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

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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.

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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 guidelines6–9 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-naive 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) major18 or clinically relevant non-major19 bleeding event. Further safety endpoints included major bleeding events according to ISTH18 and Thrombolyis 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 χ² 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 an 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. 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 6.6% 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
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 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 1 Baseline characteristics by indication for percutaneous coronary intervention |
|-----------------------------------------------|----------------|-----------------|
| ACS (N = 1375)                              | Elective PCI* (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) | 78.6 (29.6) | 0.1832 |
| CHA2DS2-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 naive<sup>d</sup>                 | 1021 (74.3) | 775 (57.4) |              |
| Complexity factors, n (%)                  | <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 χ² 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.

<sup>a</sup>Elective PCI includes stable angina and/or positive stress test, staged procedure, or other indication.
<sup>b</sup>Data missing for 26 patients.
<sup>c</sup>Mean creatinine clearance missing at baseline for 138 patients in ACS and 93 patients in elective PCI group.
<sup>d</sup>Less than 14 days’ consecutive OAC treatment.
<sup>e</sup>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).
<sup>f</sup>Type of stent missing for four patients in ACS and three patients in elective PCI group.

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.
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, and 15% of AF patients have a history of myocardial infarction. 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.

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.

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**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.
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, dabigatran 150 mg was superior to warfarin with a 35% 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, 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, 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

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**Figure 3** Death, thromboembolic events, and unplanned revascularization by percutaneous coronary intervention indication at index event.

*From Cox proportional hazard model stratified by age (elderly vs. non-elderly). For the comparison with dabigatran 150 mg dual therapy, elderly patients outside the USA were excluded. 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.
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, 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. Not surprisingly, patients treated with ticagrelor had a higher bleeding risk than the patients who the physician treated with clopidogrel.

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).
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. 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 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.

A randomized post-ACS trial comparing dabigatran 110 mg + P2Y12 inhibitor vs. warfarin triple therapy showed 48% reduction in ISTH major or clinically relevant non-major bleeding for dabigatran 110 mg dual therapy compared with warfarin triple therapy. However, the increased bleeding risk with ticagrelor compared to clopidogrel was somewhat higher in the present study than in the randomized post-ACS trial comparing dabigatran 150 mg + P2Y12 inhibitor vs. warfarin triple therapy, with a 28% reduction in ISTH major or clinically relevant non-major bleeding.

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 dabigatran 110 mg + P2Y12 inhibitor vs. warfarin triple therapy.
ticagrelor vs. clopidogrel on top of aspirin but not oral anticoagu- 
lation treatment. This might imply an incremental bleeding risk with 
ticagrelor in combination with oral anticoagulants, also indicated by 
small observational studies. However, this interpretation is lim-
ited 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 assign-
ment of patients to the P2Y12 inhibitor was not randomized but 
chosen at the discretion of the investigator, so that residual con-
founding 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 sub-
groups 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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