ESC European Society of Cardiology

European Heart Journal (2019) **40**, 1553–1562
doi:10.1093/eurheartj/ehz059

CLINICAL RESEARCH
Thrombosis and antithrombotic therapy

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. Hohnloser[4], Gregory Y.H. Lip[5,6,7], Takeshi Kimura[8], Matias Nordaby[9], Martina Brueckmann[9,10], Eva Kleine[9], Jurrien M. ten Berg[11], Deepak L. Bhatt[12], and Christopher P. Cannon[12,13]; on behalf of the RE-DUAL PCI Steering Committee and Investigators

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

Received 11 May 2018; revised 8 August 2018; editorial decision 22 January 2019; accepted 23 January 2019; online publish-ahead-of-print 21 February 2019

See page 1563 for the editorial comment on this article (doi: 10.1093/eurheartj/ehz192)

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

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 dual therapy); dabigatran 150 mg twice daily plus either clopidogrel or ticagrelor (dabigatran 150 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) major[18] or clinically relevant non-major[19] bleeding event. Further safety endpoints included major bleeding events according to ISTH[18] 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 factors[21] 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 CHA_2DS_2-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_2DS_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.
[a]Elective PCI includes stable angina and/or positive stress test, staged procedure, or other indication.
[b]Data missing for 26 patients.
[c]Mean creatinine clearance missing at baseline for 138 patients in ACS and 93 patients in elective PCI group.
[d]Less than 14 days' consecutive OAC treatment.
[e]Clinical 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]).
[f]Type 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_2DS_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.
[a]Fifty-eight patients who received ticagrelor + clopidogrel are included in the ticagrelor subgroup.
[b]Ninety-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.
[c]Elective PCI includes stable angina and/or positive stress test, staged procedure, or other indication.
[d]Data missing for two patients in the ticagrelor and for 24 patients in the clopidogrel group.
[e]Less than 14 days' consecutive OAC treatment.
[f]Clinical 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]).
[g]Type 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 CHA_2DS_2-VASc and modified HAS-BLED scores,

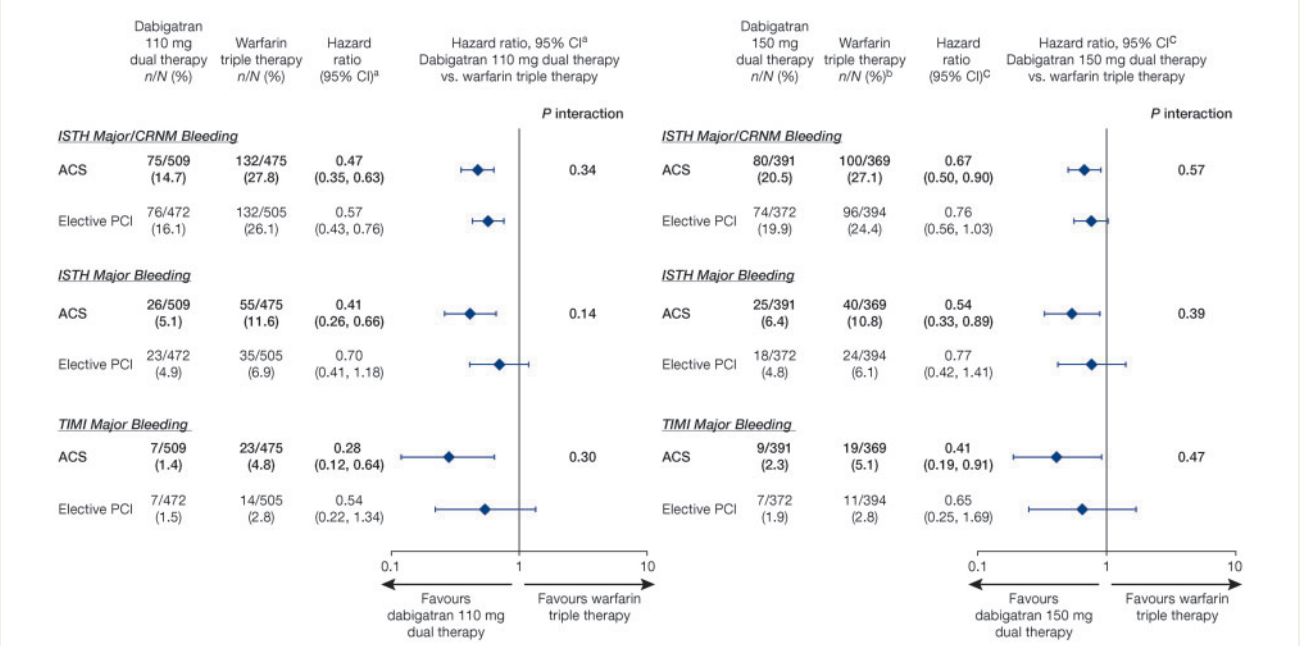


Figure 1 Bleeding events by percutaneous coronary intervention indication at index event. [a]From Cox proportional hazard model stratified by age (elderly vs. non-elderly). [b]For the comparison with dabigatran 150 mg dual therapy, elderly patients outside the USA were excluded. [c]From unstratified 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.

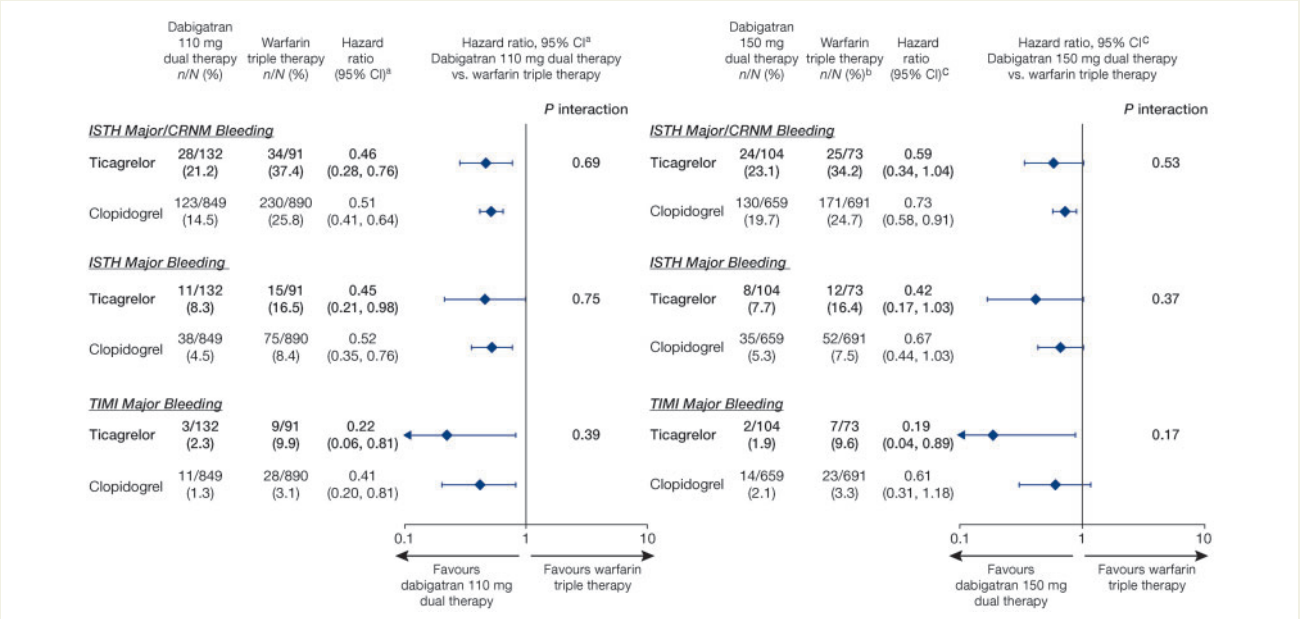


Figure 2 Bleeding events by treatment with ticagrelor or clopidogrel. Fifty-eight patients who received ticagrelor + clopidogrel are included in the ticagrelor subgroup; 93 patients who received neither clopidogrel nor ticagrelor are included in the clopidogrel subgroup. The choice of ticagrelor or clopidogrel was at the discretion of the investigator, these groups are not directly comparable due to allocation bias. [a]From Cox proportional hazard model stratified by age (elderly vs. non-elderly). [b]For the comparison with dabigatran 150 mg dual therapy, elderly patients outside the USA were excluded. [c]From 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.

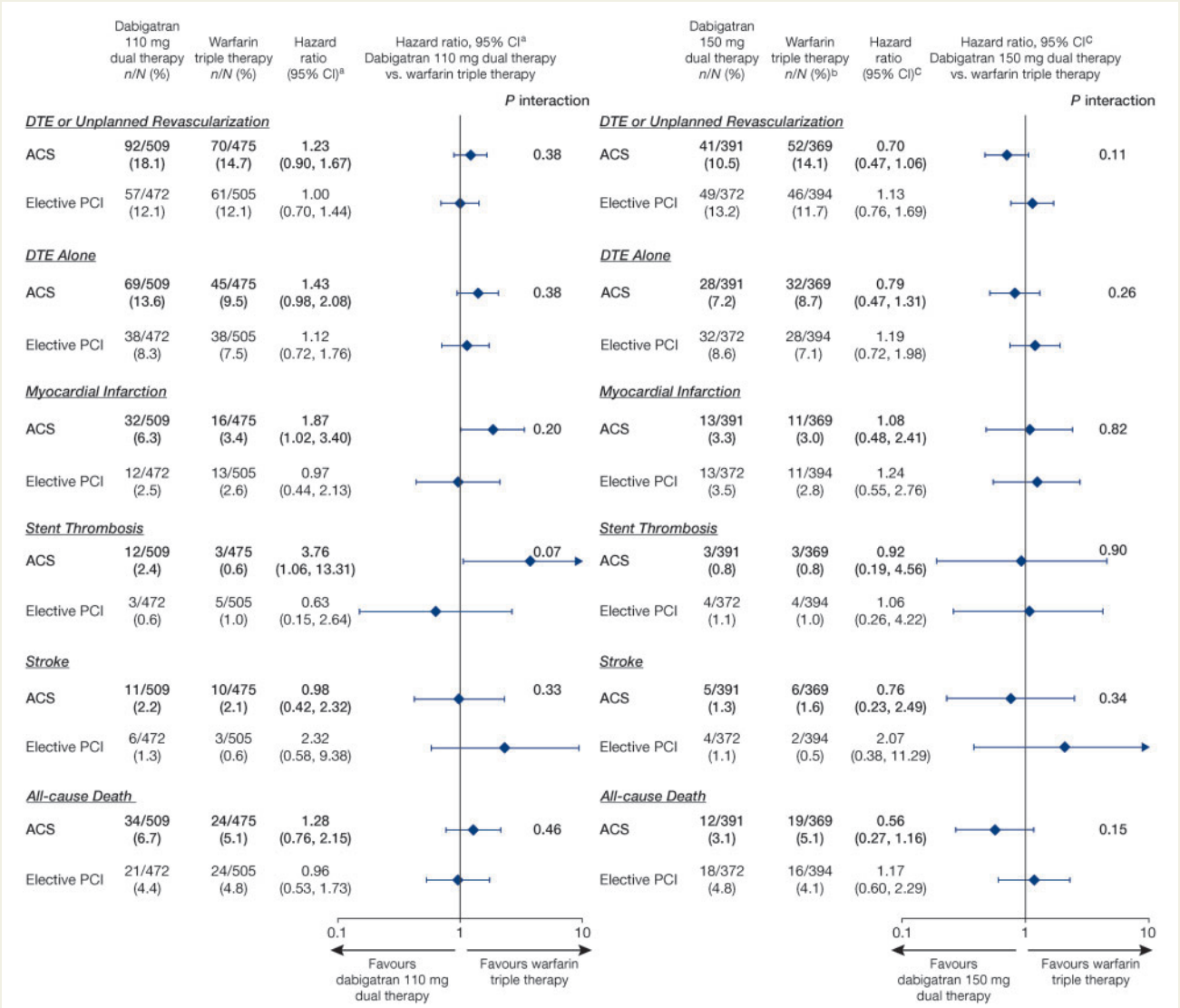


Figure 3 Death, thromboembolic events, and unplanned revascularization by percutaneous coronary intervention indication at index event. [a]From Cox proportional hazard model stratified by age (elderly vs. non-elderly). [b]For the comparison with dabigatran 150 mg dual therapy, elderly patients outside the USA were excluded. [c]From 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

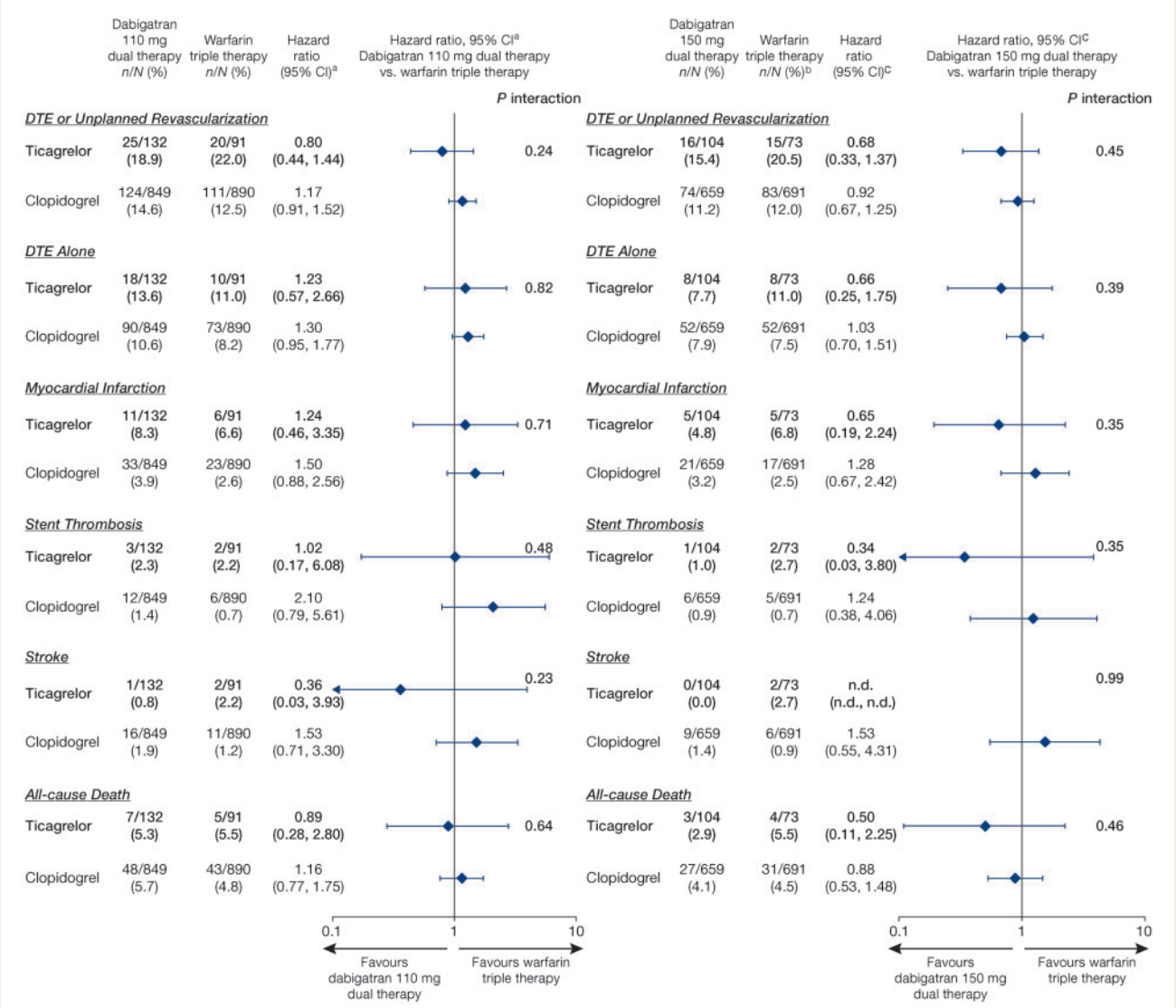
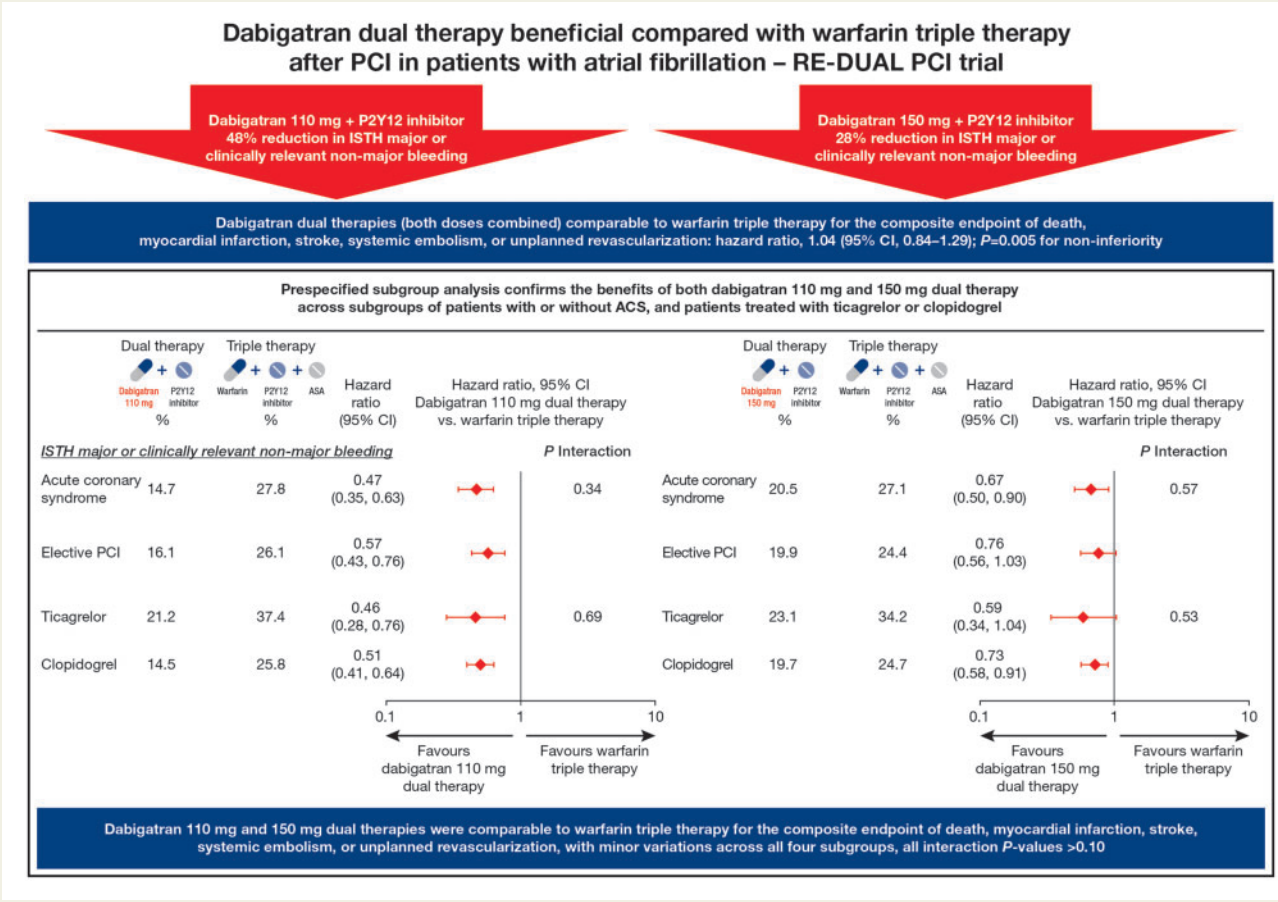


Figure 4 Death, thromboembolic events, and unplanned revascularization by treatment with ticagrelor or clopidogrel. The choice of ticagrelor or clopidogrel was at the discretion of the investigator, these groups are not directly comparable due to allocation bias. [a]From Cox proportional hazard model stratified by age (elderly vs. non-elderly). [b]For the comparison with dabigatran 150 mg dual therapy, elderly patients outside the USA were excluded. [c]From 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 prespecified, 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.

Acknowledgements

Editorial assistance consisting of formatting and collation of author comments was provided by Sarah Petit, PhD from PAREXEL, with funding from Boehringer Ingelheim. Assistance with statistical analyses was provided by Corinna Miede, an employee of HMS Analytical Software GmbH, with funding from Boehringer Ingelheim. Assistance with programming was provided by Clemens Tilke from Boehringer Ingelheim.

Funding

This work was supported by Boehringer Ingelheim International GmbH.

Conflict of interest: J.O. reports fees to his institution from AstraZeneca, Boehringer Ingelheim, Bayer, Bristol-Myers Squibb, Daichii Sankyo, Pfizer, Portola, Roche Diagnostics, and Sanofi. P.G.S. reports research grant from Bayer, Merck, Sanofi, and Servier, speaking or consulting fees from Amarin, Amgen, AstraZeneca, Bayer/Janssen, Boehringer Ingelheim, Bristol-Myers-Squibb, Lilly, Merck, Novartis, Novo-Nordisk, Pfizer, Regeneron, Sanofi, and Servier; S.H.H. reports personal fees from Bayer HealthCare, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Medtronic, Pfizer, SJM, and Zol; G.Y.H.L. has served as a consultant for Bayer/Janssen, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Novartis, Verseon and Daiichi Sankyo, and has been on the speaker's bureau for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, and Daiichi Sankyo; T.K. reports grants from Boehringer Ingelheim GmbH; M.N., M.B., and E.K. are employees of Boehringer Ingelheim; J.M.t.B. reports advisory/consulting/speakers' fees from Accumetrics, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Eli Lily, The Medicines Company, and Pfizer, and research grants from AstraZeneca and ZonMw; D.L.B. discloses the following relationships—Advisory Board: Cardax, Elsevier Practice Update Cardiology, Medscape Cardiology, Regado Biosciences; Board of Directors: Boston VA Research Institute, Society of Cardiovascular Patient Care, and TobeSoft; Chair: American Heart Association Quality Oversight Committee; Data Monitoring Committees: Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute, for the PORTICO trial, funded by St. Jude Medical, now Abbott), Cleveland Clinic, Duke Clinical Research Institute, Mayo Clinic, Mount Sinai School of Medicine (for the ENVISAGE trial, funded by Daiichi Sankyo), Population Health Research Institute; Honoraria: American College of Cardiology (Senior Associate Editor, Clinical Trials and News, ACC.org; Vice-Chair, ACC Accreditation Committee), Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute; RE-DUAL PCI clinical trial steering committee funded by Boehringer Ingelheim), Belvoir Publications (Editor in Chief, Harvard Heart Letter), Duke Clinical Research Institute (clinical trial steering committees), HMP Global (Editor in Chief, Journal of Invasive Cardiology), Journal of the American College of Cardiology (Guest Editor; Associate Editor), Population Health Research Institute (for the COMPASS operations committee, publications committee, steering committee, and USA national co-leader, funded by Bayer), Slack Publications (Chief Medical Editor, Cardiology Today's Intervention), Society of Cardiovascular Patient Care (Secretary/Treasurer), WebMD (CME steering committees); Other: Clinical Cardiology (Deputy Editor), NCDR-ACTION Registry Steering Committee (Chair), VA CART Research and Publications Committee (Chair); Research Funding: Abbott, Amarin, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Chiesi, Eisai, Ethicon, Forest Laboratories, Idorsia, Ironwood, Ischemix, Lilly, Medtronic, PhaseBio, Pfizer, Regeneron, Roche, Sanofi Aventis, Synaptic, and The Medicines Company; Royalties: Elsevier (Editor, Cardiovascular Intervention: A Companion to Braunwald's Heart Disease); Site Co-Investigator: Biotronik, Boston Scientific, St. Jude Medical (now Abbott), Svelte; Trustee: American College of Cardiology; Unfunded Research: FlowCo, Merck, Novo-Nordisk, PLx Pharma, Takeda; C.P.C. reports research grants from Amgen, Boehringer Ingelheim (BI), Bristol-Myers Squibb (BMS), Daiichi Sankyo, Janssen, Merck and consulting fees from Alnylam, Amarin, Amgen, BI, BMS, Eisai, Janssen, Kowa, Merck, Pfizer, Regeneron, Sanofi.

References

1. Bjorck S, Palaszewski B, Friberg L, Bergfeldt L. Atrial fibrillation, stroke risk, and warfarin therapy revisited: a population-based study. *Stroke* 2013;**44**:3103–3108.
2. Haim M, Hoshen M, Reges O, Rabi Y, Balicer R, Leibowitz M. Prospective national study of the prevalence, incidence, management and outcome of a large contemporary cohort of patients with incident non-valvular atrial fibrillation. *J Am Heart Assoc* 2015;**4**:e001486.
3. Goto S, Bhatt DL, Rother J, Alberts M, Hill MD, Ikeda Y, Uchiyama S, D'Agostino R, Ohman EM, Liau CS, Hirsch AT, Mas JL, Wilson PW, Corbalan R, Aichner F, Steg PG; REACH Investigators. Prevalence, clinical profile, and cardiovascular outcomes of atrial fibrillation patients with atherothrombosis. *Am Heart J* 2008; **156**:855–863.e852.
4. Pilgrim T, Kalesan B, Zanchin T, Pulver C, Jung S, Mattle H, Carrel T, Moschovitis A, Stortecky S, Wenaweser P, Stefanini GG, Raber L, Meier B, Juni P, Windecker S. Impact of atrial fibrillation on clinical outcomes among patients with coronary artery disease undergoing revascularisation with drug-eluting stents. *EuroIntervention* 2013;**8**:1061–1071.
5. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC Jr, Conti JB, Ellinor PT, Ezekowitz MD, Field ME, Murray KT, Sacco RL, Stevenson WG, Tchou PJ, Tracy CM, Yancy CW. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation. *Circulation* 2014;**130**:e199–e267.
6. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, Diener H-C, Heidbuchel H, Hendriks J, Hindricks G, Manolis AS, Oldgren J, Popescu BA, Schotten U, Van Putte B, Vardas P, Agewall S, Camm J, Baron Esquivias G, Budts W, Carerj S, Casselman F, Coca A, De Caterina R, Deftereos S, Dobrev D, Ferro JM, Filippatos G, Fitzsimons D, Gorenek B, Guenoun M, Hohnloser SH, Kolh P, Lip GYH, Manolis A, McMurray J, Ponikowski P, Rosenhek R, Ruschitzka F, Savelieva I, Sharma S, Suwalski P, Tamargo JL, Taylor CJ, Van Gelder IC, Voors AA, Windecker S, Zamorano JL, Zeppenfeld K. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J* 2016;**37**:2893–2962.
7. Valgimigli M, Bueno H, Byrne RA, Collet J-P, Costa F, Jeppsson A, Jüni P, Kastrati A, Kolh P, Mauri L, Montalescot G, Neumann F-J, Petricevic M, Roffi M, Steg PG, Windecker S, Zamorano JL, Levine GN; ESC Scientific Document

Group; ESC Committee for Practice Guidelines (CPG); ESC National Cardiac Societies. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS. *Eur Heart J* 2018;**39**: 213–260.
8. Steffel J, Verhamme P, Potpara TS, Albaladejo P, Antz M, Desteghe L, Haeusler KG, Oldgren J, Reinecke H, Roldan-Schilling V, Rowell N, Sinnaeve P, Collins R, Camm AJ, Heidbüchel H, Lip GYH, Weitz J, Fauchier L, Lane D, Boriani G, Goette A, Keegan R, MacFadyen R, Chiang C-E, Joung B, Shimizu W. The 2018 European Heart Rhythm Association practical guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. *Eur Heart J* 2018; **39**:1330–1393.
9. Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, Byrne RA, Collet JP, Falk V, Head SJ, Juni P, Kastrati A, Koller A, Kristensen SD, Niebauer J, Richter DJ, Seferovic PM, Sibbing D, Stefanini GG, Windecker S, Yadav R, Zembala MO; ESC Scientific Document Group. 2018 ESC/EACTS guidelines on myocardial revascularization. *Eur Heart J* 2018; doi: 10.1093/eurheartj/ehy394. [Epub ahead of print].
10. Angiolillo JD, Goodman SG, Bhatt DL, Eikelboom JW, Price Matthew J., Moliterno DJ, Cannon CP, Tanguay J-F, 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: a North American perspective—2018 update. *Circulation* 2018; **38**:527–536.
11. Lamberts M, Gislason GH, Olesen JB, Kristensen SL, Schjerning Olsen AM, Mikkelsen A, Christensen CB, Lip GY, Kober L, Torp-Pedersen C, Hansen ML. Oral anticoagulation and antiplatelets in atrial fibrillation patients after myocardial infarction and coronary intervention. *J Am Coll Cardiol* 2013;**62**: 981–989.
12. Dewilde WJM, Oirbans T, Verheugt FWA, Kelder JC, De Smet BJGL, Herrman J-P, Adriaenssens T, Vrolix M, Heestermans AACM, Vis MM, Tijsen JGP, van't Hof AW, ten Berg JM; WOEST Investigators. Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, controlled trial. *Lancet* 2013; **381**:1107–1115.
13. Gibson CM, Mehran R, Bode C, Halperin J, Verheugt FW, Wildgoose P, Birmingham M, Ianus J, Burton P, van Eickels M, Korjian S, Daaboul Y, Lip GY, Cohen M, Husted S, Peterson ED, Fox KA. Prevention of bleeding in patients with atrial fibrillation undergoing PCI. *N Engl J Med* 2016;**375**: 2423–2434.
14. Agarwal N, Jain A, Mahmoud AN, Bishnoi R, Golwala H, Karimi A, Mojadidi MK, Garg J, Gupta T, Patel NK, Wayangankar S, Anderson RD. Safety and efficacy of dual versus triple antithrombotic therapy in patients undergoing percutaneous coronary intervention. *Am J Med* 2017;**130**:1280–1289.
15. Batra G, Friberg L, Erlinge D, James S, Jernberg T, Svennblad B, Wallentin L, Oldgren J. Antithrombotic therapy after myocardial infarction in patients with atrial fibrillation undergoing percutaneous coronary intervention. *Eur Heart J Cardiovasc Pharmacother* 2018;**4**:36–45.
16. 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; RE-DUAL PCI Investigators. Dual antithrombotic therapy with dabigatran after PCI in atrial fibrillation. *N Engl J Med* 2017;**377**:1513–1524.
17. 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. Design and rationale of the RE-DUAL PCI trial. *Clin Cardiol* 2016;**39**:555–564.
18. Schulman S, Kearon C. Subcommittee on Control of Anticoagulation, The Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb Haemost* 2005;**3**:692–694.
19. Kaatz S, Ahmad D, Spyropoulos AC, Schulman S; Subcommittee on Control of Anticoagulation. Definition of clinically relevant non-major bleeding in studies of anticoagulants in atrial fibrillation and venous thromboembolic disease in non-surgical patients: communication from the SSC of the ISTH. *J Thromb Haemost* 2015;**13**:2119–2126.
20. Bovill EG, Terrin ML, Stump DC, Berke AD, Frederick M, Collen D, Feit F, Gore JM, Hillis LD, Lambrew CT, Leiboff R, Mann KG, Markis JE, Pratt CM, Sharkey SW, Sopko G, Tracy RP, Chesebro JH. Hemorrhagic events during therapy with recombinant tissue-type plasminogen activator, heparin, and aspirin for acute myocardial infarction. Results of the Thrombolysis in Myocardial Infarction (TIMI), Phase II Trial. *Ann Intern Med* 1991;**115**:256–265.
21. Yeh RW, Kereiakes DJ, Steg PG, Cutlip DE, Croce KJ, Massaro JM, Mauri L; DAPT Study Investigators. Lesion complexity and outcomes of extended dual antiplatelet therapy after percutaneous coronary intervention. *J Am Coll Cardiol* 2017;**70**:2213–2223.
22. Oldgren J, Healey JS, Ezekowitz M, Commerford P, Avezum A, Pais P, Zhu J, Jansky P, Sigamani A, Morillo CA, Liu L, Damasceno A, Grinvalds A, Nakamya J, Reilly PA, Keltai K, Van Gelder IC, Yusufali AH, Watanabe E, Wallentin L, Connolly SJ, Yusuf S; RE-LY Atrial Fibrillation Registry Investigators. Variations in cause and management of atrial fibrillation in a prospective registry of 15, 400 emergency department patients in 46 countries: the RE-LY Atrial Fibrillation Registry. *Circulation* 2014;**129**:1568–1576.
23. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, Camm AJ, Weitz JI, Lewis BS, Parkhomenko A, Yamashita T, Antman EM. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet* 2014; **383**:955–962.
24. Schmitt J, Duray G, Gersh BJ, Hohnloser SH. Atrial fibrillation in acute myocardial infarction: a systematic review of the incidence, clinical features and prognostic implications. *Eur Heart J* 2009;**30**:1038–1045.
25. Batra G, Svennblad B, Held C, Jernberg T, Johanson P, Wallentin L, Oldgren J. All types of atrial fibrillation in the setting of myocardial infarction are associated with impaired outcome. *Heart* 2016;**102**:926–933.
26. 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; RE-LY Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009; **361**:1139–1151.
27. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, Horrow J, Husted S, James S, Katus H, Mahaffey KW, Scirica BM, Skene A, Steg PG, Storey RF, Harrington RA, Freij A, Thorsén M; PLATO Investigators. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2009;**361**:1045–1057.
28. Angiolillo DJ, Fernandez-Ortiz A, Bernardo E, Alfonso F, Macaya C, Bass TA, Costa MA. Variability in individual responsiveness to clopidogrel: clinical implications, management, and future perspectives. *J Am Coll Cardiol* 2007;**49**:1505–1516.
29. Sarafoff N, Martischnig A, Wealer J, Mayer K, Mehilli J, Sibbing D, Kastrati A. Triple therapy with aspirin, prasugrel, and vitamin K antagonists in patients with drug-eluting stent implantation and an indication for oral anticoagulation. *J Am Coll Cardiol* 2013;**61**:2060–2066.
30. Sra S, Tan MK, Mehta SR, Fisher HN, Dery JP, Welsh RC, Eisenberg MJ, Overgaard CB, Rose BF, Siega AJ, Cheema AN, Wong BY, Henderson MA, Lutchmedial S, Lavi S, Goodman SG, Yan AT; Canadian Observational AntiPlatelet sTudy I. Ischemic and bleeding events in patients with myocardial infarction undergoing percutaneous coronary intervention who require oral anticoagulation: insights from the Canadian observational AntiPlatelet sTudy. *Am Heart J* 2016;**180**:82–89.
31. Verlinden NJ, Coons JC, Iasella CJ, Kane-Gill SL. Triple antithrombotic therapy with aspirin, P2Y12 inhibitor, and warfarin after percutaneous coronary intervention: an evaluation of prasugrel or ticagrelor versus clopidogrel. *J Cardiovasc Pharmacol Ther* 2017;**22**:546–551.