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ORIGINAL ARTICLE

Effect of Lesion Complexity and Clinical Risk Factors on the Efficacy and Safety of Dabigatran Dual Therapy Versus Warfarin Triple Therapy in Atrial Fibrillation After Percutaneous Coronary Intervention

A Subgroup Analysis From the REDUAL PCI Trial

Natalia C. Berry, MD; Laura Mauri, MD, MSc; Philippe Gabriel Steg, MD; Deepak L. Bhatt, MD, MPH; Stefan H. Hohnloser, MD; Matias Nordaby, MD; Corinna Miede, MSc; Takeshi Kimura, MD, PhD; Gregory Y.H. Lip, MD; Jonas Oldgren, MD; Jurriën M. ten Berg, MD, PhD; Christopher P. Cannon, MD; on behalf of the REDUAL PCI Steering Committee and Investigators

BACKGROUND: The REDUAL PCI trial (Evaluation of Dual Therapy With Dabigatran vs Triple Therapy With Warfarin in Patients With AF That Undergo a PCI With Stenting) demonstrated that, in patients with atrial fibrillation following percutaneous coronary intervention, bleeding risk was lower with dabigatran plus clopidogrel or ticagrelor (dual therapy) than warfarin plus clopidogrel or ticagrelor and aspirin (triple therapy). Dual therapy was noninferior for risk of thromboembolic events. Whether these results apply equally to patients at higher risk of ischemic events due to lesion complexity or clinical risk factors is unclear.

METHODS: The primary end point was time to first major or clinically relevant nonmajor bleeding event. The composite efficacy end point was death, thromboembolic event, or unplanned revascularization. Our prespecified subgroup analysis categorized patients by presence of procedural complexity and/or clinical complexity factors at baseline. A modified dual antiplatelet therapy score categorized patients according to degree of clinical risk.

RESULTS: Of 2725 patients, 43.1% had clinical complexity factors alone, 9.9% procedural factors alone, 10.0% both, and 37.0% neither. Risk of the primary bleeding end point was lower in both dabigatran dual therapy groups than warfarin triple therapy groups, regardless of procedural and/or clinical lesion complexity (interaction *P* values: 0.90 and 0.37, respectively). Importantly, a similar risk of the efficacy end point was observed between dabigatran dual and warfarin triple therapy, regardless of the presence of clinical or procedural complexity factors (interaction *P* values: 0.67 and 0.54, dabigatran 110 and 150 mg dual therapy, respectively). Similar benefit was seen for each dose of dabigatran dual therapy for bleeding events regardless of dual antiplatelet therapy score (interaction *P* values: 0.53 and 0.54, respectively), with similar risk of thromboembolic events (interaction *P* values: 0.20 and 0.08, respectively).

CONCLUSIONS: In patients with atrial fibrillation undergoing percutaneous coronary intervention, dabigatran 110 and 150 mg dual therapy reduced bleeding risk compared with warfarin triple therapy, with a similar risk of thromboembolic outcomes, irrespective of procedural and/or clinical complexity and modified dual antiplatelet therapy score.

REGISTRATION: URL: https://clinicaltrials.gov/; Unique identifier: NCT02164864.

VISUAL OVERVIEW: A visual overview is available for this article.

Key Words: atrial fibrillation ■ clopidogrel ■ dabigatran ■ percutaneous coronary intervention ■ risk factors ■ warfarin

Correspondence to: Natalia C. Berry, MD, Mid-Atlantic Permanente Medical Group, Tyson's Corner Medical Center, 8008 Westpark Dr, McLean, VA 22102. Email nataliaberry@gmail.com

For Sources of Funding and Disclosures, see page 7.

WHAT IS KNOWN

- The REDUAL PCI trial (Evaluation of Dual Therapy With Dabigatran vs Triple Therapy With Warfarin in Patients With AF That Undergo a PCI With Stenting) showed that dual therapy with dabigatran (110 or 150 mg twice daily) and clopidogrel or ticagrelor reduced the risk of bleeding events compared with triple therapy consisting of warfarin, aspirin, and clopidogrel or ticagrelor in patients with atrial fibrillation who underwent percutaneous coronary intervention, with similar thromboembolic outcomes.

WHAT THE STUDY ADDS

- This subgroup analysis of the REDUAL PCI trial categorized patients into clinical complexity risk factors alone, procedural risk factors alone, both, or neither.
- We observed that dabigatran dual therapy consistently reduced bleeding risk compared with warfarin triple therapy in patients with and without procedural and/or clinical risk factors for adverse events and showed similar thromboembolic outcomes.

Nonstandard Abbreviations and Acronyms

ACS	acute coronary syndrome
AF	atrial fibrillation
DAPT	dual antiplatelet therapy
DTE	death or thromboembolic event
MI	myocardial infarction
PCI	percutaneous coronary intervention

Antiplatelet therapy is indicated following percutaneous coronary intervention (PCI) to prevent stent thrombosis and cardiovascular events,[1] and systemic anticoagulation is required in most patients with atrial fibrillation (AF) for prevention of stroke and systemic embolism.[2,3] Balancing the requirements for antiplatelet and antithrombotic therapy against the risk of major bleeding associated with this combination treatment can be challenging in patients with AF post-PCI.[4–6]

The DAPT (dual antiplatelet therapy) trial demonstrated that prolonged DAPT (clopidogrel or prasugrel plus aspirin) beyond 12 months after coronary stent placement significantly reduced ischemic events but increased bleeding compared with aspirin monotherapy.[7] Subsequent subgroup analysis of the DAPT trial showed that patients with complex lesion anatomy had higher rates of stent thrombosis and myocardial infarction (MI) than those without complex anatomy in the first year independent of treatment arm, and a scoring system assessing clinical risk (the DAPT score) could predict the ischemic benefit of prolonged DAPT.[8] This study did not include subjects treated with concomitant anticoagulation, and it is unknown whether anticoagulation and antiplatelet strategy in subjects with AF undergoing PCI should be adjusted according to the presence of risk factors for ischemic or bleeding events.

The REDUAL PCI trial (Evaluation of Dual Therapy With Dabigatran vs Triple Therapy With Warfarin in Patients With AF That Undergo a PCI With Stenting; NCT02164864) showed that dual therapy with dabigatran (110 or 150 mg twice daily) and clopidogrel or ticagrelor reduced the risk of the primary end point of International Society on Thrombosis and Haemostasis-defined major bleeding events (MBEs) or clinically relevant nonmajor bleeding events versus triple therapy consisting of warfarin, aspirin, and clopidogrel or ticagrelor in patients with AF who underwent PCI.[9,10] Dabigatran dual therapy was noninferior to warfarin triple therapy for the risk of thromboembolic events.[9] This prespecified subgroup analysis assessed the effects of procedural or clinical complexity and clinical risk factors, as well as DAPT score category, on safety and efficacy outcomes in the REDUAL PCI trial.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Design and Patients

REDUAL PCI was a multicenter, prospective, randomized, open-label, blinded-end point, active-comparator study in which 2725 patients with AF who underwent PCI were randomized to 1 of 2 doses of dabigatran dual therapy (110 or 150 mg twice daily) or warfarin triple therapy. Elderly patients (aged ≥80 years outside the United States [≥70 years in Japan]) were randomized to warfarin triple therapy or dabigatran 110 mg dual therapy only.[9,10]

The REDUAL PCI trial included patients aged ≥18 years with nonvalvular AF following successful PCI within the previous 120 hours. The indication for PCI was acute coronary syndrome (ACS) or stable coronary artery disease. Key exclusion criteria included the presence of bioprosthetic or mechanical heart valves, severe renal insufficiency (ie, creatinine clearance <30 mL/minute), or other major coexisting conditions. International Review Board approval was obtained at all sites, and all patients provided written informed consent.

Study Assessments

The primary safety end point of REDUAL PCI was time to first International Society on Thrombosis and Haemostasis-defined MBE or clinically relevant nonmajor bleeding event in a time-to-event analysis over a mean follow-up of 14 months.[9,10] A key secondary end point was a composite of death or thromboembolic event (DTE; MI, stroke, or systemic embolism) or unplanned revascularization (PCI or coronary artery bypass grafting).[9,10]

Complexity Factors

Procedural and clinical complexity factors in the current analysis are based on prespecified risk factors employed in the DAPT trial.[11]

Procedural complexity factors included the following: >2 vessels stented, in-stent restenosis of a drug-eluting stent, prior brachytherapy, unprotected left main stented, >2 lesions per vessel, lesion length ≥30 mm, bifurcation lesion with a side branch ≥2.5 mm, vein bypass graft, and a thrombus-containing lesion. Clinical complexity factors comprised the following: ACS, acute ST-elevation MI, renal insufficiency/failure, and left ventricular ejection fraction <30%.[11]

Complexity factors were analyzed in 4 subgroups in the REDUAL PCI trial: group 1, no procedural or clinical complexity factors; group 2, procedural complexity factors alone; group 3, clinical complexity factors alone; and group 4, both procedural and clinical complexity factors.

Modified DAPT Score Assessments

The DAPT score is a clinical risk score to predict the difference between the anticipated benefit (ie, reduction in ischemic events) versus harm (increased bleeding events) associated with DAPT following PCI.[12] The original DAPT score ranged from −2 to 10, assigning points as follows: 0, age <65 years; −1, 65 to <75 years, and −2, ≥75 years; 2, vein graft PCI; 1, cigarette smoking, current or within past year; 1, diabetes mellitus; 1, MI at presentation; 1, stent diameter <3 mm; 2, history of congestive heart failure or left ventricular ejection fraction <30%; 1, prior PCI or prior MI; and 1, paclitaxel-eluting stent.[12] In the original analysis, higher DAPT score (≥2) predicted a larger reduction in ischemic risk and lesser increase in bleeding with continued therapy beyond 12 months relative to score <2.

A modified DAPT score was employed in the current analysis, with 0 points allocated to paclitaxel-eluting stent and stent diameter <3 mm, as these data were not collected in REDUAL PCI. For cigarette smoking, 1 point was allocated for the currently smoker category but not the ex-smoker category, as information was not available on when patients stopped smoking. Two modified DAPT score subgroups were included in this analysis: score <2 (Group A) and ≥2 (Group B).

Statistical Analysis

Cox proportional hazard regression models, stratified by age—nonelderly versus elderly (age <70 years versus ≥70 years in Japan; <80 years versus ≥80 years elsewhere)—were used to compare dabigatran 110 mg dual therapy versus warfarin triple therapy, and unstratified Cox proportional hazard regression models to compare dabigatran 150 mg dual therapy versus warfarin triple therapy. Exploratory treatment by subgroup interaction *P* values were provided. An additional treatment-independent stratified Cox proportional hazard regression analysis included complexity factor subgroup or modified DAPT score subgroup, respectively, as the only factor in the model.

RESULTS

Study Population

Most of the 2725 patients included in REDUAL PCI had either no procedural or clinical complexity factors (Group 1: 37.0%) or clinical complexity factors alone (Group 3: 43.1%; Table). Patients with procedural complexity factors had numerically higher rates of diabetes mellitus, stroke, and prior coronary artery disease with prior revascularization by PCI or coronary artery bypass graft than patients without complexity factors. CHA_2DS_2-VASc and modified HAS-BLED scores were similar between all groups. DAPT score at baseline was <2 in 67% of patients.

Effect of Complexity Factors on Treatment Outcomes

Bleeding Events

Complexity factor (clinical or procedural) had no effect on bleeding risk in the unadjusted, treatment-independent analysis. Compared with patients without complexity factors, hazard ratios (HRs) for bleeding risk were 0.90 (95% CI, 0.66–1.21) for procedural complexity alone, 1.04 (95% CI, 0.86–1.25) for clinical complexity alone, and 1.03 (95% CI, 0.77–1.37) for both procedural and clinical complexity factors.

Risk of the primary bleeding end point was lower in both dabigatran dual therapy groups than warfarin triple therapy groups in all categories of clinical or procedural complexity (Figure 1). In the dabigatran 110 mg group, HRs were 0.56 (95% CI, 0.40–0.78) for no complexity factors, 0.58 (95% CI, 0.30–1.10) for procedural complexity alone, 0.48 (95% CI, 0.35–0.65) for clinical complexity alone, and 0.47 (95% CI, 0.25–0.88) for both procedural and clinical complexity factors (interaction *P* value: 0.90). Respective HRs in the dabigatran 150 mg group were 0.85 (95% CI, 0.60–1.20), 0.48 (0.22–1.02), 0.63 (0.46–0.86), and 0.92 (0.48–1.77; interaction *P* value: 0.37).

Thromboembolic Events

In the unadjusted treatment-independent analysis, there was a trend to increased risk of DTE or unplanned revascularization with greater complexity factor involvement. HRs for thromboembolic event or unplanned revascularization were 1.13 (95% CI, 0.78–1.64) for procedural complexity alone, 1.29 (95% CI, 1.02–1.63) for clinical complexity alone, and 1.48 (95% CI, 1.05–2.08) for both procedural and clinical complexity factors compared with no complexity factors.

There was no significant interaction between complexity factor subgroup and treatment on comparing dabigatran dual therapy and warfarin triple therapy with respect to thromboembolic events (interaction *P* values: 0.67 and 0.54 for dabigatran 110 and 150 mg, respectively; Figure 2). Efficacy seemed similar in both dabigatran dual therapy groups compared with warfarin triple therapy groups, irrespective of procedural and/or clinical complexity.

Numbers of stent thromboses were low in all groups, precluding interpretation of subgroup differences. Stent thrombosis rates were 1.2% (14/1174) for patients with clinical complexity alone, 0.4% (1/270) for procedural complexity alone, 1.8% (5/273) for both procedural and clinical complexity, and 1.0% (10/1008) for no complexity factors.

Table. Baseline Characteristics According to Complexity Factor and Modified DAPT Score Subgroups

	Complexity Factor Subgroups				Modified DAPT Score Subgroups	
	Group 1	Group 2	Group 3	Group 4	Group A	Group B
Characteristic	No Complexity Factors n=1008 (37.0%)	Procedural Complexity Factors Only n=270 (10.0%)	Clinical Complexity Factors Only n=1174 (43.1%)	Both Procedural and Complexity Factors n=273 (9.9%)	DAPT <2 n=1816 (66.6%)	DAPT ≥2 n=909 (33.4%)
Mean age, y (SD)	70.4 (8.1)	71.8 (8.0)	70.7 (9.2)	71.6 (8.8)	73.0 (7.7)	66.3 (8.8)
Age group						
Elderly	149 (14.8)	56 (20.7)	196 (16.7)	57 (20.9)	380 (20.9)	78 (8.6)
Nonelderly	859 (85.2)	214 (79.3)	978 (83.3)	216 (79.1)	1436 (79.1)	831 (91.4)
Male sex	770 (76.4)	226 (83.7)	860 (73.3)	214 (78.4)	1341 (73.8)	729 (80.2)
Risk scores, mean (SD)						
CHA_2DS_2-VASc*	3.5 (1.5)	3.8 (1.5)	3.6 (1.6)	3.8 (1.6)	3.5 (1.5)	3.8 (1.6)
Modified HAS-BLED†	2.7 (0.7)	2.8 (0.7)	2.7 (0.7)	2.7 (0.7)	2.8 (0.7)	2.5 (0.8)
Diabetes mellitus‡	369 (36.6)	107 (39.6)	407 (34.7)	110 (40.3)	497 (27.4)	496 (54.6)
Renal insufficiency/failure§	0 (0.0)	0 (0.0)	15 (1.3)	2 (0.7)	10 (0.6)	7 (0.8)
Previous stroke‡	90 (8.9)	26 (9.6)	90 (7.7)	20 (7.3)	153 (8.4)	73 (8.0)
Previous PCI‡	357 (35.4)	120 (44.4)	344 (29.3)	91 (33.3)	484 (26.7)	428 (47.1)
Previous stent thrombosis‖	24 (2.4)	9 (3.3)	27 (2.3)	8 (2.9)	33 (1.8)	35 (3.9)
Previous CAD‡	757 (75.1)	215 (79.6)	687 (58.5)	169 (61.9)	1126 (62.0)	702 (77.2)
Previous MI	215 (21.3)	68 (25.2)	321 (27.3)	95 (34.8)	330 (18.2)	369 (40.6)
Previous CABG‡	89 (8.8)	49 (18.1)	106 (9.0)	43 (15.8)	158 (8.7)	129 (14.2)
Previous PE¶	11 (1.1)	6 (2.2)	17 (1.4)	2 (0.7)	19 (1.0)	17 (1.9)
Previous SE‡	5 (0.5)	2 (0.7)	10 (0.9)	4 (1.5)	12 (0.7)	9 (1.0)

Values are n (%) unless otherwise stated. AF indicates atrial fibrillation; CABG, coronary artery bypass graft; CAD, coronary artery disease; DAPT, dual antiplatelet therapy; MI, myocardial infarction; PCI, percutaneous coronary intervention; PE, pulmonary embolism; and SE, systemic embolism.

*CHA_2DS_2-VASc score reflects risk of stroke, with values ranging from 0 to 9 and higher scores indicating greater risk.

†HAS-BLED score reflects risk of major bleeding in patients with AF receiving anticoagulant therapy, with values ranging from 0 to 9 and higher scores indicating greater risk.

‡Data missing from 1 patient in Group 1 and 1 in Group A.

§Defined as baseline creatinine (CRE) value ≥2 mg/dL (using formula CRE/88.42).

‖Data missing from 16, 3, 21, and 4 patients in Groups 1, 2, 3, and 4, respectively; and 28 patients in Group A and 16 patients in Group B.

¶Data missing from 4, 1, and 3 patients in Groups 1, 2, and 3, respectively; and 5 patients in Group A and 3 patients in Group B.

Effect of Modified DAPT Score on Treatment Outcomes

Bleeding Events

As expected, modified DAPT score ≥2 tended to be associated with lower bleeding risk than score <2 (HR, 0.86 [95% CI, 0.71–1.03]). Dabigatran dual therapy showed a benefit over warfarin triple therapy in bleeding risk events regardless of modified DAPT score. No interaction between modified DAPT score subgroup and treatment was observed (interaction *P* values: 0.53 and 0.54 for dabigatran 110 and 150 mg, respectively; Figure 3).

Thromboembolic Events

In the unadjusted treatment-independent analysis, patients with modified DAPT score ≥2 were at higher risk of DTE or unplanned revascularization compared with patients with score <2 (HR, 1.59 [95% CI, 1.29–1.96]).

No interaction between modified DAPT score subgroup and treatment was observed (interaction *P* values: 0.20 and 0.08 for dabigatran 110 and 150 mg, respectively; Figure 4). Similar efficacy was observed with dabigatran dual therapy versus warfarin triple therapy, with some variations, that is, slightly higher risk of DTE or unplanned revascularization for both dabigatran dual therapy groups versus warfarin triple therapy in patients with modified DAPT score ≥2.

Stent thrombosis rates were low in both subgroups: 1.0% (19/1816) for patients with modified DAPT score <2 and 1.2% (11/909) for those with score ≥2.

DISCUSSION

There has been a trend in recent years to replace triple therapy with dual therapy in patients with AF following PCI, by eliminating the aspirin component.[13–16] The WOEST study demonstrated that vitamin K antagonist and clopidogrel alone following PCI in patients on oral anticoagulation therapy reduced risk of bleeding without increasing the rate of thrombotic events versus triple therapy.[17,18] Guidelines from the European

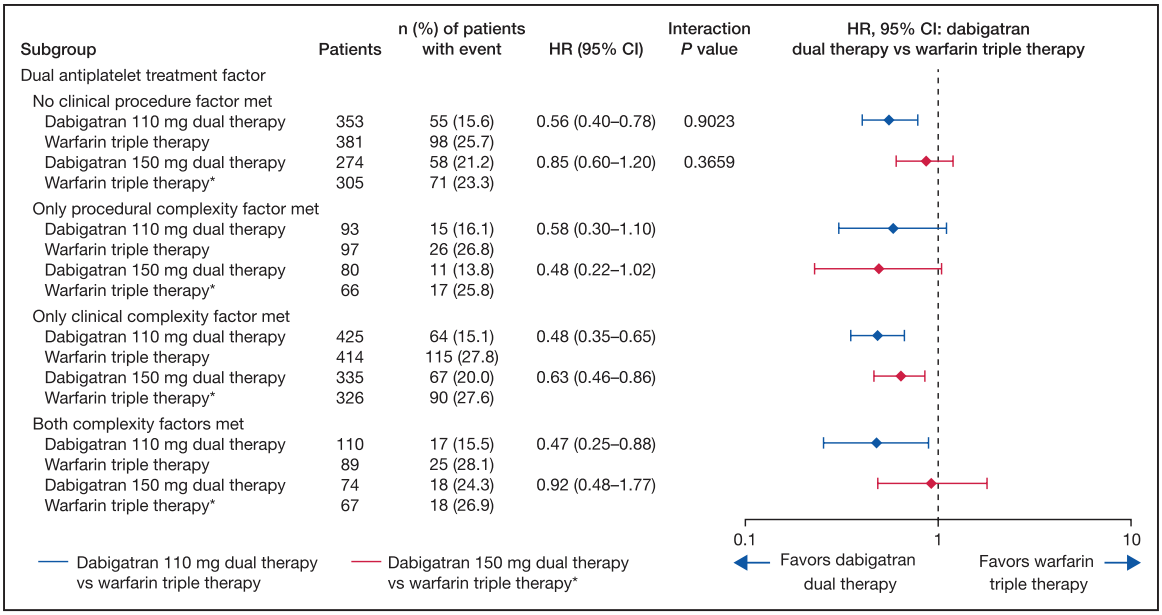

Figure 1. Bleeding events (International Society on Thrombosis and Haemostasis major bleeding event or clinically relevant nonmajor bleeding event) according to procedural and/or clinical complexity factor subgroups.
Hazard ratios (HRs) and 95% CIs from Cox proportional hazard model; stratified by age (elderly vs nonelderly) for dabigatran 110 mg dual therapy vs warfarin triple therapy; unstratified for dabigatran 150 mg dual therapy vs warfarin triple therapy. *For the comparison with dabigatran 150 mg dual therapy, elderly patients outside the United States are excluded.

Society of Cardiology and CHEST recommend that triple therapy should be limited in duration in patients requiring anticoagulation post-PCI, based on individual patient risk of bleeding and ischemic events.[3,19–21] The randomized trials of rivaroxaban (PIONEER AF-PCI) and dabigatran (REDUAL PCI) combined with single antiplatelet therapy support use of these novel oral anticoagulant dual therapies over vitamin K antagonist with triple therapy in patients with AF post-PCI,[9,22] consistent with North American and European Expert Consensus recommendations.[6,23]

This prespecified subgroup analysis of the REDUAL PCI trial found that dabigatran dual therapy following PCI was associated with consistently reduced bleeding risk compared with warfarin triple therapy, independent of the presence of procedural or clinical complexity factors. Dabigatran dual therapy at both doses had similar thrombotic risk to warfarin triple therapy, irrespective of complexity of PCI or modified DAPT score.

The DAPT trial reported that lesion complexity was a predictor of ischemic outcomes in patients who underwent PCI.[8,24] Patients with complex lesions experienced significantly increased rates of MI and stent thrombosis during 12 months post-PCI compared with patients without complex anatomy.[8] On a shorter timescale, a substudy of the CHAMPION PHOENIX trial (Cangrelor Versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition PHOENIX) evaluating intravenous cangrelor versus a loading dose of clopidogrel in patients undergoing PCI reported that lesion complexity was predictive of early (<48 hour) major adverse cardiovascular events.[25] Longer-term analysis of patients treated with biodegradable polymer versus durable polymer stents in the BIOSCIENCE trial showed that clinical and lesion complexity were associated with higher rates of the composite end point of death, MI, or revascularization.[26] Finally, anatomic complexity measured by a simplified scoring system (the Veterans Affairs SYNTAX score) successfully assessed longitudinal risk for adverse events in patients after PCI.[27]

The question was raised whether a dual antithrombotic strategy is sufficient in difficult-to-manage subpopulations of patients with AF post-PCI. Our data suggest there may not be an increased risk of thrombotic complications with dabigatran dual therapy compared with warfarin triple therapy, even in patients with clinical or procedural complexity. Of note, we have limited statistical power in any individual subgroup, but the overall benefit on bleeding and no major difference in thrombotic events seems consistent across the 4 patient groups with one or even both complexity factors. This provides reassurance to clinicians on using this strategy as a means to reduce bleeding risk in patients needing both antiplatelet and anticoagulant therapy.

These findings parallel our analysis of patients with ACS versus non-ACS as the indication for PCI.[28] Indeed, ACS is the main component of the prespecified clinical complexity definition. The current analysis, however, adds procedural complexity and assesses patients with both clinical and procedural complexities.

Although the analysis based on DAPT score was not prespecified, as the score was developed after the trial was started, the study provides support for the modified

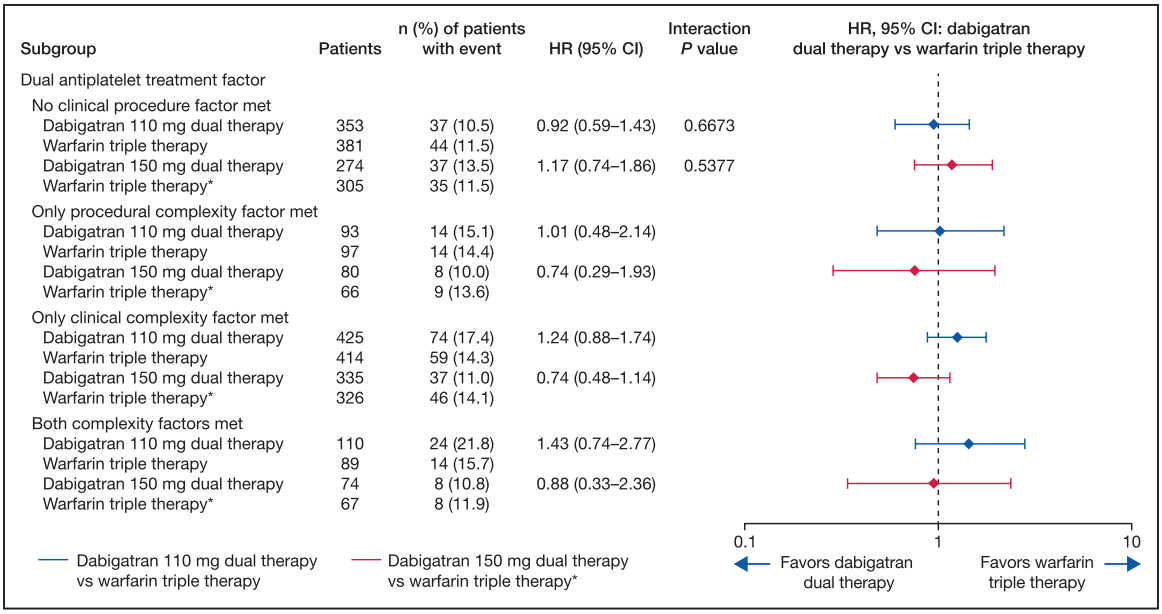

Figure 2. Thromboembolic events (death or thromboembolic event or unplanned revascularization) according to procedural and/or clinical complexity factor subgroups.
See Figure 1 for statistical summary. HR indicates hazard ratio.

DAPT score. The fact that patients with a DAPT score ≥2 had higher risk of DTE or unplanned revascularization than patients with score <2 in the unadjusted treatment-independent analysis is expected, given that higher DAPT scores are predictive of greater ischemic risk. For patients with DAPT score ≥2, a trend toward lower bleeding risk was observed, as would also be expected. The lack of a more considerable difference in bleeding risk between patients with DAPT scores ≥2 or <2 might be explained by the different score distribution in this population, the effect of other contributing factors, or simply a lack of adequately powered analysis.

A limitation of this study is that it is a subgroup analysis and not powered for formal statistical analysis. Interaction *P* values are exploratory. We also have insufficient power to examine individual end points across these 4 subgroups. A further limitation is the use of a modified DAPT score, which was required because 2 score components in the DAPT trial were not collected in REDUAL PCI; such a modification has not yet been validated.

In conclusion, these findings support the primary REDUAL PCI study and highlight the important finding that, even in higher-risk patients with clinical or lesion

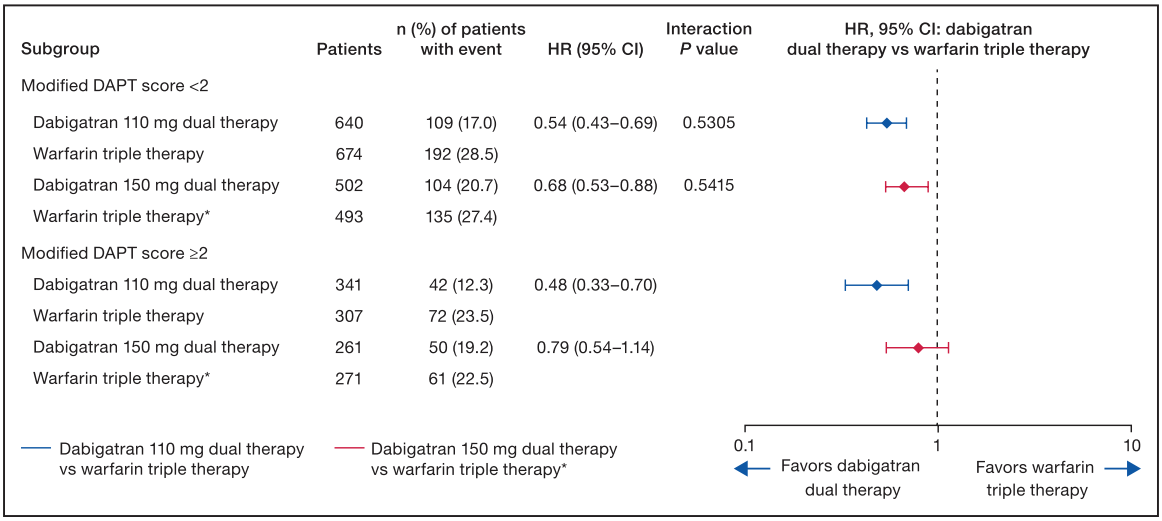

Figure 3. Bleeding events (International Society on Thrombosis and Haemostasis major bleeding event or clinically relevant nonmajor bleeding event) according to modified dual antiplatelet therapy (DAPT) score (<2 versus ≥2).
For calculation of modified DAPT score see text. Missing values for calculation of DAPT score were imputed to 0 points. See Figure 1 for other statistical summary. HR indicates hazard ratio.

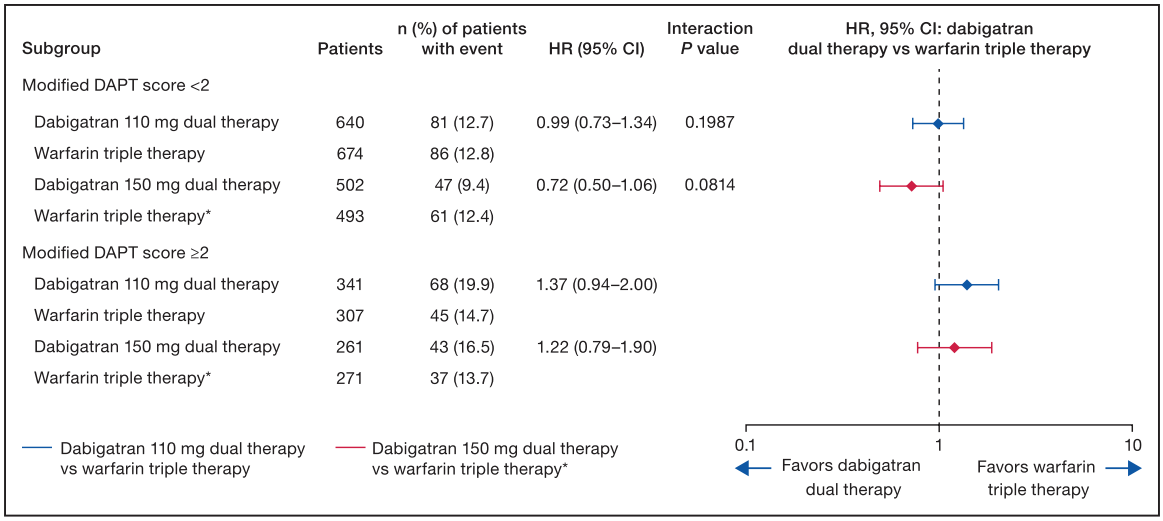

Figure 4. Thromboembolic events (death or thromboembolic event or unplanned revascularization) according to modified dual antiplatelet therapy (DAPT) score (<2 versus ≥2).
See Figures 1 and 3 for statistical summary. HR indicates hazard ratio.

complexity, bleeding risk can be mitigated without any apparent increase in ischemic risk by dabigatran dual therapy compared with warfarin triple therapy.

ARTICLE INFORMATION

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Affiliations

Mid-Atlantic Permanente Medical Group, McLean, VA (N.C.B.). Medtronic, Minneapolis, MN (L.M.). Université de Paris, FACT, INSERM U_1148 and Hôpital Bichat, Assistance Publique-Hôpitaux de Paris, France (P.G.S.). Brigham and Women's Hospital Heart and Vascular Center and Harvard Medical School, Boston, MA (D.L.B., C.P.C.). Johann Wolfgang Goethe University, Frankfurt am Main, Germany (S.H.H.). Boehringer Ingelheim International GmbH, Ingelheim am Rhein, Germany (M.N.). HMS Analytical Software GmbH, Weimar (Lahn), Germany (C.M.). Kyoto University, Japan (T.K.). Liverpool Centre for Cardiovascular Science, University of Liverpool and Liverpool Heart and Chest Hospital, United Kingdom (G.Y.H.L.). Aalborg Thrombosis Research Unit, Department of Clinical Medicine, Aalborg University, Denmark (G.Y.H.L). Uppsala Clinical Research Center and Department of Medical Sciences, Uppsala University, Sweden (J.O.). St Antonius Ziekenhuis, Nieuwegein, the Netherlands (J.M.t.B.).

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Disclosures

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REFERENCES

1. Levine GN, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B, Chambers CE, Ellis SG, Guyton RA, Hollenberg SM, et al. 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention: a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines and the Society for Cardiovascular Angiography and Interventions. *Circulation*. 2011;124:e574–e651. doi: 10.1161/CIR.0b013e31823ba622
2. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC, Jr, Conti JB, Ellinor PT, Ezekowitz MD, Field ME, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association task force on practice guidelines and the Heart Rhythm Society. *J Am Coll Cardiol*. 2014;64:e1–76. doi: 10.1016/j.jacc.2014.03.022
3. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, Diener HC, Heidbuchel H, Hendriks J, et al; ESC Scientific Document Group. 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J*. 2016;37:2893–2962. doi: 10.1093/eurheartj/ehw210
4. Ruff CT, Bhatt DL, Steg PG, Gersh BJ, Alberts MJ, Hoffman EB, Ohman EM, Eagle KA, Lip GY, Goto S; REACH Registry Investigators. Long-term cardiovascular outcomes in patients with atrial fibrillation and atherothrombosis in the REACH Registry. *Int J Cardiol*. 2014;170:413–418. doi: 10.1016/j.ijcard.2013.11.030
5. Steg PG, Bhatt DL. Viewpoint: a proposal for a simple algorithm for managing oral anticoagulation and antiplatelet therapy in patients with non-valvular atrial fibrillation and coronary stents. *Eur Heart J Acute Cardiovasc Care*. 2017;6:93–97. doi: 10.1177/2048872615610868
6. Angiolillo DJ, Goodman SG, Bhatt DL, Eikelboom JW, Price MJ, Moliterno DJ, Cannon CP, Tanguay JF, Granger CB, Mauri L, et al. Antithrombotic therapy in patients with atrial fibrillation treated with oral anticoagulation undergoing percutaneous coronary intervention. *Circulation*. 2018;138:527–536. doi: 10.1161/CIRCULATIONAHA.118.034722
7. Mauri L, Kereiakes DJ, Yeh RW, Driscoll-Shempp P, Cutlip DE, Steg PG, Normand SL, Braunwald E, Wiviott SD, Cohen DJ, et al; DAPT Study Investigators. Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. *N Engl J Med*. 2014;371:2155–2166. doi: 10.1056/NEJMoa1409312
8. 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. doi: 10.1016/j.jacc.2017.09.011
9. Cannon CP, Bhatt DL, Oldgren J, Lip GYH, Ellis SG, Kimura T, Maeng M, Merkely B, Zeymer U, Gropper S, et al. Dual antithrombotic therapy with dabigatran after PCI in atrial fibrillation. *New Engl J Med*. 2017;377:1513–1524. doi: 10.1056/NEJMoa1708454
10. Cannon CP, Gropper S, Bhatt DL, Ellis SG, Kimura T, Lip GY, Steg PG, Ten Berg JM, Manassie J, Kreuzer J, et al. Design and rationale of the RE-DUAL PCI trial: a prospective, randomized, phase 3b study comparing the safety and efficacy of dual antithrombotic therapy with dabigatran etexilate versus warfarin triple therapy in patients with nonvalvular atrial fibrillation who have undergone percutaneous coronary intervention with stenting. *Clin Cardiol*. 2016;39:555–564. doi: 10.1002/clc.22572
11. Mauri L, Kereiakes DJ, Normand SL, Wiviott SD, Cohen DJ, Holmes DR, Bangalore S, Cutlip DE, Pencina M, Massaro JM. Rationale and design of the dual antiplatelet therapy study, a prospective, multicenter, randomized, double-blind trial to assess the effectiveness and safety of 12 versus 30 months of dual antiplatelet therapy in subjects undergoing percutaneous coronary intervention with either drug-eluting stent or bare metal stent placement for the treatment of coronary artery lesions. *Am Heart J*. 2010;160:1035–1041, 1041 e1031. doi: 10.1016/j.ahj.2010.07.038
12. Yeh RW, Secemsky EA, Kereiakes DJ, Normand SL, Gershlick AH, Cohen DJ, Spertus JA, Steg PG, Cutlip DE, Rinaldi MJ, et al; DAPT Study Investigators. Development and validation of a prediction rule for benefit and harm of dual antiplatelet therapy beyond 1 year after percutaneous coronary intervention. *JAMA*. 2016;315:1735–1749. doi: 10.1001/jama.2016.3775
13. Capodanno D, Angiolillo DJ. Management of antiplatelet and anticoagulant therapy in patients with atrial fibrillation in the setting of acute coronary syndromes or percutaneous coronary interventions. *Circ Cardiovasc Interv*. 2014;7:113–124. doi: 10.1161/CIRCINTERVENTIONS.113.001150
14. Golwala HB, Cannon CP, Steg PG, Doros G, Qamar A, Ellis SG, Oldgren J, Ten Berg JM, Kimura T, Hohnloser SH, et al. Safety and efficacy of dual vs. triple antithrombotic therapy in patients with atrial fibrillation following percutaneous coronary intervention: a systematic review and meta-analysis of randomized clinical trials. *Eur Heart J*. 2018;39:1726–1735a. doi: 10.1093/eurheartj/ehy162
15. Lopes RD, Heizer G, Aronson R, Vora AN, Massaro T, Mehran R, Goodman SG, Windecker S, Darius H, Li J, et al. Antithrombotic therapy after acute coronary syndrome or PCI in atrial fibrillation. *N Engl J Med*. 2019;380:1509–1524. doi: 10.1056/NEJMoa1817083
16. Lopes RD, Hong H, Harskamp RE, Bhatt DL, Mehran R, Cannon CP, Granger CB, Verheugt FWA, Li J, Ten Berg JM, et al. Safety and efficacy of antithrombotic strategies in patients with atrial fibrillation undergoing percutaneous coronary intervention: a network meta-analysis of randomized controlled trials. *JAMA Cardiol*. 2019. doi: 10.1001/jamacardio.2019.1880
17. Lamberts M, Gislason GH, Olesen JB, Kristensen SL, Schjerning Olsen AM, Mikkelsen A, Christensen CB, Lip GY, Kober L, Torp-Pedersen C, et al. Oral anticoagulation and antiplatelets in atrial fibrillation patients after myocardial infarction and coronary intervention. *J Am Coll Cardiol*. 2013;62:981–989. doi: 10.1016/j.jacc.2013.05.029
18. Dewilde WJ, Oirbans T, Verheugt FW, Kelder JC, De Smet BJ, Herrman JP, Adriaenssens T, Vrolix M, Heestermans AA, Vis MM, et al. 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. doi: 10.1016/S0140-6736(12)62177-1
19. Valgimigli M, Bueno H, Byrne RA, Collet JP, Costa F, Jeppsson A, Juni P, Kastrati A, Kolh P, Mauri L, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: the task force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J*. 2018;39:213–260. doi: 10.1093/eurheartj/ehx419
20. Steffel J, Verhamme P, Potpara TS, Albaladejo P, Antz M, Desteghe L, Haeusler KG, Oldgren J, Reinecke H, Roldan-Schilling V, et al. 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. doi: 10.1093/eurheartj/ehy136
21. Lip GYH, Banerjee A, Boriani G, Chiang CE, Fargo R, Freedman B, Lane DA, Ruff CT, Turakhia M, Werring D, et al. Antithrombotic therapy for atrial fibrillation: CHEST guideline and expert panel report. *Chest*. 2018;154:1121–1201. doi: 10.1016/j.chest.2018.07.040
22. Gibson CM, Mehran R, Bode C, Halperin J, Verheugt FW, Wildgoose P, Birmingham M, Ianus J, Burton P, van Eickels M, et al. Prevention of bleeding in patients with atrial fibrillation undergoing PCI. *N Engl J Med*. 2016;375:2423–2434. doi: 10.1056/NEJMoa1611594
23. Lip GYH, Collet JP, Haude M, Byrne R, Chung EH, Fauchier L, Halvorsen S, Lau D, Lopez-Cabanillas N, Lettino M, et al. 2018 Joint European consensus document on the management of antithrombotic therapy in atrial fibrillation patients presenting with acute coronary syndrome and/or undergoing percutaneous cardiovascular interventions: a joint consensus document of the European Heart Rhythm Association (EHRA), European Society of Cardiology Working Group on Thrombosis, European Association of Percutaneous Cardiovascular Interventions (EAPCI), and European Association of Acute Cardiac Care (ACCA) endorsed by the Heart Rhythm Society (HRS), Asia-Pacific Heart Rhythm Society (APHRS), Latin America Heart Rhythm Society (LAHRS), and Cardiac Arrhythmia Society of Southern Africa (CASSA). *Europace*. 2019;21:192–193. doi: 10.1093/europace/euy174
24. Giustino G, Chieffo A, Palmerini T, Valgimigli M, Feres F, Abizaid A, Costa RA, Hong MK, Kim BK, Jang Y, et al. Efficacy and safety of dual antiplatelet therapy after complex PCI. *J Am Coll Cardiol*. 2016;68:1851–1864. doi: 10.1016/j.jacc.2016.07.760
25. Stone GW, Généreux P, Harrington RA, White HD, Gibson CM, Steg PG, Hamm CW, Mahaffey KW, Price MJ, Prats J, et al. Impact of lesion complexity on peri-procedural adverse events and the benefit of potent intravenous platelet adenosine diphosphate receptor inhibition after percutaneous coronary intervention: core laboratory analysis from 10 854 patients from the CHAMPION PHOENIX trial. *Eur Heart J*. 2018;39:4112–4121. doi: 10.1093/eurheartj/ehy562
26. Koskinas KC, Taniwaki M, Rigamonti F, Heg D, Roffi M, Tüller D, Muller O, Vuillomenet A, Cook S, Weilenmann D, et al. Impact of patient and lesion complexity on long-term outcomes following coronary revascularization with new-generation drug-eluting stents. *Am J Cardiol*. 2017;119:501–507. doi: 10.1016/j.amjcard.2016.10.038

27. Valle JA, Glorioso TJ, Bricker R, Baron AE, Armstrong EJ, Bhatt DL, Rao SV, Plomondon ME, Serruys PW, Keppetein AP, et al. Association of coronary anatomical complexity with clinical outcomes after percutaneous or surgical revascularization in the veterans affairs clinical assessment reporting and tracking program. *JAMA Cardiol*. 2019. doi: 10.1001/jamacardio.2019.1923

28. Oldgren J, Steg PG, Hohnloser SH, Lip GYH, Kimura T, Nordaby M, Brueckmann M, Kleine E, Ten Berg JM, Bhatt DL, et al. Dabigatran dual therapy with ticagrelor or clopidogrel after percutaneous coronary intervention in atrial fibrillation patients with or without acute coronary syndrome: a subgroup analysis from the RE-DUAL PCI trial. *Eur Heart J*. 2019;40:1553–1562. doi: 10.1093/eurheartj/ehz059