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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

Jonas Oldgren^{1*}, Philippe Gabriel Steg^{2,3}, Stefan H. Hohnloser⁴, Gregory Y.H. Lip^{5,6,7}, Takeshi Kimura⁸, Matias Nordaby⁹, Martina Brueckmann^{9,10}, Eva Kleine⁹, Jurrien M. ten Berg¹¹, Deepak L. Bhatt¹², and Christopher P. Cannon^{12,13}; on behalf of the RE-DUAL PCI Steering Committee and Investigators

¹Uppsala Clinical Research Center and Department of Medical Sciences, Uppsala University, Dag Hammarskjölds väg 38, SE-751 85 Uppsala, Sweden; ²FACT, an F-CRIN Network, Université Paris Diderot, INSERM U_1148 and Hôpital Bichat Assistance Publique, Paris 75018, France; ³Royal Brompton Hospital, Imperial College, Sydney Street, London SW3 6NP, UK; ⁴Department of Medicine, Division of Cardiology, Johann Wolfgang Goethe University, Theodor Stern-Kai 7, DE-60590 Frankfurt/Main, Germany; ⁵Institute of Cardiovascular Sciences, University of Birmingham, Birmingham B15 2TT, UK; ⁶Liverpool Centre for Cardiovascular Science, University of Liverpool, Liverpool Heart & Chest Hospital, Liverpool, L69 3BX, UK; ⁷Department of Clinical Medicine, Aalborg Thrombosis Research Unit, Søndre Skovvej 15, 9000 Aalborg, Denmark; ⁸Department of Cardiovascular Medicine, Kyoto University, 54 Shogoin Kawahara-cho, Sakyo-ku, Kyoto 606-8507, Japan; ⁹Boehringer Ingelheim International GmbH, TA CardioMetabolism, Binger Str. 173, Ingelheim 55216, Germany; ¹⁰Faculty of Medicine, University of Heidelberg, Theodor-Kutzer-Ufer 1-3, D-68167 Mannheim, Germany; ¹¹Department of Cardiology, St. Antonius Ziekenhuis, Koekoekslaan 1, Nieuwegein 3435 CM, The Netherlands; ¹²Brigham and Women's Hospital, Heart and Vascular Center and Harvard Medical School, 75 Francis Street, Boston, MA 02115, USA; and ¹³Baim Institute for Clinical Research, 930-W Commonwealth Avenue, Boston, MA 02215, USA

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Aims

After percutaneous coronary intervention (PCI) in patients with atrial fibrillation, safety and efficacy with dabigatran dual therapy were evaluated in pre-specified subgroups of patients undergoing PCI due to acute coronary syndrome (ACS) or elective PCI, and those receiving ticagrelor or clopidogrel treatment.

Methods and results

In the RE-DUAL PCI trial, 2725 patients were randomized to dabigatran 110 mg or 150 mg with P2Y₁₂ inhibitor, or warfarin with P2Y₁₂ inhibitor and aspirin. Mean follow-up was 14 months, 50.5% had ACS, and 12% received ticagrelor. The risk of the primary endpoint, major or clinically relevant non-major bleeding event, was reduced with both dabigatran dual therapies vs. warfarin triple therapy in patients with ACS [hazard ratio (95% confidence interval), 0.47 (0.35–0.63) for 110 mg and 0.67 (0.50–0.90) for 150 mg]; elective PCI [0.57 (0.43–0.76) for 110 mg and 0.76 (0.56–1.03) for 150 mg]; receiving ticagrelor [0.46 (0.28–0.76) for 110 mg and 0.59 (0.34–1.04) for 150 mg]; or clopidogrel [0.51 (0.41–0.64) for 110 mg and 0.73 (0.58–0.91) for 150 mg], all interaction *P*-values >0.10. Overall, dabigatran dual therapy was comparable to warfarin triple therapy for the composite endpoint of death, myocardial infarction, stroke, systemic embolism, or unplanned revascularization, with minor variations across the subgroups, all interaction *P*-values >0.10.

* Corresponding author. Tel: +46 18 6112765, Email: jonas.oldgren@ucr.uu.se

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Conclusion

The benefits of both dabigatran 110 mg and 150 mg dual therapy compared with warfarin triple therapy in reducing bleeding risks were consistent across subgroups of patients with or without ACS, and patients treated with ticagrelor or clopidogrel.

Keywords

Atrial fibrillation • Acute coronary syndrome • Coronary artery disease • Percutaneous coronary intervention • Oral anticoagulants • P2Y12 inhibitors

Introduction

Recent estimates suggest an atrial fibrillation (AF) prevalence of ~3% in adults above the age of 20 years.^{1,2} Coronary artery disease commonly co-exists with AF and at least 5% of unselected patients undergoing percutaneous coronary interventions (PCIs) have AF, which poses an antithrombotic treatment dilemma.^{3,4} Oral anticoagulation for prevention of stroke is indicated in the majority of patients with AF,^{5,6} whereas dual antiplatelet therapy with a P2Y12 inhibitor plus aspirin is indicated for patients undergoing PCI with stent implantation and/or after an acute coronary syndrome (ACS).⁷

Contemporary guidelines^{5–9} recommend a short period of triple therapy with both oral anticoagulation and dual antiplatelet therapy with aspirin and clopidogrel, although these triple regimens are inevitably associated with higher rates of major bleeding. The use of the newer P2Y12 inhibitors prasugrel or ticagrelor as part of triple therapy is discouraged,^{6,7,9,10} given the lack of evidence of the safety of those drugs in combination with oral anticoagulation therapy.

Results of observational studies, randomized trials, and meta-analyses suggest that dual antithrombotic treatment, i.e. an oral anticoagulant—either a non-vitamin K antagonist oral anticoagulant (NOAC) or a vitamin K antagonist (VKA)—in combination with one antiplatelet agent, most commonly a P2Y12 inhibitor, reduces bleeding events without increased risk of thromboembolic events compared with triple treatment.^{11–15} More recently, the RE-DUAL PCI (Randomized Evaluation of DUAL Antithrombotic Therapy With Dabigatran vs. Triple Therapy With Warfarin In Patients With Nonvalvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention) trial showed that the risk of major or clinically relevant non-major bleeding events was reduced by 48% with dabigatran 110 mg dual therapy without aspirin, and by 28% with dabigatran 150 mg dual therapy without aspirin, respectively, with non-inferiority for overall thromboembolic events with dabigatran (both doses combined) dual therapy compared with warfarin triple therapy with both aspirin and a P2Y12 inhibitor.^{16,17} In the present analysis, we evaluated the safety and efficacy of dabigatran dual vs. warfarin triple therapy in the pre-specified patient subgroups with PCI due to ACS or undergoing elective PCI, and those treated with ticagrelor or clopidogrel.

Methods

The RE-DUAL PCI trial was a prospective, randomized, open-label study comparing the safety and efficacy of dabigatran dual antithrombotic therapy vs. warfarin triple therapy. The detailed design and primary results of RE-DUAL PCI have been published (RE-DUAL PCI ClinicalTrials.gov number, NCT02164864).^{16,17} Men and women who were at least 18 years of age were eligible for inclusion if they had non-valvular AF and

had been successfully treated with PCI with a bare-metal or drug-eluting stent within the prior 120 h. Non-valvular AF could be paroxysmal, persistent, or permanent, but not secondary to a reversible disorder unless long-term treatment with an oral anticoagulant was anticipated. Patients could be either treatment-naïve or receiving an oral anticoagulant prior to PCI. The indication for PCI could be either an ACS or stable coronary artery disease. Exclusion criteria included patients with bioprosthetic or mechanical heart valves, severe renal insufficiency (creatinine clearance <30 mL/min), or other major comorbidities.

Patients were randomized to dabigatran 110 mg twice daily plus either clopidogrel or ticagrelor (dabigatran 110 mg dual therapy); dabigatran 150 mg twice daily plus either clopidogrel or ticagrelor (dabigatran 150 mg dual therapy); or warfarin plus either clopidogrel or ticagrelor, and aspirin at a daily dose of 100 mg or less (warfarin triple-therapy) in a 1:1:1 ratio. In the warfarin arm, aspirin was discontinued after 1 month in patients implanted with a bare-metal stent, and after 3 months in patients implanted with a drug-eluting stent. Outside the USA, patients aged ≥80 years (≥70 years in Japan) were only randomized to the 110-mg dabigatran dose vs. warfarin in a 1:1 ratio. All patients received either clopidogrel 75 mg daily or ticagrelor 90 mg twice daily for at least 12 months following randomization, with the choice of agent at the discretion of the investigator, but the protocol specified that this decision was to be taken prior to randomization. Prasugrel was not allowed in the study. The dose of warfarin was adjusted to ensure the patient's international normalized ratio was in the range of 2.0–3.0.

The present subgroup analyses of patients with or without ACS at index PCI and patients treated with ticagrelor or clopidogrel were pre-specified. The RE-DUAL PCI trial primary endpoint was time to first International Society on Thrombosis and Haemostasis (ISTH) major¹⁸ or clinically relevant non-major¹⁹ bleeding event. Further safety endpoints included major bleeding events according to ISTH¹⁸ and Thrombolysis in Myocardial Infarction (TIMI)²⁰ definitions; and efficacy outcomes including the composite of death or thromboembolic events (myocardial infarction, stroke, or systemic embolism), or unplanned revascularization (PCI/coronary artery bypass graft), myocardial infarction and all-cause death. All clinical endpoints were adjudicated by an independent committee blinded to treatment assignment.

Statistics

Patients were grouped according to the index PCI indication, i.e. patients either undergoing PCI due to ACS, or undergoing elective PCI due to stable angina and/or positive stress test, staged procedure, or other, and according to the P2Y12 inhibitor use at baseline. The latter subgroup analysis was performed by grouping the patients uniquely into patients who received ticagrelor at baseline (further referred 'ticagrelor'), which included 58 patients who took both ticagrelor and clopidogrel on the day of randomization (i.e. at baseline), and patients who did not receive ticagrelor at baseline (further referred 'clopidogrel'), which included 93 patients who received neither ticagrelor nor clopidogrel at baseline.

The clinical characteristics were summarized descriptively by ACS or elective PCI at index event as well as by treatment with ticagrelor or

clopidogrel at baseline, with *P*-values using the *t*-test for continuous variables and the χ^2 test for categorical variables. For the comparison of treatment groups within the index PCI indication and P2Y12 inhibitor subgroups, stratified Cox proportional hazards regression models including age group as a stratifying factor [non-elderly or elderly (<70 years or ≥ 70 years old in Japan and <80 years or ≥ 80 years old elsewhere)] and treatment (dabigatran 110 dual therapy vs. warfarin triple therapy) as explanatory factor were applied. For the dabigatran 150 dual therapy vs. warfarin triple therapy comparison, unstratified models were applied. A corresponding triple-therapy warfarin group that included only patients eligible for dabigatran 150 dual therapy (i.e. not elderly patients outside the USA) was used for this comparison. Hazard ratios (HRs) and two-sided 95% Wald confidence intervals (CIs) for HRs resulting from Cox proportional hazard models were calculated within the index PCI indication and P2Y12 inhibitor subgroups. Exploratory treatment by subgroup interaction *P*-values resulting from Cox proportional hazard regression models stratified by age for dabigatran 110 dual therapy vs. warfarin triple therapy and unstratified for dabigatran 150 dual therapy vs. warfarin triple therapy, respectively, were provided. Additionally, the risk of the primary endpoint (ISTH major or clinically relevant non-major bleeding events) and of the composite efficacy endpoint of death, thromboembolic events, or unplanned revascularization, respectively, was compared between ticagrelor- and clopidogrel-treated patients as well as between patients with ACS and elective PCI with a multivariable adjusted treatment-independent and stratified (non-elderly or elderly) Cox proportional hazard regression model. For the bleeding endpoint, the Cox model was adjusted for bleeding risk factors, i.e. age, creatinine clearance, previous stroke, prior major bleeding events or bleeding predisposition, diabetes, and ACS or ticagrelor use, respectively. For the composite efficacy endpoint, adjustment was performed for risk factors of death and thromboembolic events, i.e. age, creatinine clearance, prior myocardial infarction, previous stroke, diabetes, multi-vessel disease, and ACS or ticagrelor use, respectively. HRs and two-sided 95% CIs from this Cox model were provided.

Results

Baseline characteristics

Baseline characteristics of the 2725 patients enrolled in RE-DUAL PCI are presented by ACS or elective PCI at index event in Table 1, and by treatment with ticagrelor or clopidogrel are presented in Table 2.

The index indication for PCI was ACS in 1375 (50.5%) patients; within the treatment groups, the index indication for PCI was ACS for 509 (51.9%) of the 981 patients randomized to dabigatran 110 mg dual therapy, 391 (51.2%) of the 763 patients randomized to dabigatran 150 mg dual therapy, 475 (48.4%) of the 981 patients randomized to warfarin triple therapy, and 369 (48.3%) of the 764 patients randomized to warfarin triple therapy excluding elderly patients outside the USA. Patients in the ACS and elective PCI subgroups were of similar age but a lower proportion of ACS patients were males (73.5% vs. 78.5%). The most common type of ACS was non-ST-elevation myocardial infarction (42.3%), followed by unstable angina (33.6%) and ST-elevation myocardial infarction (22.2%). The proportions of oral anticoagulant treatment-naïve patients at baseline, defined as having <14 days of consecutive oral anticoagulant treatment, were 74.3% in the ACS subgroup and 57.4% in the elective PCI group. Clinical and procedural complexity factors²¹ and prior myocardial infarction were more common in the ACS group, Table 1. Drug-eluting stents were predominantly used in all

patients but slightly more commonly in the elective PCI group than the ACS group.

Ticagrelor was chosen (by the investigators) as the P2Y12 inhibitor in 327 (12.0%) patients; within each treatment group, ticagrelor was chosen in 132 (13.5%) of the 981 patients randomized to dabigatran 110 mg dual therapy, in 104 (13.6%) of those 763 patients randomized to dabigatran 150 mg dual therapy, in 91 (9.3%) of those 981 patients randomized to warfarin triple therapy, and in 73 (9.6%) of those 764 patients randomized to warfarin triple therapy excluding elderly patients outside the USA. Mean age was 69.7 years and 70.9 years in the ticagrelor- and clopidogrel-treated patients. Type of AF was paroxysmal in 56.6% and 48.6%, and permanent in 26.9% and 33.4%, of patients treated with ticagrelor or clopidogrel, respectively. The proportions of patients with prior stroke were 6.1% in the ticagrelor group and 8.6% in the clopidogrel group, and 76.1% and 64.5% were oral anticoagulant treatment-naïve, respectively. In the ticagrelor group, 73.4% of the patients had an ACS at index event, and 47.3% had ACS at index in the clopidogrel group. Mean CHA₂DS₂-VASc and modified HAS-BLED scores were slightly higher in patients treated with clopidogrel, but clinical complexity factors, and the combination of clinical and procedural factors, were more common in those treated with ticagrelor, Table 2.

Bleeding events

The overall incidence (independent of study treatment, i.e. dabigatran or warfarin) of the first ISTH major or clinically relevant non-major bleeding event was 20.9% in patients with PCI due to ACS, and 20.9% in those who had undergone elective PCI; multivariable adjusted treatment independent HR 0.97 with a two-sided 95% CI of 0.81–1.15. The risk of experiencing ISTH major or clinically relevant non-major bleeding was reduced with dabigatran dual therapy vs. warfarin triple therapy in patients with ACS and undergoing elective PCI, Figure 1. Compared with warfarin triple therapy, the risks of experiencing ISTH major bleeding events alone and TIMI major bleeding events were also consistently reduced with both dabigatran 110 mg dual therapy and dabigatran 150 mg dual therapy for patients with ACS and undergoing elective PCI. All interaction *P*-values were non-significant; thus no interaction between study treatment and index PCI indication could be detected.

In the group of patients treated with ticagrelor, the study treatment-independent incidence of the first ISTH major or clinically relevant non-major bleeding event was 26.3%, and in those treated with clopidogrel 20.1%; multivariable adjusted HR 1.35, 95% CI 1.05–1.72. Across the subgroups of patients with ticagrelor or clopidogrel, the risks of experiencing the primary outcome of ISTH major or clinically relevant non-major bleeding, as well as ISTH major bleeding events alone, and TIMI major bleeding events, were consistently reduced with dabigatran 110 mg dual therapy and dabigatran 150 mg dual therapy vs. warfarin triple therapy, Figure 2 and Supplementary material online, Figure S1. All interaction *P*-values were non-significant.

Death, thromboembolic events, or unplanned revascularization

The study treatment-independent incidence of death, thromboembolic events, or unplanned revascularization was 14.8% in patients with ACS and 12.4% in patients undergoing elective PCI; multivariable adjusted HR 1.13, 95% CI 0.91–1.41. The study treatment

Table 1 Baseline characteristics by indication for percutaneous coronary intervention

	ACS (N = 1375)	Elective PCI ^a (N = 1349)	P-value
Age (years), mean (SD)	70.9 (9.1)	70.6 (8.1)	0.3406
Male, n (%)	1010 (73.5)	1059 (78.5)	0.0021
Type of atrial fibrillation, n (%)			0.1047
Paroxysmal	708 (51.5)	643 (47.7)	
Persistent	229 (16.7)	255 (18.9)	
Permanent	437 (31.8)	451 (33.4)	
Type of ACS, n (%) ^b			NA
Unstable angina	462 (33.6)	NA	
STEMI	305 (22.2)	NA	
NSTEMI	582 (42.3)	NA	
Diabetes, n (%)	492 (35.8)	501 (37.1)	0.4620
Prior stroke, n (%)	106 (7.7)	120 (8.9)	0.2617
Prior myocardial infarction, n (%)	390 (28.4)	309 (22.9)	0.0011
Creatinine clearance (mL/min), mean (SD) ^c	77.2 (29.9)	78.8 (29.6)	0.1832
CHA ₂ DS ₂ -VASc, mean (SD)	3.6 (1.6)	3.6 (1.5)	0.3887
Modified HAS-BLED, mean (SD)	2.7 (0.7)	2.7 (0.7)	0.1105
OAC treatment at baseline, n (%)			<0.0001
Long-term	354 (25.7)	574 (42.6)	
Treatment naïve ^d	1021 (74.3)	775 (57.4)	
Complexity factors, n (%) ^e			<0.0001
No clinical/procedural factors	0	1007 (74.6)	
Clinical complexity factors only	1114 (81.0)	60 (4.4)	
Procedural complexity factors only	0	270 (20.0)	
Both clinical and procedural factors	261 (19.0)	12 (0.9)	
Type of stent, ^f n (%)			0.0006
DES only	1099 (79.9)	1152 (85.4)	
BMS only	239 (17.4)	165 (12.2)	
DES and BMS, or other	33 (2.4)	29 (2.1)	

Information on indication for PCI was missing for one patient. Statistics: using the t-test for continuous variables and the χ^2 test for categorical variables. ACS, acute coronary syndrome; BMS, bare-metal stent; DES, drug-eluting stent; NA, not applicable; NSTEMI, non-ST-elevation myocardial infarction; OAC, oral anticoagulant; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction.

^aElective PCI includes stable angina and/or positive stress test, staged procedure, or other indication.

^bData missing for 26 patients.

^cMean creatinine clearance missing at baseline for 138 patients in ACS and 93 patients in elective PCI group.

^dLess than 14 days' consecutive OAC treatment.

^eClinical complexity factors considered are acute coronary syndrome, acute ST-elevation myocardial infarction, renal insufficiency/failure, and left ventricular ejection fraction <30%. Procedural (including lesion) complexity factors are >2 vessels stented, in-stent restenosis of a drug-eluting stent, prior brachytherapy, unprotected left main stenting, >2 lesions per vessel, lesion length ≥30 mm, bifurcation lesion with side branch ≥2.5 mm, vein bypass graft, and thrombus-containing lesion (from Yeh et al.²¹).

^fType of stent missing for four patients in ACS and three patients in elective PCI group.

independent incidence of death, thromboembolic events, or unplanned revascularization was 18.7% in those treated with ticagrelor and 12.9% in those treated with clopidogrel; multivariable adjusted HR 1.34, 95% CI 1.00–1.82.

Minor variations were observed for the composite endpoint of death, thromboembolic events, or unplanned revascularization, for dabigatran 110 mg or 150 mg dual therapy vs. warfarin triple across subgroups of ACS and elective PCI, *Figure 3*, and those treated with ticagrelor or clopidogrel, *Figure 4* and *Supplementary material online, Figure S2*, but all interaction *P*-values were non-significant. Numerical differences in the composite of death or thromboembolic events, and for the individual thromboembolic endpoints stroke and all-cause mortality, respectively, were also observed for dabigatran 110 mg or 150 mg dual therapy vs. warfarin triple therapy across subgroups of

ACS and elective PCI, *Figure 3*, but all interaction *P*-values were non-significant. In the ACS subgroup, numerically higher rates of myocardial infarction and stent thrombosis were observed with dabigatran 110 mg dual therapy vs. warfarin triple therapy, interaction *P*=0.20 and 0.07, respectively. Numerical differences in the composite of death or thromboembolic events and the individual thromboembolic endpoints were also observed for those patients treated with ticagrelor or clopidogrel, *Figure 4*, but all interaction *P*-values were non-significant.

Discussion

The benefits of both dabigatran 110 mg and 150 mg dual therapy, with substantial reduction in major and clinically relevant non-major

Table 2 Baseline characteristics by treatment with ticagrelor or clopidogrel

	Ticagrelor ^a (N = 327)	Clopidogrel ^b (N = 2398)	P-value
Age (years), mean (SD)	69.7 (9.6)	70.9 (8.5)	0.0323
Male, n (%)	253 (77.4)	1817 (75.8)	0.5257
Type of atrial fibrillation, n (%)			0.0197
Paroxysmal	185 (56.6)	1166 (48.6)	
Persistent	53 (16.2)	431 (18.0)	
Permanent	88 (26.9)	800 (33.4)	
Indication for PCI, n (%)			<0.0001
Elective PCI ^c	87 (26.6)	1262 (52.6)	
ACS	240 (73.4)	1135 (47.3)	<0.0001
Type of ACS, n (%) ^d			
Unstable angina	54 (22.5)	408 (35.9)	
NSTEMI	105 (43.8)	477 (42.0)	
STEMI	79 (32.9)	226 (19.9)	
Diabetes, n (%)	123 (37.6)	870 (36.3)	0.6419
Prior stroke, n (%)	20 (6.1)	206 (8.6)	0.1275
Prior myocardial infarction, n (%)	91 (27.8)	608 (25.4)	0.3365
Creatinine clearance (mL/min), mean (SD)	80.5 (32.2)	77.7 (29.4)	0.1507
CHA ₂ DS ₂ -VASc, mean (SD)	3.4 (1.6)	3.6 (1.5)	0.0282
Modified HAS-BLED, mean (SD)	2.6 (0.7)	2.7 (0.7)	0.0057
OAC treatment at baseline, n (%)			<0.0001
Long-term	78 (23.9)	851 (35.5)	
Treatment naïve ^e	249 (76.1)	1547 (64.5)	
Complexity factors, n (%) ^f			<0.0001
No clinical/procedural factors	67 (20.5)	941 (39.2)	
Clinical factors only	193 (59.0)	981 (40.9)	
Procedural factors only	16 (4.9)	254 (10.6)	
Both clinical and procedural factors	51 (15.6)	222 (9.3)	
Type of stent, n (%) ^g			0.1556
DES only	275 (84.1)	1976 (82.4)	
BMS only	40 (12.2)	364 (15.2)	
DES and BMS, or other	11 (3.4)	51 (2.1)	

Statistics: using the t-test for continuous variables and the χ^2 test for categorical variables.

ACS, acute coronary syndrome; BMS, bare-metal stent; DES, drug-eluting stent; NSTEMI, non-ST-elevation myocardial infarction; OAC, oral anticoagulant; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction.

^aFifty-eight patients who received ticagrelor + clopidogrel are included in the ticagrelor subgroup.

^bNinety-three patients who received neither clopidogrel nor ticagrelor are included in the clopidogrel subgroup; data on atrial fibrillation, diabetes, prior stroke, and indication for PCI were missing for one patient in the clopidogrel group.

^cElective PCI includes stable angina and/or positive stress test, staged procedure, or other indication.

^dData missing for two patients in the ticagrelor and for 24 patients in the clopidogrel group.

^eLess than 14 days' consecutive OAC treatment.

^fClinical complexity factors considered are acute coronary syndrome, acute ST-elevation myocardial infarction, renal insufficiency/failure, and left ventricular ejection fraction <30%. Procedural (including lesion) complexity factors are >2 vessels stented, in-stent restenosis of a drug-eluting stent, prior brachytherapy, unprotected left main stenting, >2 lesions per vessel, lesion length ≥ 30 mm, bifurcation lesion with side branch ≥ 2.5 mm, vein bypass graft, and thrombus-containing lesion (from Yeh *et al.* ²¹).

^gType of stent was missing for one patient in the ticagrelor and seven patients in the clopidogrel group.

bleeding events, and ISTH and TIMI major bleeding events, compared with warfarin triple therapy were consistent across the pre-specified subgroups of patients with ACS or elective PCI and in those treated with the P2Y₁₂ inhibitors ticagrelor or clopidogrel.

At least 5% of unselected patients undergoing PCI have AF,⁴ and ~15% of AF patients have a history of myocardial infarction.^{22,23} In patients hospitalized for an ACS, an AF incidence up to 21% has been reported, and this combination is associated with worse outcome including higher risk for stroke, myocardial infarction, and death.^{24,25}

Therefore, patients with AF undergoing PCI with stent implantation are most often at sufficient increased risk for thromboembolic complications warranting long-term oral anticoagulation therapy, irrespective of the indication for PCI being ACS or elective PCI. However, the choice of antiplatelet drugs and treatment durations may differ after an ACS or an elective PCI.

In the RE-DUAL PCI trial, the equally sized subgroups of patients with ACS or elective PCI as the index event had similar baseline characteristics, mean CHA₂DS₂-VASc and modified HAS-BLED scores,

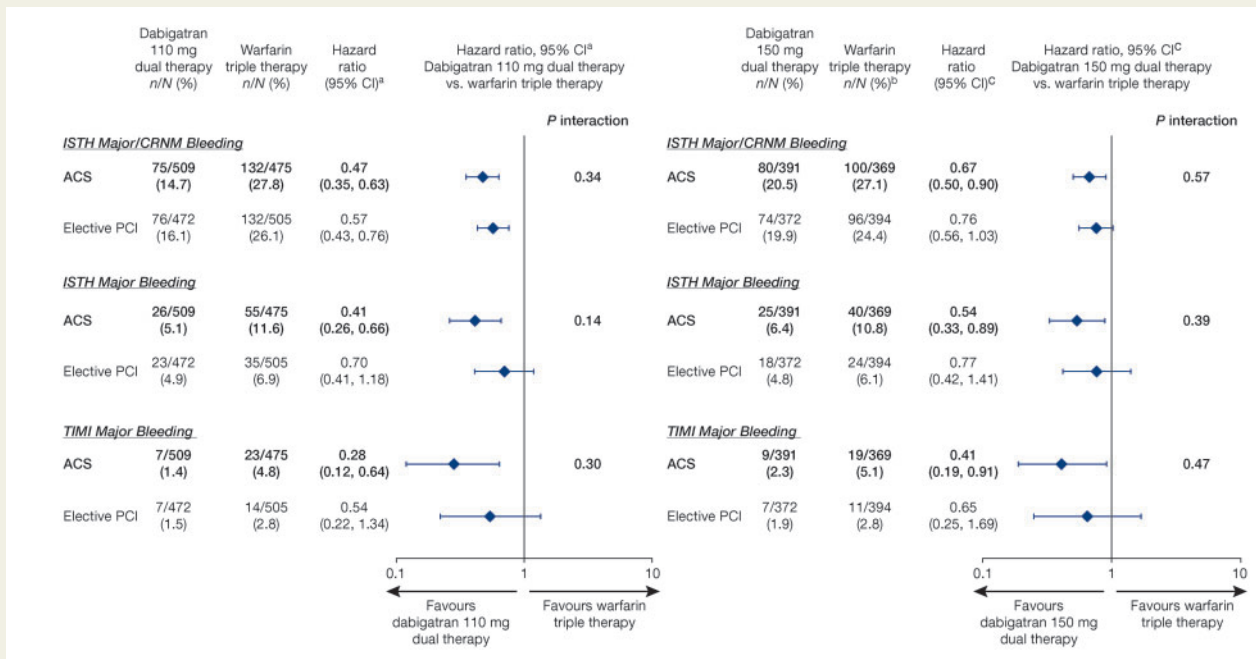


Figure 1 Bleeding events by percutaneous coronary intervention indication at index event. ^aFrom Cox proportional hazard model stratified by age (elderly vs. non-elderly). ^bFor the comparison with dabigatran 150 mg dual therapy, elderly patients outside the USA were excluded. ^cFrom unstratified Cox proportional hazard model. ACS, acute coronary syndrome; CI, confidence interval; CRNM, clinically relevant non-major; ISTH, International Society on Thrombosis and Haemostasis; PCI, percutaneous coronary intervention; TIMI, thrombolysis in myocardial infarction.

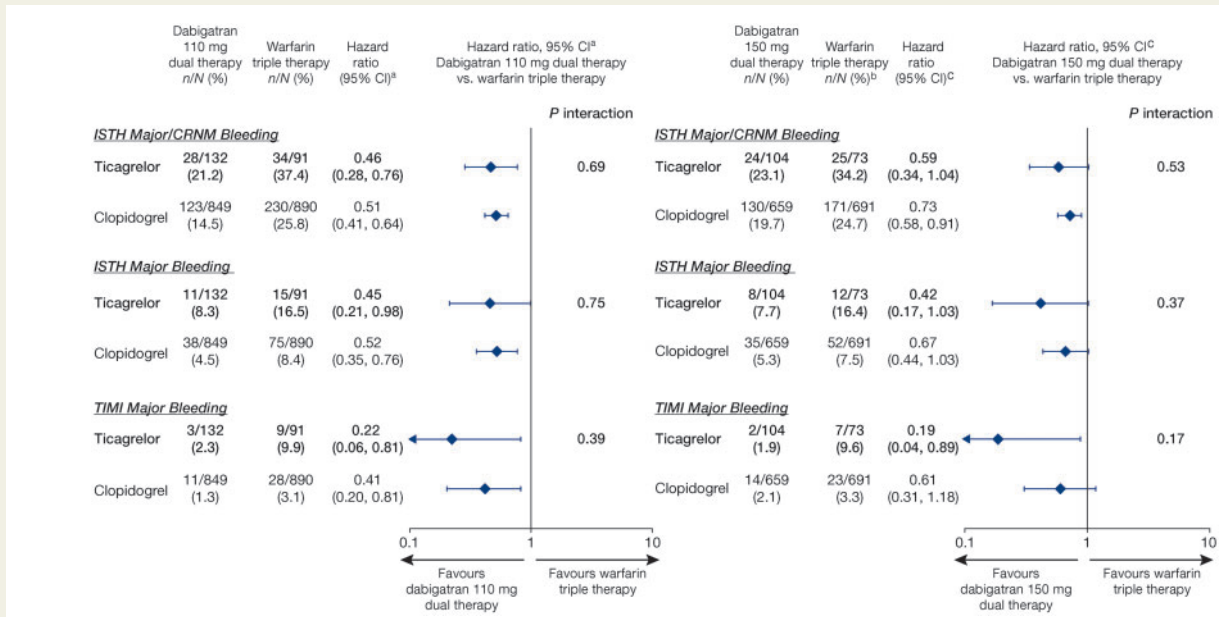


Figure 2 Bleeding events by treatment with ticagrelor or clopidogrel. Fifty-eight patients who received ticagrelor + clopidogrel are included in the ticagrelor subgroup; 93 patients who received neither clopidogrel nor ticagrelor are included in the clopidogrel subgroup. The choice of ticagrelor or clopidogrel was at the discretion of the investigator, these groups are not directly comparable due to allocation bias. ^aFrom Cox proportional hazard model stratified by age (elderly vs. non-elderly). ^bFor the comparison with dabigatran 150 mg dual therapy, elderly patients outside the USA were excluded. ^cFrom unstratified Cox proportional hazard model. ACS, acute coronary syndrome; CI, confidence interval; CRNM, clinically relevant non-major; ISTH, International Society on Thrombosis and Haemostasis; PCI, percutaneous coronary intervention; TIMI, thrombolysis in myocardial infarction.

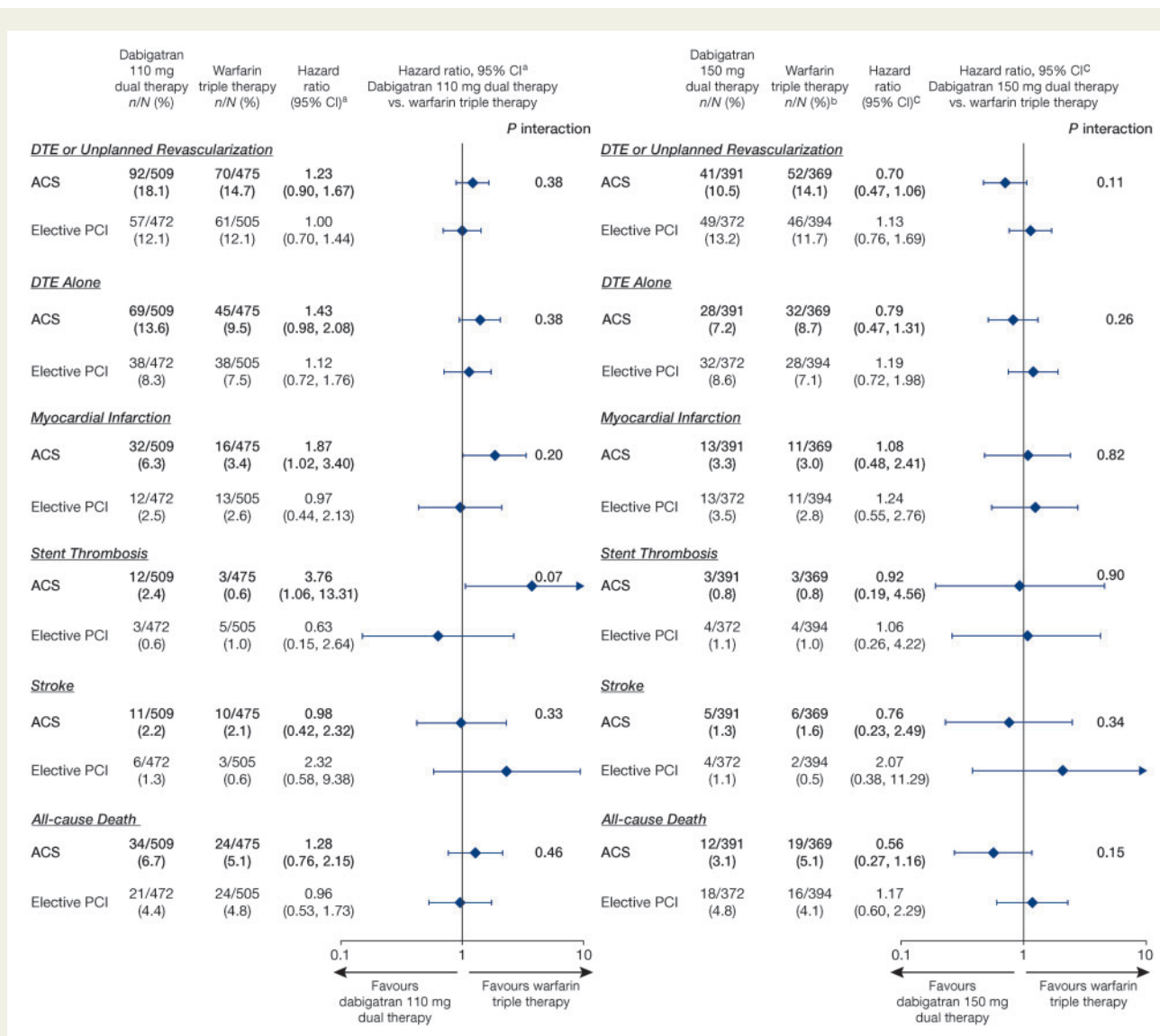


Figure 3 Death, thromboembolic events, and unplanned revascularization by percutaneous coronary intervention indication at index event. ^aFrom Cox proportional hazard model stratified by age (elderly vs. non-elderly). ^bFor the comparison with dabigatran 150 mg dual therapy, elderly patients outside the USA were excluded. ^cFrom unstratified Cox proportional hazard model. ACS, acute coronary syndrome; CI, confidence interval; DTE, death or thromboembolic event (myocardial infarction, stroke, or systemic embolism); PCI, percutaneous coronary intervention.

and primary safety outcome incidences. Both dabigatran dual therapies were associated with substantially reduced risk of bleeding events compared with warfarin triple therapy without signs of interaction between study treatment and the indication for PCI (ACS or elective). The risk of the composite of death, thromboembolic events, or unplanned revascularization with dabigatran dual therapies seemed comparable to warfarin triple therapy in the ACS and elective PCI subgroups. While there was substantially less bleeding with dabigatran 110 mg dual therapy compared with warfarin triple therapy, numerically higher risks of myocardial infarction and stent thrombosis were observed in the ACS population, although the number of events was small and interaction *P*-values were non-significant. These differences should be interpreted with caution as the main RE-DUAL PCI study was not adequately powered for individual thromboembolic events,

and the results in the present analysis are based on even smaller numbers of patients and events within each subgroup. Importantly, both dabigatran doses in the dual therapy groups have previously been evaluated for stroke prevention compared with warfarin. In the pivotal RE-LY study,²⁶ dabigatran 150 mg was superior to warfarin with a 35% risk reduction in stroke, whereas dabigatran 110 mg was non-inferior to warfarin for stroke prevention. Thus, irrespective of ACS or elective PCI at the index event, dabigatran 150 mg dual therapy is an attractive option after PCI in patients with AF,⁹ whereas dabigatran 110 mg dual therapy should be considered in very elderly patients and those at increased bleeding risk.

In the PIONEER-AF PCI trial,¹³ both dual therapy with rivaroxaban 15 mg once daily and triple therapy with rivaroxaban 2.5 mg twice daily also reduced clinically relevant bleeding events compared with

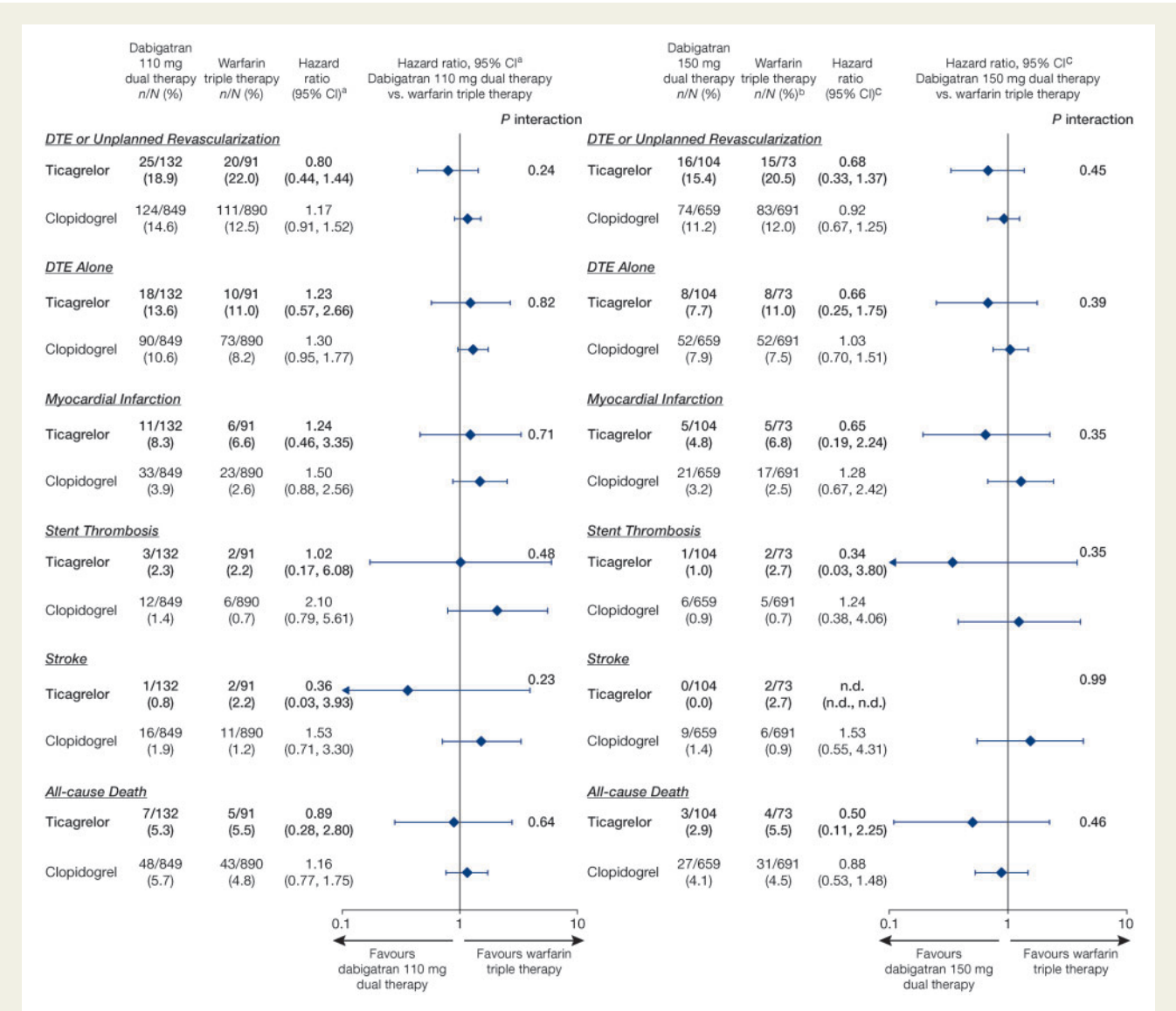


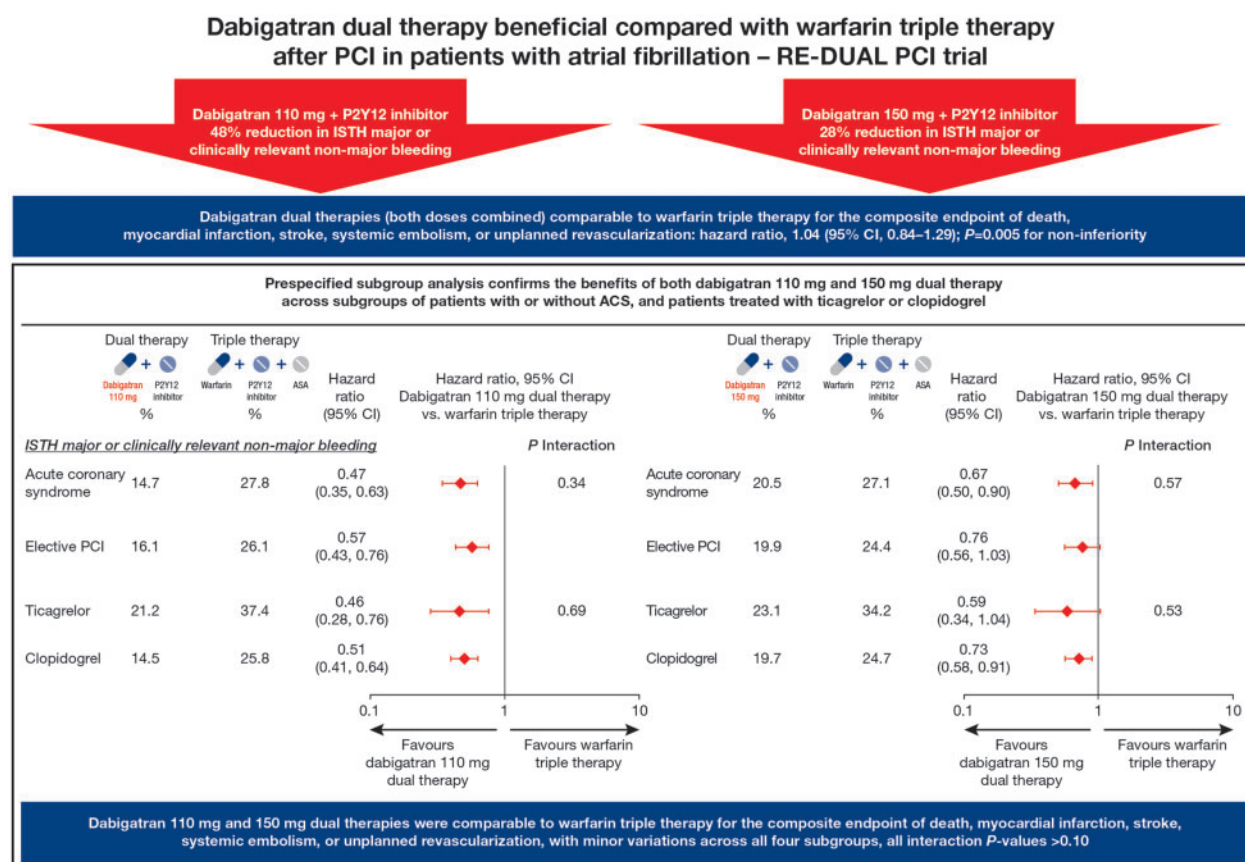
Figure 4 Death, thromboembolic events, and unplanned revascularization by treatment with ticagrelor or clopidogrel. The choice of ticagrelor or clopidogrel was at the discretion of the investigator, these groups are not directly comparable due to allocation bias. ^aFrom Cox proportional hazard model stratified by age (elderly vs. non-elderly). ^bFor the comparison with dabigatran 150 mg dual therapy, elderly patients outside the USA were excluded. ^cFrom unstratified Cox proportional hazard model. CI, confidence interval; DTE, death or thromboembolic event (myocardial infarction, stroke, or systemic embolism); HR, hazard ratio; n.d., not done (one treatment group had zero events and HR is not given).

VKA triple therapy in patients with AF after PCI. Similar to the present trial, the groups of patient with or without ACS at index PCI intervention were of equal size in PIONEER-AF PCI, and the authors reported consistent results in the ACS subgroup.

In the RE-DUAL PCI trial, the choice of the P2Y12 inhibitors clopidogrel or ticagrelor was at the discretion of the investigator. The vast majority of the study patients were treated with clopidogrel, but 12% of the patients received ticagrelor as part of their antithrombotic regimen. In the PIONEER-AF PCI trial,¹³ the choice of P2Y12 inhibitor was likewise at the investigators' discretion, but only 4.3% of the patients received ticagrelor and 1.3% received prasugrel (the latter not allowed in RE-DUAL PCI). In the present study, the majority of

patients treated with ticagrelor (73%) had an ACS at index event, in line with contemporary guidelines recommending ticagrelor in preference to clopidogrel on top of aspirin after an ACS episode.⁷ Not surprisingly, patients treated with ticagrelor had a higher bleeding risk than the patients who the physician treated with clopidogrel. A higher risk of bleeding in patients with ACS treated with ticagrelor (but not on oral anticoagulants) compared with clopidogrel has also been reported in the PLATO trial.²⁷

Patients treated with ticagrelor at investigator's discretion were also associated with higher risk of the composite of death, thromboembolic events, or unplanned revascularization, of borderline statistical significance, than patients receiving clopidogrel in the present



Take home figure The benefits of both dabigatran 110 mg and 150 mg dual therapy compared with warfarin triple therapy in reducing bleeding risks were consistent across subgroups of patients with or without ACS, and patients treated with ticagrelor or clopidogrel. ACS, acute coronary syndrome; ASA, aspirin; CI, confidence interval; ISTH, International Society on Thrombosis and Haemostasis; PCI, percutaneous coronary intervention.

study. In contrast, ticagrelor was significantly associated with 16% lower risk for the primary composite outcome of cardiovascular death, myocardial infarction, or stroke, compared to clopidogrel in the aforementioned randomized PLATO trial.²⁷ Despite multivariable statistical adjustments, our findings may merely reflect that patients receiving ticagrelor, at the choice of the investigator, were at higher risk for thromboembolic and bleeding events, e.g. because of clinical and procedural complexity factors.

Despite the higher bleeding risk observed in patients treated with ticagrelor, the benefits of both dabigatran 110 mg and 150 mg dual therapy compared with warfarin triple therapy were consistent across the ticagrelor and clopidogrel subgroups. In patients with AF where more intensive platelet inhibition is warranted, e.g. after an ACS with high risk for new coronary events, or in patients who are non-responders to clopidogrel and thereby at high risk for thromboembolic events,²⁸ dabigatran dual therapy with ticagrelor might be an attractive alternative after PCI as recently suggested in a North American consensus document.¹⁰ Notably the trend for higher risk for myocardial infarction and stent thrombosis in patients treated with dabigatran 110 mg dual therapy compared with warfarin triple therapy seemed attenuated in those patients receiving ticagrelor,

with the caveat that this finding is based on a small subgroup of patients.

Approximately 10% of patients in the warfarin triple therapy group received ticagrelor in combination with aspirin and warfarin in the present study. Albeit based on modest numbers, the high bleeding rates in these patients support current guideline recommendations to avoid newer P2Y12 inhibitors as part of oral anticoagulant triple therapy.^{6,7,9,10} In addition, in previous small observational studies,^{29–31} VKA or NOAC triple therapy with ticagrelor or prasugrel have been associated with up to three times higher risk of bleeding events compared to triple therapy with clopidogrel.

This report has limitations. Subgroup analyses, albeit pre-specified, should always be interpreted cautiously as these individual subgroups were not powered for formal statistical testing of each individual subgroup, and therefore the CIs were inevitably wider than in the main study due to the smaller numbers of patients and events, especially in the relatively small subgroup of patients receiving ticagrelor. Also, interaction P -values should be regarded as exploratory. The magnitude of increased bleeding risk with ticagrelor compared to clopidogrel was somewhat higher in the present study than in the randomized post-ACS trial comparing

ticagrelor vs. clopidogrel on top of aspirin but not oral anticoagulant treatment.²⁷ This might imply an incremental bleeding risk with ticagrelor in combination with oral anticoagulants, also indicated by small observational studies.^{29–31} However, this interpretation is limited by the non-randomized comparisons of P2Y12 inhibitors in the present study, as well as in the observational studies, and the small subgroup of patients receiving ticagrelor. Lastly, the assignment of patients to the P2Y12 inhibitor was not randomized but chosen at the discretion of the investigator, so that residual confounding or classification bias cannot be excluded.

Conclusions

In patients with AF who had undergone PCI, the benefits of both dabigatran 110 mg and 150 mg dual therapy compared with warfarin triple therapy in reducing bleeding risks were consistent across subgroups of patients with or without ACS at index event, and those treated with ticagrelor or clopidogrel.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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