigatran 150 mg dual therapy vs warfarin triple therapy.

* For the comparison with 150mg dabigatran DAT, elderly patients outside US are excluded.

DAT: Dual Antithrombotic Therapy; MBE: Major Bleeding Events; PD: PRECISE-DAPT Score; TAT: Triple Antithrombotic Therapy.

Figure 1: Interaction plot for the PRECISE-DAPT score and the risk of primary endpoint for the allocated treatment. Interaction for varying values of the PRECISE-DAPT score as a continuous variable are presented. Comparison between dual antithrombotic therapy with dabigatran 110mg and triple antithrombotic therapy with warfarin (A) and dual antithrombotic therapy with dabigatran 150mg and triple antithrombotic therapy with warfarin (B). For the comparison with 150mg dabigatran DAT, elderly patients outside US are excluded.

Figure 2: Efficacy of antithrombotic treatment according to the baseline bleeding risk.

Results for the main secondary endpoint. . Statistical models as in Central Figure. DAT: Dual Antithrombotic Therapy; DTE: death or thromboembolic events; PD: PRECISE-DAPT Score; TAT: Triple Antithrombotic Therapy.

* For the comparison with 150mg dabigatran DAT, elderly patients outside US are excluded.

Figure 3: Clinical events according to the PRECISE-DAPT score and the allocated treatment with triple antithrombotic therapy with warfarin or dual antithrombotic therapy with dabigatran.

High bleeding risk defined as a PRECISE-DAPT score ≥ 25 (a).

Non-high bleeding risk as a PRECISE-DAPT score <25 (b). NACE is defined as a composite

of Death, stroke, MI, SE, major bleeding. CRNMB: Clinically Relevant Non-Major Bleeding.

Statistical models as in Central Figure. * For the comparison with 150mg dabigatran DAT,

elderly patients outside US are excluded; DAT: Dual Antithrombotic Therapy; DTE: Death or

Thromboembolic Events; ICH: Intracranial Haemorrhage; ISTH: International Society of

Thrombosis and Haemostasis; MI: Myocardial Infarction; TAT: Triple Antithrombotic

Therapy.

NACE: Net Adverse Clinical Events.

Table 1: Baseline characteristics according to the bleeding risk status

	Non-High Bleeding Risk (PRECISE-DAPT <25) (N=1,451)	High Bleeding Risk (PRECISE-DAPT ≥25) (N=885)
Age (years)	67.1 ± 7.6	76.8 ± 6.5
Women (vs. Man)	259 (17.8%)	299 (33.8%)
Hypertension	750 (51.7%)	475 (53.7%)
Hyperlipidaemia	944 (65.1%)	580 (65.5%)
Current Smoking ^a	226 (15.6%)	60 (6.8%)
Diabetes	537 (37.0%)	311 (35.1%)
PAD ^b	88 (6.1%)	69 (7.8%)
AF Type		
Paroxysmal	753 (51.9%)	420 (47.5%)
Persistent	256 (17.6%)	153 (17.3%)
Permanent	441 (30.4%)	312 (35.3%)
CHA2DS2-VASc score	3.2 ± 1.4	4.3 ± 1.5
Modified HAS-BLED	2.5 ± 0.7	3.0 ± 0.6
Left Ventricular Disfunction ^c	496 (34.2%)	326 (36.8%)
LVEF ^d	51.5 ± 12.3	50.7 ± 12.9
ACEF ^d	1.40 ± 0.49	1.66 ± 0.61
History		
Prior MI	373 (25.7%)	226 (25.5%)
Prior STE ^e	37 (2.5%)	21/874 (2.4%)
Prior PCI	474 (32.7%)	308 (34.8%)

Prior CABG	136 (9.4%)	102 (11.5%)
Prior TIA/Stroke	144 (9.9%)	128 (14.5%)
Prior major bleeding or predisposition to bleeding	0 (0.0%)	31 (3.5%)
OAC treatment at baseline ^f	497 (34.3%)	313 (35.4%)
Weight (Kg)	88.5 ± 17.2	76.4 ± 14.7
BMI (Kg/m ²) ^g	29.8 ± 5.2	27.3 ± 4.6
Creatinine clearance (ml/min)	90.8 ± 27.4	57.2 ± 18.2
Abnormal Troponin at Baseline ^h	1073 (73.9%)	716 (80.9%)
Clinical presentation		
Stable CAD	665 (45.8%)	368 (41.6%)
ACS ⁱ	678 (46.7%)	468 (52.9%)
Unstable angina	247 (17.0%)	139 (15.7%)
NSTEMI	257 (17.7%)	224 (25.3%)
STEMI	162 (11.2%)	96 (10.8%)
Type of P2Y12 inhibitor		
Clpidogrel	1248 (86.0%)	784 (88.6%)
Ticagrelor	188 (13.0%)	98 (11.1%)
Type of intervention		
BMS only ^j	218 (15.0%)	125 (14.1%)
DES only ^j	1194 (82.3%)	743 (84.0%)
>1 vessel disease ^k	639 (44.0%)	433 (48.9%)

>1 vessel stented ^l	254 (17.5%)	172 (19.4%)
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^aMissing in 1 patient. ^bUnknown for 157 patients. ^cMissing for 2 patients. ^dMissing for 165 patients.

^eMissing in 33 patients. ^f14 days of consecutive OAC treatment used to classify into treatment naïve or experienced OAC patients. ^gMissing in 3 patients. ^hMissing in 154 patients; based on the assay's overall 99th percentile, baseline troponin values are considered abnormal, if ≥ 0.04 ng/mL ($\mu\text{g/L}$). ⁱType of ACS missing in 21 patients. ^j34 patients with BMS+DES, 18 patients with other stent type, stent type missing in 4 patients. ^kMissing in 50 patients. ^lMissing in 43 patients. ACEF: Age, creatinine, and ejection fraction; ACS: Acute Coronary Syndrome; AF: Atrial Fibrillation; BMI: Body mass index; BMS: Bare Metal Stent; CABG: Coronary Artery Bypass Graft; CAD: Coronary Artery Disease; DES: Drug Eluting Stent; LVEF: Left Ventricle Ejection Fraction; MI: Myocardial Infarction; NSTEMI: Non ST segment Elevated Myocardial Infarction; OAC: Oral Anticoagulant; PAD: Peripheral Arterial Disease; PCI: Percutaneous Coronary Intervention; ST: Stent Thrombosis; STEMI: ST segment Elevated Myocardial Infarction; TIA: Transient Ischemic Attack;

Table 2: Discrimination and Calibration of the PRECISE-DAPT score and the modified HAS-BLED score for bleeding events.

	Discrimination C-Statistics (95% CI)	Calibration p Value*
ISTH Major or CRNMB		
PRECISE-DAPT	0.57 (0.54-0.60)	0.93
HAS-BLED	0.55 (0.53-0.57)	0.02
ISTH Major		
PRECISE-DAPT	0.62 (0.58-0.67)	0.50
HAS-BLED	0.56 (0.53-0.59)	0.02
TIMI Major		
PRECISE-DAPT	0.54 (0.47-0.61)	0.73
HAS-BLED	0.56 (0.51-0.62)	0.17
TIMI Major or minor		
PRECISE-DAPT	0.61 (0.56-0.67)	0.71
HAS-BLED	0.55 (0.51-0.59)	0.07
BARC class ≥ 3		
PRECISE-DAPT	0.62 (0.57-0.67)	0.72
HAS-BLED	0.55 (0.51-0.59)	0.03
ICH		
PRECISE-DAPT	0.58 (0.40-0.76)	0.71
HAS-BLED	0.55 (0.42-0.69)	0.75
Any Bleed		
PRECISE-DAPT	0.55 (0.53-0.58)	0.61

HAS-BLED	0.53 (0.51-0.55)	0.38
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BARC: Bleeding Academic Research Consortium;
 CRNMB: Clinically Relevant Non-Major Bleeding;
 ICH: Intracranial Haemorrhage;
 ISTH: International Society of Thrombosis and Haemostasis;
 TIMI: Thrombosis in Myocardial Infarction

* Hosmer-Lemeshow Goodness of Fit Test

Table 3: Clinical events according to the bleeding risk at baseline

	Non-HBR (N=1,451)	HBR (N=885)	Hazard Ratio (95%CI)^a	p Value^a
ISTH MBE or CRNMBE	18.6%	25.6%	1.38 (1.13-1.69)	<0.01
ISTH MBE	4.9%	8.7%	1.71 (1.19-2.45)	<0.01
Any Bleed	33.1%	39.8%	1.18 (1.01-1.38)	0.04
DTE or unplanned revasc	12.4%	16.2%	1.29 (1.01-1.66)	0.04
DTE	7.7%	12.2%	1.62 (1.20-2.17)	<0.01
Definite Stent Thrombosis	1.2%	1.2%	1.09 (0.48-2.49)	0.84
Death, MI or stroke	7.6%	11.9%	1.56 (1.15-2.10)	<0.01
Death	3.9%	6.7%	1.64 (1.09-2.48)	0.02
NACE	11.6%	18.6%	1.64 (1.29-2.08)	<0.01

^afrom Cox proportional hazard model stratified by age, non-elderly vs elderly [<70 or ≥70 in Japan and <80 or ≥80 years old elsewhere].

HBR= High Bleeding Risk (PRECISE-DAPT ≥25)

CRNMB: Clinically Relevant Non-Major Bleeding;

DTE: Death or Thromboembolic Events;

ICH: Intracranial Haemorrhage;

ISTH: International Society of Thrombosis and Haemostasis;

MI: Myocardial Infarction;

NACE: Net Adverse Clinical Events;

References:

1. Angiolillo DJ, Goodman SG, Bhatt DL, Eikelboom JW, Price MJ, Moliterno DJ, Cannon CP, Tanguay JF, Granger CB, Mauri L, Holmes DR, Gibson CM, Faxon DP. Antithrombotic Therapy in Patients With Atrial Fibrillation Treated With Oral Anticoagulation Undergoing Percutaneous Coronary Intervention. *Circulation* 2018;**138**(5):527-536.
2. Valgimigli M, Bueno H, Byrne RA, Collet JP, Costa F, Jeppsson A, Juni P, Kastrati A, Kolh P, Mauri L, Montalescot G, Neumann FJ, Petricevic M, Roffi M, Steg PG, Windecker S, Zamorano JL, Levine GN, Group ESCSD, Guidelines ESCCfP, Societies ESCNC. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: The Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2018;**39**(3):213-260.
3. Capodanno D, Huber K, Mehran R, Lip GYH, Faxon DP, Granger CB, Vranckx P, Lopes RD, Montalescot G, Cannon CP, Ten Berg J, Gersh BJ, Bhatt DL, Angiolillo DJ. Management of Antithrombotic Therapy in Atrial Fibrillation Patients Undergoing PCI: JACC State-of-the-Art Review. *J Am Coll Cardiol* 2019;**74**(1):83-99.
4. van Rein N, Heide-Jorgensen U, Lijfering WM, Dekkers OM, Sorensen HT, Cannegieter SC. Major Bleeding Rates in Atrial Fibrillation Patients on Single, Dual, or Triple Antithrombotic Therapy. *Circulation* 2019;**139**(6):775-786.
5. Lopes RD, Hong H, Harskamp RE, Bhatt DL, Mehran R, Cannon CP, Granger CB, Verheugt FWA, Li J, Ten Berg JM, Sarafoff N, Vranckx P, Goette A, Gibson CM, Alexander JH. Optimal Antithrombotic Regimens for Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention: An Updated Network Meta-analysis. *JAMA Cardiol* 2020. **5**(5):582-589.
6. Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, Prescott E, Storey RF, Deaton C, Cuisset T, Agewall S, Dickstein K, Edvardsen T, Escaned J, Gersh BJ, Svitil P, Gilard M, Hasdai D, Hatala R, Mahfoud F, Masip J, Muneretto C, Valgimigli M, Achenbach S, Bax JJ, Group ESCSD. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J* 2020;**41**(3):407-477.
7. Costa F, van Klaveren D, James S, Heg D, Raber L, Feres F, Pilgrim T, Hong MK, Kim HS, Colombo A, Steg PG, Zanchin T, Palmerini T, Wallentin L, Bhatt DL, Stone GW, Windecker S, Steyerberg EW, Valgimigli M, Investigators P-DS. Derivation and validation of the predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy (PRECISE-DAPT) score: a pooled analysis of individual-patient datasets from clinical trials. *Lancet* 2017;**389**(10073):1025-1034.
8. Cannon CP, Bhatt DL, Oldgren J, Lip GYH, Ellis SG, Kimura T, Maeng M, Merkely B, Zeymer U, Gropper S, Nordaby M, Kleine E, Harper R, Manassie J, Januzzi JL, Ten Berg JM, Steg PG, Hohnloser SH, Committee R-DPS, Investigators. Dual Antithrombotic Therapy with Dabigatran after PCI in Atrial Fibrillation. *N Engl J Med* 2017;**377**(16):1513-1524.
9. Cannon CP, Gropper S, Bhatt DL, Ellis SG, Kimura T, Lip GY, Steg PG, Ten Berg JM, Manassie J, Kreuzer J, Blatchford J, Massaro JM, Brueckmann M, Ferreiros Ripoll E, Oldgren J, Hohnloser SH, Committee R-DPS, Investigators. Design and Rationale of the RE-DUAL PCI Trial: A Prospective, Randomized, Phase 3b Study Comparing the Safety and Efficacy of Dual Antithrombotic Therapy With Dabigatran Etxilate Versus Warfarin Triple Therapy in Patients With Nonvalvular Atrial Fibrillation Who Have Undergone Percutaneous Coronary Intervention With Stenting. *Clin Cardiol* 2016;**39**(10):555-564.
10. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. *Chest* 2010;**138**(5):1093-100.

11. Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, Kaul S, Wiviott SD, Menon V, Nikolsky E, Serebruany V, Valgimigli M, Vranckx P, Taggart D, Sabik JF, Cutlip DE, Krucoff MW, Ohman EM, Steg PG, White H. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. *Circulation* 2011;**123**(23):2736-47.
12. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H, Diener HC, Joyner CD, Wallentin L, Committee R-LS, Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009;**361**(12):1139-51.
13. Nielsen PB, Skjoth F, Sogaard M, Kjaeldgaard JN, Lip GY, Larsen TB. Effectiveness and safety of reduced dose non-vitamin K antagonist oral anticoagulants and warfarin in patients with atrial fibrillation: propensity weighted nationwide cohort study. *BMJ* 2017;**356**:j510.
14. Yao X, Shah ND, Sangaralingham LR, Gersh BJ, Noseworthy PA. Non-Vitamin K Antagonist Oral Anticoagulant Dosing in Patients With Atrial Fibrillation and Renal Dysfunction. *J Am Coll Cardiol* 2017;**69**(23):2779-2790.
15. Stam-Slob MC, Connolly SJ, van der Graaf Y, van der Leeuw J, Dorresteijn JAN, Eikelboom JW, Peters RJG, Alings M, Visseren FLJ. Individual Treatment Effect Estimation of 2 Doses of Dabigatran on Stroke and Major Bleeding in Atrial Fibrillation. *Circulation* 2019;**139**(25):2846-2856.
16. Steg PG, Ducrocq G, Bhatt DL, Hohnloser SH, Nordaby M, Miede C, Lip GYH, Oldgren J, Ten Berg JM, Cannon CP. Dabigatran Dual Therapy Versus Warfarin Triple Therapy Post PCI in Patients With Atrial Fibrillation. *J Am Coll Cardiol* 2020;**75**(2):238-240.
17. Hijazi Z, Hohnloser SH, Oldgren J, Andersson U, Connolly SJ, Eikelboom JW, Ezekowitz MD, Reilly PA, Siegbahn A, Yusuf S, Wallentin L. Efficacy and safety of dabigatran compared with warfarin in relation to baseline renal function in patients with atrial fibrillation: a RE-LY (Randomized Evaluation of Long-term Anticoagulation Therapy) trial analysis. *Circulation* 2014;**129**(9):961-70.
18. Ten Berg JM, Steg PG, Bhatt DL, Hohnloser SH, de Veer A, Nordaby M, Miede C, Kimura T, Lip GYH, Oldgren J, Cannon CP, Committee R-DPS, Investigators. Comparison of the Effect of Age (< 75 Versus ≥ 75) on the Efficacy and Safety of Dual Therapy (Dabigatran+Clopidogrel or Ticagrelor) Versus Triple Therapy (Warfarin+Aspirin+Clopidogrel or Ticagrelor) in Patients With Atrial Fibrillation After Percutaneous Coronary Intervention (from the RE-DUAL PCI Trial). *Am J Cardiol* 2020;**125**(5):735-743.
19. Hohnloser SH, Steg PG, Oldgren J, Nickenig G, Kiss RG, Ongen Z, Navarro Estrada JL, Oude Ophuis T, Lip GYH, Nordaby M, Kleine E, Ten Berg JM, Bhatt DL, Cannon CP, Committee R-DPS, Investigators. Renal Function and Outcomes With Dabigatran Dual Antithrombotic Therapy in Atrial Fibrillation Patients After PCI. *JACC Cardiovasc Interv* 2019;**12**(16):1553-1561.
20. Pollack CV, Jr., Reilly PA, van Ryn J, Eikelboom JW, Glund S, Bernstein RA, Dubiel R, Huisman MV, Hylek EM, Kam CW, Kamphuisen PW, Kreuzer J, Levy JH, Royle G, Sellke FW, Stangier J, Steiner T, Verhamme P, Wang B, Young L, Weitz JI. Idarucizumab for Dabigatran Reversal - Full Cohort Analysis. *N Engl J Med* 2017;**377**(5):431-441.
21. Ando G, Costa F. Double or triple antithrombotic therapy after coronary stenting and atrial fibrillation: A systematic review and meta-analysis of randomized clinical trials. *Int J Cardiol* 2020.
22. Alexander JH, Wojdyla D, Vora AN, Thomas L, Granger CB, Goodman SG, Aronson R, Windecker S, Mehran R, RD. L. Risk/Benefit Tradeoff of Antithrombotic Therapy in Patients With Atrial Fibrillation Early and Late After an Acute Coronary Syndrome or Percutaneous Coronary Intervention: Insights From AUGUSTUS. *Circulation* 2020;**141**(20):1618-1627.
23. Oldgren J, Steg PG, Hohnloser SH, Lip GYH, Kimura T, Nordaby M, Brueckmann M, Kleine E, Ten Berg JM, Bhatt DL, CP C. Dabigatran dual therapy with ticagrelor or clopidogrel after percutaneous coronary intervention in atrial fibrillation patients with or without acute coronary syndrome: a subgroup analysis from the RE-DUAL PCI trial. *Eur Heart J* 2019;**40**(19):1553-1562.

ISTH major bleeding or clinically relevant non-major bleeding

Figure 1
A

B

*p-value for the interaction term between score (continuous) and treatment

Figure 2

Death or thromboembolism or unplanned revascularization

Figure 3