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Dabigatran Dual Therapy Versus Warfarin Triple Therapy Post–PCI in Patients With Atrial Fibrillation and Diabetes

Michael Maeng, MD, PhD,[a] Philippe Gabriel Steg, MD,[b,c,d,e] Deepak L. Bhatt, MD, MPH,[f] Stefan H. Hohnloser, MD,[g] Matias Nordaby, MD,[h] Corinna Miede, MSc,[i] Takeshi Kimura, MD, PhD,[j] Gregory Y.H. Lip, MD,[k,l] Jonas Oldgren, MD, PhD,[m] Jurriën M. ten Berg, MD, PhD,[n] Christopher P. Cannon, MD,[f] on behalf of the RE-DUAL PCI Steering Committee and Investigators

ABSTRACT

OBJECTIVES The aim of this study was to evaluate dabigatran dual therapy versus warfarin triple therapy in patients with or without diabetes mellitus in the RE-DUAL PCI (Randomized Evaluation of Dual Antithrombotic Therapy With Dabigatran Versus Triple Therapy With Warfarin in Patients With Nonvalvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention) trial.

BACKGROUND It is unclear whether dual therapy is as safe and efficacious as triple therapy in patients with atrial fibrillation with diabetes following percutaneous coronary intervention.

METHODS In RE-DUAL PCI, 2,725 patients with atrial fibrillation (993 with diabetes) who had undergone PCI were assigned to warfarin triple therapy (warfarin, clopidogrel or ticagrelor, and aspirin) or dabigatran dual therapy (dabigatran 110 mg or 150 mg twice daily and clopidogrel or ticagrelor). Median follow-up was 13 months. The primary outcome was the composite of major bleeding or clinically relevant nonmajor bleeding, and the main efficacy outcome was the composite of death, thromboembolic events, or unplanned revascularization.

RESULTS Among patients with diabetes, the incidence of major bleeding or clinically relevant nonmajor bleeding was 15.2% in the dabigatran 110 mg dual therapy group versus 27.5% in the warfarin triple therapy group (hazard ratio [HR]: 0.48; 95% confidence interval [CI] 0.35 to 0.67) and 23.8% in the dabigatran 150 mg dual therapy group versus 25.1% in the warfarin triple therapy group (HR: 0.87; 95% CI: 0.62 to 1.22). Risk for major bleeding or clinically relevant nonmajor bleeding was also reduced with both dabigatran doses among patients without diabetes (dabigatran 110 mg dual therapy: HR: 0.54; 95% CI: 0.42 to 0.70; dabigatran 150 mg dual therapy: HR: 0.63; 95% CI: 0.48 to 0.83). Risk for the efficacy endpoint was comparable between treatment groups for both patients with and those without diabetes. No interaction between treatment and diabetes subgroup could be observed, either for bleeding or for composite efficacy endpoints.

CONCLUSIONS In this subgroup analysis, dabigatran dual therapy had a lower risk for bleeding and a comparable rate of the efficacy endpoint compared with warfarin triple therapy in patients with atrial fibrillation with or without diabetes following percutaneous coronary intervention. (J Am Coll Cardiol Intv 2019;12:2346–55) © 2019 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

From the [a]Aarhus University Hospital, Aarhus, Denmark; [b]FACT, an F-CRIN Network, DHU FIRE, Hôpital Bichat, Paris, France; [c]Université Paris Diderot, Paris, France; [d]INSERM U_1148, Paris, France; [e]Hôpital Bichat Assistance Publique-Hôpitaux de Paris, Paris, France; [f]Brigham and Women's Hospital and Heart and Vascular Center Harvard Medical School, Boston, Massachusetts; [g]Johann Wolfgang Goethe University, Frankfurt am Main, Germany; [h]Boehringer Ingelheim International, Ingelheim, Germany; [i]HMS Analytical Software, Weimar (Lahn), Germany; [j]Kyoto University, Kyoto, Japan; [k]Liverpool Centre for Cardiovascular Science, University of Liverpool and Liverpool Heart & Chest Hospital, Liverpool, United Kingdom; [l]Aalborg Thrombosis Research Unit, Department of Clinical Medicine, Aalborg University, Aalborg, Denmark; [m]Uppsala Clinical Research Center and Department of Medical Sciences, Uppsala University, Uppsala, Sweden; and the [n]St. Antonius Ziekenhuis, Nieuwegein, the Netherlands.
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Patients with diabetes mellitus and coronary artery disease have a higher risk for major adverse cardiac events than patients without diabetes (1-3). Patients with diabetes and atrial fibrillation (AF) also have a higher risk for ischemic stroke (4,5), and it was found in the RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) trial that also dabigatran-treated patients with combined AF and diabetes have a higher risk for both major bleeding events and thromboembolic events compared with those without diabetes (6). Furthermore, in patients with AF, coronary artery disease was recently shown to be an independent risk factor for thromboembolic events, including ischemic stroke (7). Patients with diabetes and AF who undergo percutaneous coronary intervention (PCI) may therefore have a particularly high risk of thromboembolic events. In the RE-DUAL PCI (Randomized Evaluation of Dual Antithrombotic Therapy With Dabigatran Versus Triple Therapy With Warfarin in Patients With Nonvalvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention) trial, dual-antithrombotic therapy with dabigatran was compared with triple-antithrombotic therapy with warfarin in patients with AF who underwent PCI (8). The RE-DUAL PCI trial was powered for noninferiority for adverse bleeding events as well as thrombotic-related events using a composite of death, myocardial infarction, stroke, systemic embolism, and unplanned revascularization. While meeting its primary endpoints concerning bleeding and efficacy, it was further found, as part of formal hierarchical testing, that dabigatran 110 mg dual-antithrombotic therapy was superior to warfarin triple therapy with regard to bleeding events (8).

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

CI = confidence interval

CRNMBE = clinically relevant nonmajor bleeding event

DTE = death or thromboembolic event

HR = hazard ratio

MBE = major bleeding event

PCI = percutaneous coronary intervention

SEE PAGE 2356

There are limited data regarding the impact of diabetes in this group of patients, and it remains unknown if dual therapy is adequate for PCI patients with combined AF and diabetes. The aim of this predefined subgroup analysis of the RE-DUAL PCI trial

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was to assess if patients with diabetes and AF who underwent PCI were adequately protected against thromboembolic events by dual- versus triple-antithrombotic therapy, while remaining protected against bleeding events.

METHODS

The RE-DUAL PCI trial design, methods, and primary results have been published (8,9). A brief summary of design and methods is provided here.

PATIENT POPULATION. Key inclusion criteria were men and women ≥18 years of age, with nonvalvular AF, who underwent successful PCI with a bare-metal or drug-eluting stent within the previous 120 h. Nonvalvular AF could be paroxysmal, persistent, or permanent, but it could not be secondary to a reversible disorder unless long-term treatment with an oral anticoagulant agent was anticipated. The indication for PCI could be either an acute coronary syndrome or stable coronary artery disease. Key exclusion criteria were the presence of bioprosthetic or mechanical heart valves, severe renal insufficiency (creatinine clearance <30 ml/min), or other major comorbidities.

TREATMENTS. Patients were randomly assigned to receive 1 of 3 treatments: dual therapy with dabigatran etexilate 110 mg twice daily plus either clopidogrel or ticagrelor, dual therapy with dabigatran etexilate 150 mg twice daily plus either clopidogrel or ticagrelor, or triple therapy with warfarin plus either clopidogrel or ticagrelor plus aspirin (≤100 mg/day). In the warfarin triple therapy group, aspirin was discontinued after 1 month in patients in whom bare-metal stents were implanted and after 3 months in patients in whom drug-eluting stents were implanted.

Randomization was performed with the use of permuted blocks, with stratification according to age group (nonelderly or elderly [<80 or ≥80 years; <70 or ≥70 years in Japan]) and region (United States, Japan, or other countries). All patients in the United States and nonelderly patients in other countries were randomly assigned to the dabigatran 110 mg dual therapy group, the dabigatran 150 mg dual therapy group, or the warfarin triple therapy group in a 1:1:1 ratio. Elderly patients outside the United States were randomly assigned to the dabigatran 110 mg dual therapy or the warfarin triple therapy group in a 1:1 ratio; they were not eligible to be assigned to the dabigatran 150 mg dual therapy group, in accordance with the recommendations of the dabigatran label in those countries. All the patients were to receive either clopidogrel (75 mg/day) or ticagrelor (90 mg twice daily) for at least 12 months after randomization; the choice of agent was at the discretion of the investigator. The dose of warfarin was adjusted to ensure that the patient's international normalized ratio was within a range of 2.0 to 3.0.

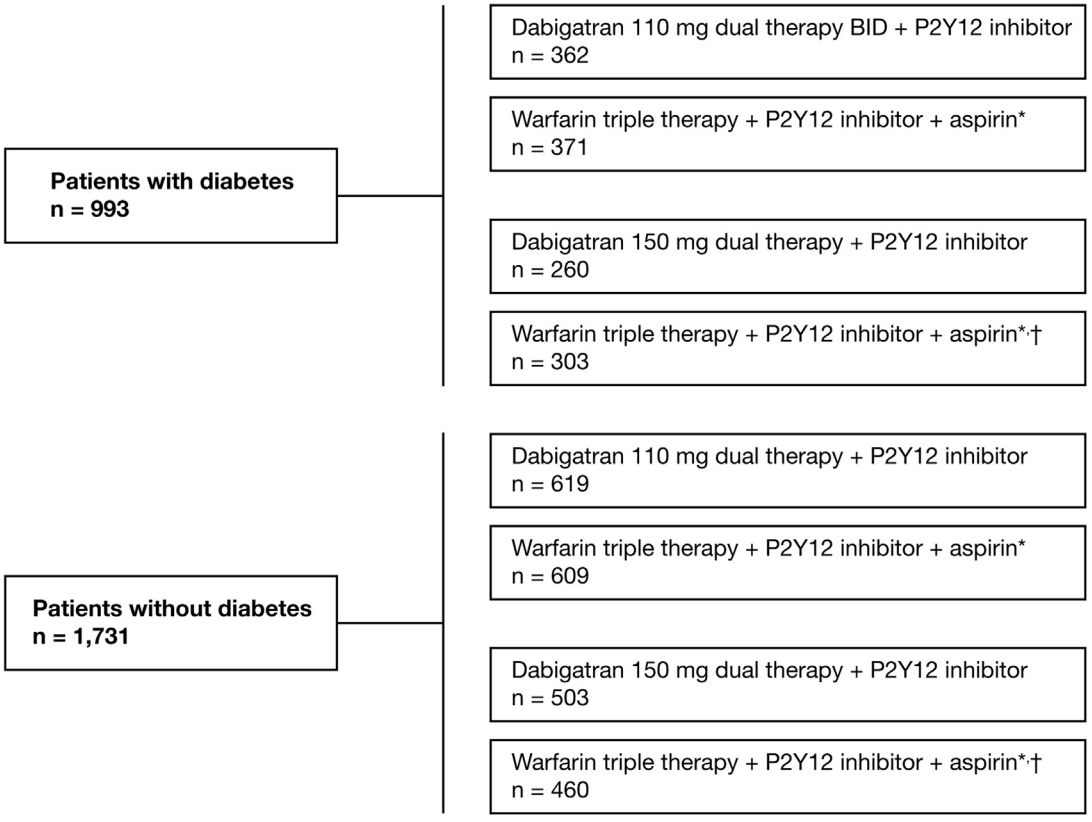
ENDPOINTS. The endpoints in this subgroup analysis reflect the primary endpoint in the primary publication, which was the time to first major bleeding event (MBE) or clinically relevant nonmajor bleeding event (CRNMBE) (as defined by the International Society on Thrombosis and Haemostasis), and the main secondary endpoint, which was a composite efficacy endpoint of time to death, first thromboembolic event (myocardial infarction, stroke, or systemic embolism), or unplanned revascularization (PCI or coronary artery bypass grafting). Other endpoints were the individual endpoints of International Society on Thrombosis and Haemostasis MBE alone, CRNMBE alone, intracranial hemorrhage, a combined endpoint of death or thromboembolic event (DTE), as well as death, myocardial infarction, definite stent thrombosis, and stroke. Detailed definitions of the endpoints have been published (8). All clinical endpoint events were adjudicated by an independent committee whose members were unaware of the treatment assignments.

STATISTICAL ANALYSIS. Clinical characteristics of patients were summarized according to whether they had diabetes. For comparison of the dabigatran 110 mg dual therapy group versus the warfarin triple therapy group within the diabetes subgroup categories, stratified Cox proportional hazards regression models, stratified by age (nonelderly vs. elderly [age <70 vs. ≥70 years in Japan; <80 vs. ≥80 years elsewhere]), were applied. Unstratified Cox proportional hazard regression models were used for comparison of the dabigatran 150 mg dual therapy group versus the warfarin triple therapy group. Exploratory treatment-by-subgroup interaction p values resulting from Cox proportional hazard regression models were provided. A treatment-independent, stratified Cox proportional hazard regression analysis was performed including diabetes subgroup as the only factor in the model. Furthermore, a multivariate stratified Cox proportional hazard regression analysis including diabetes subgroup as factor in the model and additionally adjusting for continuous variable age and categorical variables sex and previous stroke was performed.

RESULTS

The RE-DUAL PCI trial included 993 patients with diabetes and 1,731 patients without diabetes; diabetes

FIGURE 1 Patients With and Without Diabetes in Each Treatment Group



*One month of aspirin for bare-metal stent; 3 months of aspirin for drug-eluting stent. †For the comparison with dabigatran 150 mg dual therapy, elderly patients outside the United States were excluded. BID = twice daily.

status at inclusion was unknown for 1 patient, who was excluded from this analysis (Figure 1). The median duration of follow-up was 13 months (interquartile range: 9 to 18 months).

IMPACT OF DIABETES. The baseline characteristics of patients with and without diabetes are presented in Table 1. Rates of previous stroke, PCI, and coronary artery bypass grafting were higher among patients with diabetes.

Table 2 presents the clinical outcome events according to the presence of diabetes. Patients with and those without diabetes had a comparable bleeding risk, but patients with diabetes had a higher risk for the composite efficacy-related endpoints (DTE or unplanned revascularization, as well as DTE alone) (Table 2). The risk for the individual endpoints of death (6.1% vs. 4.2%; hazard ratio [HR]: 1.50; 95% confidence interval [CI]: 1.06 to 2.11) and stroke (2.4% vs. 0.9%; HR: 2.86; 95% CI: 1.50 to 5.45) was also higher for patients with diabetes, whereas risk for myocardial infarction was comparable (3.9% vs. 3.5%; HR: 1.14; 95% CI: 0.76 to 1.70) and risk for definite stent thrombosis was numerically lower (0.8% vs. 1.3%; HR: 0.63; 95% CI: 0.28 to 1.41) for patients with versus those without diabetes. Similar results were observed for the multivariable Cox proportional hazard regression model.

DUAL VERSUS TRIPLE THERAPY IN PATIENTS WITH AND WITHOUT DIABETES. The safety outcomes by treatment group in patients with and those without diabetes are presented in Figure 2, and the efficacy-related endpoints are shown in Figure 3. No interaction between treatment and diabetes subgroup could be detected, either for the bleeding or for the efficacy endpoints (Figures 2 and 3).

In patients with diabetes, the risk for bleeding events was reduced by dabigatran 110 mg dual therapy (Figure 2, Central Illustration). The bleeding reduction by dabigatran 110 mg dual therapy was numerically higher than that by dabigatran 150 mg

TABLE 1 Baseline Characteristics of Patients With Versus Those Without Diabetes in the RE-DUAL PCI Trial

	Patients With Diabetes (n = 993)	Patients Without Diabetes (n = 1,731)
Age, yrs	71 ± 8	71 ± 9
Male	720 (72.5)	1,349 (77.9)
BMI*, kg/m^2	30.2 ± 5.5	28.1 ± 5.0
Diabetes treatment		
Insulin only	122 (12.3)	–
Insulin + other	155 (15.6)	–
Other only	716 (72.1)	–
Previous stroke	95 (9.6)	131 (7.6)
CHA_2DS_2-VASc score	4.4 ± 1.4	3.2 ± 1.5
HAS-BLED score	2.8 ± 0.7	2.7 ± 0.7
Creatinine clearance†, ml/min	79.1 ± 31.6	77.4 ± 28.6
Previous MI	250 (25.2)	449 (25.9)
Previous PCI	376 (37.9)	536 (31.0)
Previous CABG	128 (12.9)	159 (9.2)
Type of AF		
Persistent	165 (16.6)	319 (18.4)
Permanent	343 (34.5)	545 (31.5)
Paroxysmal	485 (48.8)	866 (50.0)
Baseline OAC treatment‡		
Long term	355 (35.8)	573 (33.1)
Treatment naive	638 (64.2)	1,158 (66.9)
Indication for PCI§		
Stable angina	453 (45.6)	729 (42.1)
Acute coronary syndrome	492 (49.5)	883 (51.0)
Staged procedure	170 (17.1)	292 (16.9)
Other	54 (5.4)	116 (6.7)
Type of stent‖		
Drug eluting	827 (83.3)	1,424 (82.3)
Bare metal	136 (13.7)	268 (15.5)
Drug eluting and bare metal	21 (2.1)	20 (1.2)
Other	5 (0.5)	16 (0.9)

Values are mean ± SD or n (%). *Data missing from 1 and 3 patients with and without diabetes, respectively. †Data missing from 88 and 143 patients with and without diabetes, respectively. ‡Fourteen days of consecutive OAC treatment used to classify into treatment-naive or long-term OAC patients. §More than 1 indication per patient is possible. ‖Data missing from 4 and 3 patients with and without diabetes, respectively.

AF = atrial fibrillation; BMI = body mass index; CABG = coronary artery bypass graft; MI = myocardial infarction; OAC = oral anticoagulant agents (both non-vitamin K and vitamin K antagonists); PCI = percutaneous coronary intervention; RE-DUAL PCI = Randomized Evaluation of Dual Antithrombotic Therapy With Dabigatran Versus Triple Therapy With Warfarin in Patients With Nonvalvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention.

dual therapy (**Figure 2, Central Illustration**). The risk for the efficacy endpoint events for dabigatran 110 mg dual therapy and dabigatran 150 mg dual therapy, respectively, versus warfarin triple therapy did not differ relevantly (**Figure 3, Central Illustration**).

In patients without diabetes, dabigatran 110 mg dual therapy and dabigatran 150 mg dual therapy were both found to reduce the risk for bleeding endpoints compared with warfarin triple therapy (**Figure 2**). The risks for the composite efficacy endpoint of DTE or unplanned revascularization were comparable for the dabigatran 110 mg dual therapy and dabigatran 150 mg dual therapy groups, respectively, versus the warfarin triple therapy group (**Figure 3**).

DISCUSSION

In the RE-DUAL PCI trial, dabigatran dual-antithrombotic therapy reduced bleeding events, without increasing the risk for major ischemic events, compared with warfarin triple-antithrombotic therapy (8). Herein, we present a subgroup analysis of the RE-DUAL PCI trial in patients with and those without diabetes. The aim was to assess if patients with AF and diabetes undergoing PCI are adequately protected against thromboembolic events by dabigatran 110 mg dual therapy and dabigatran 150 mg dual therapy versus warfarin triple-antithrombotic therapy. Our main findings are as follows: 1) patients with AF and diabetes have a higher risk for death and thromboembolic events but do not have a higher risk for bleeding compared with patients with AF alone; 2) no interactions between the diabetes subgroup and treatment could be observed, thus consistent results with main RE-DUAL PCI trial were obtained; and 3) dual therapy with dabigatran 110 mg had a lower risk for bleeding and was as efficacious as triple therapy with warfarin in patients with AF with and without diabetes following PCI.

BLEEDING AND THROMBOEMBOLIC EVENTS IN PATIENTS WITH AND THOSE WITHOUT DIABETES. Presence of diabetes in this AF plus PCI cohort was associated with a comparable risk for bleeding but a higher risk for ischemic events in comparison with patients without diabetes. The relevance of this observation has hitherto not been examined in the context of dual versus triple therapy. Risks for bleeding and thromboembolic events share some common risk factors. For example, the CHA_2DS_2-VASc and HAS-BLED scores both include age, hypertension, and previous stroke (10), and these 3 factors were associated with both stroke and bleeding events in a large Swedish study of patients with AF (4). Moreover, this coinciding increased risk was recently found in the ASCEND (A Study of Cardiovascular Events in Diabetes) trial, in which the incremental risk for vascular events from low- to high-risk patients was closely matched by a similar incremental risk for bleeding events (11). Similarly, when comparing patients with AF with and without diabetes randomized in the RE-LY trial, both major bleeding events (diabetes 4.2% vs. no diabetes

TABLE 2 Clinical Outcomes of Patients With Versus Those Without Diabetes in the RE-DUAL PCI Trial

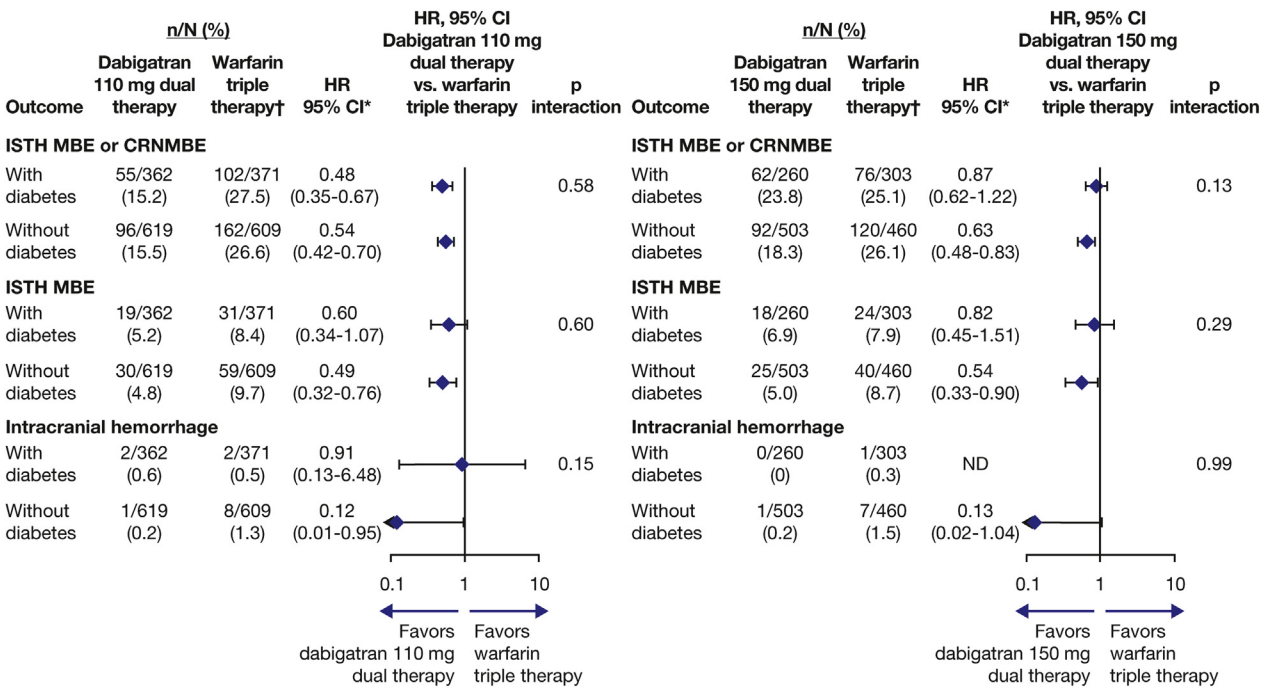
	Patients With Diabetes (n = 993)	Patients Without Diabetes (n = 1,731)	HR* (95% CI)	Adjusted HR† (95% CI)
Bleeding endpoints				
ISTH MBEs or CRNMBEs	219 (22.1)	350 (20.2)	1.12 (0.95–1.33)	1.13 (0.95–1.33)
ISTH MBEs	68 (6.8)	114 (6.6)	1.07 (0.79–1.44)	1.07 (0.79–1.45)
CRNMBEs	168 (16.8)	267 (15.4)	1.11 (0.92–1.35)	1.11 (0.92–1.35)
Intracranial hemorrhage	4 (0.4)	10 (0.6)	0.71 (0.22–2.26)	0.70 (0.22–2.23)
Efficacy endpoints				
Death, thromboembolic event, or unplanned revascularization	156 (15.7)	214 (12.4)	1.29 (1.05–1.58)	1.28 (1.04–1.58)
Death	61 (6.1)	72 (4.2)	1.50 (1.06–2.11)	1.51 (1.07–2.12)
Death or thromboembolic event	114 (11.5)	137 (7.9)	1.47 (1.15–1.89)	1.47 (1.14–1.88)
Definite stent thrombosis	8 (0.8)	22 (1.3)	0.63 (0.28–1.41)	0.60 (0.27–1.36)
MI	39 (3.9)	60 (3.5)	1.14 (0.76–1.70)	1.11 (0.74–1.66)
Stroke	24 (2.4)	15 (0.9)	2.86 (1.50–5.45)	2.82 (1.48–5.39)

Values are n (%). *Cox proportional hazard model stratified by age (nonelderly vs. elderly [<70 or ≥70 yrs in Japan and <80 or ≥80 yrs elsewhere]). †Cox proportional hazard model stratified by age (nonelderly vs. elderly [<70 or ≥70 yrs in Japan and <80 or ≥80 yrs elsewhere]) and adjusted for continuous variable age and categorical variables gender and previous stroke.

CI = confidence interval; CRNMBE = clinically relevant nonmajor bleeding event; HR = hazard ratio; ISTH = International Society on Thrombosis and Haemostasis; MBE = major bleeding event; MI = myocardial infarction; RE-DUAL PCI = Randomized Evaluation of Dual Antithrombotic Therapy With Dabigatran Versus Triple Therapy With Warfarin in Patients With Nonvalvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention.

3.0% per year) and the composite of stroke or systemic embolism (diabetes 1.9% vs. no diabetes 1.3% per year) were higher in patients with diabetes (12). In comparison, our data suggest that patients with diabetes treated with oral anticoagulant therapy and 1 or 2 antiplatelet agents do not seem to have an increased risk for bleeding compared with patients without diabetes receiving similar medications.

FIGURE 2 Bleeding Events According to Treatment Group Among Patients With and Those Without Diabetes

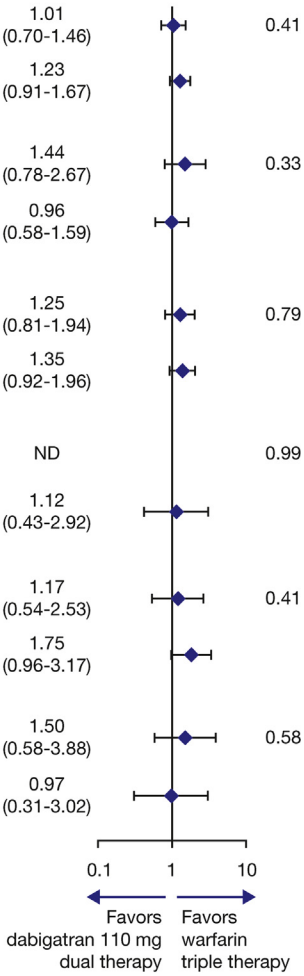


*From Cox proportional hazard model; stratified by age (elderly vs. nonelderly) for dabigatran 110 mg dual therapy versus warfarin triple therapy; unstratified for dabigatran 150 mg dual therapy versus warfarin triple therapy. †For the comparison with dabigatran 150 mg dual therapy, elderly patients outside the United States were excluded. CI = confidence interval; CRNMBE = clinically relevant nonmajor bleeding event; HR = hazard ratio; ISTH = International Society on Thrombosis and Haemostasis; MBE = major bleeding event; ND = not done (at least 1 treatment group has no events, and HR cannot be calculated).

FIGURE 3 Efficacy-Related Events According to Treatment Group Among Patients With and Those Without Diabetes

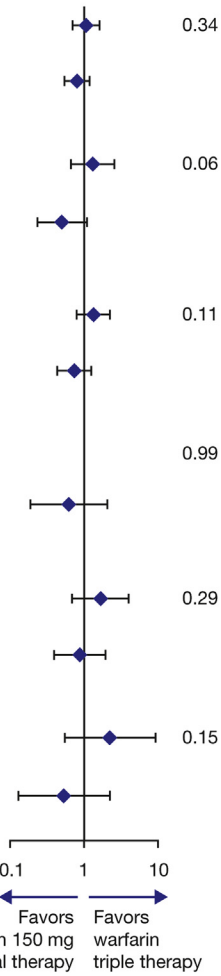
Outcome	n/N (%) Dabigatran 110 mg dual therapy	n/N (%) Warfarin triple therapy†	HR 95% CI*	p interaction
DTE or unplanned revascularization				
With diabetes	57/362 (15.7)	56/371 (15.1)	1.01 (0.70-1.46)	0.41
Without diabetes	92/619 (14.9)	75/609 (12.3)	1.23 (0.91-1.67)	
Death				
With diabetes	25/362 (6.9)	17/371 (4.6)	1.44 (0.78-2.67)	0.33
Without diabetes	30/619 (4.8)	31/609 (5.1)	0.96 (0.58-1.59)	
DTE				
With diabetes	45/362 (12.4)	36/371 (9.7)	1.25 (0.81-1.94)	0.79
Without diabetes	63/619 (10.2)	47/609 (7.7)	1.35 (0.92-1.96)	
Definite stent thrombosis				
With diabetes	6/362 (1.7)	0/371 (0)	ND	0.99
Without diabetes	9/619 (1.5)	8/609 (1.3)	1.12 (0.43-2.92)	
Myocardial infarction				
With diabetes	14/362 (3.9)	12/371 (3.2)	1.17 (0.54-2.53)	0.41
Without diabetes	30/619 (4.8)	17/609 (2.8)	1.75 (0.96-3.17)	
Stroke				
With diabetes	11/362 (3.0)	7/371 (1.9)	1.50 (0.58-3.88)	0.58
Without diabetes	6/619 (1.0)	6/609 (1.0)	0.97 (0.31-3.02)	

HR, 95% CI Dabigatran 110 mg dual therapy vs. warfarin triple therapy



Outcome	n/N (%) Dabigatran 150 mg dual therapy	n/N (%) Warfarin triple therapy†	HR 95% CI*	p interaction
DTE or unplanned revascularization				
With diabetes	43/260 (16.5)	46/303 (15.2)	1.06 (0.70-1.61)	0.34
Without diabetes	47/503 (9.3)	52/460 (11.3)	0.80 (0.54-1.19)	
Death				
With diabetes	19/260 (7.3)	16/303 (5.3)	1.30 (0.67-2.53)	0.06
Without diabetes	11/503 (2.2)	19/460 (4.1)	0.51 (0.24-1.08)	
DTE				
With diabetes	33/260 (12.7)	28/303 (9.2)	1.34 (0.81-2.22)	0.11
Without diabetes	27/503 (5.4)	32/460 (7.0)	0.75 (0.45-1.25)	
Definite stent thrombosis				
With diabetes	2/260 (0.8)	0/303 (0)	ND	0.99
Without diabetes	5/503 (1.0)	7/460 (1.5)	0.64 (0.20-2.02)	
Myocardial infarction				
With diabetes	13/260 (5.0)	9/303 (3.0)	1.67 (0.71-3.90)	0.29
Without diabetes	13/503 (2.6)	13/460 (2.8)	0.89 (0.41-1.92)	
Stroke				
With diabetes	6/260 (2.3)	3/303 (1.0)	2.25 (0.56-9.00)	0.15
Without diabetes	3/503 (0.6)	5/460 (1.1)	0.54 (0.13-2.25)	

HR, 95% CI Dabigatran 150 mg dual therapy vs. warfarin triple therapy

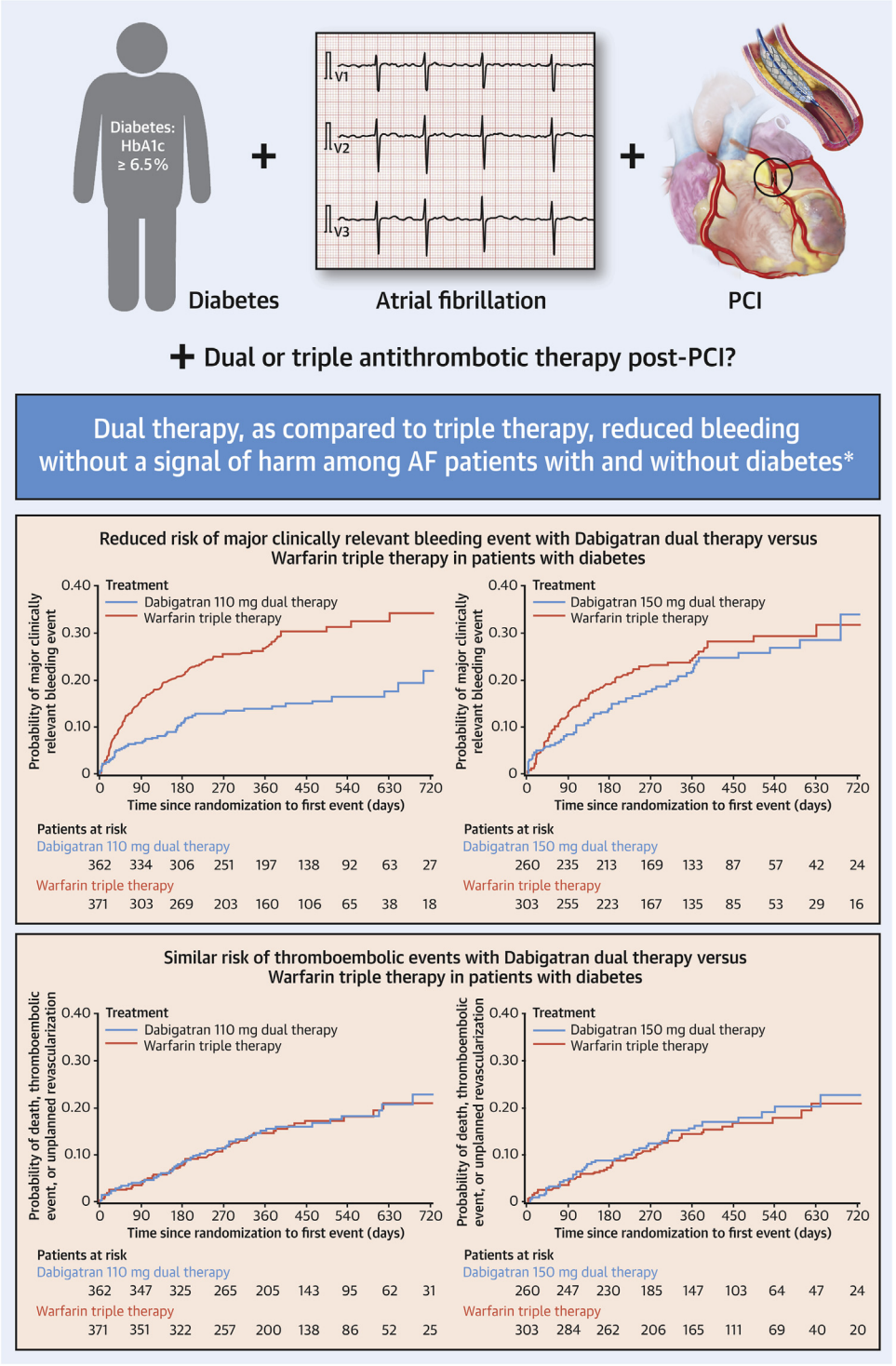


*From Cox proportional hazard model; stratified by age (elderly vs. nonelderly) for dabigatran 110 mg dual therapy versus warfarin triple therapy; unstratified for dabigatran 150 mg dual therapy versus warfarin triple therapy. †For the comparison with dabigatran 150 mg dual therapy, elderly patients outside the United States were excluded. CI = confidence interval; DTE = death or thromboembolic event; HR = hazard ratio.

However, the expected magnitude of treatment effect between patients with and without diabetes in this setting is not known and this may challenge the ability to detect differences.

DABIGATRAN DUAL THERAPY VERSUS WARFARIN TRIPLE THERAPY IN PATIENTS WITH AND THOSE WITHOUT DIABETES. There are relatively few studies on the optimal treatment strategy in patients with AF undergoing PCI, and none of these has looked at outcomes in the diabetes subpopulation. There are currently 5 randomized trials in mixed cohorts, with RE-DUAL PCI being the second largest of those, all showing that dual therapy decreases the risk for bleeding events compared with triple therapy (8,13-17). The latest of these showed elegantly that the reduction of bleeding events with dual therapy with a novel oral anticoagulant agent (apixaban) and clopidogrel was due to both the omission of aspirin and the superiority of the novel oral anticoagulant over

CENTRAL ILLUSTRATION **Outcomes Summary of Dabigatran Dual Therapy Versus Warfarin Triple Therapy Post-PCI in Patients With AF and Diabetes**



Maeng, M. et al. J Am Coll Cardiol Intv. 2019;12(23):2346–55.

*This is subgroup analysis and thus not *a priori* powered for safety or efficacy. AF = atrial fibrillation; PCI = percutaneous coronary intervention.

warfarin (17). In this RE-DUAL PCI substudy, the diabetes cohort consisted of 993 patients; this subgroup alone was thus considerably larger than the approximately 600-patient mixed cohorts included in WOEST (What Is the Optimal Antiplatelet and Anticoagulant Therapy in Patients With Oral Anticoagulation and Coronary Stenting) and ISAR-TRIPLE (Triple Therapy in Patients on Oral Anticoagulation After Drug Eluting Stent Implantation) (13,14). Moreover, this analysis hitherto represents the only subgroup evaluation using data from a randomized clinical trial.

While confirming that dabigatran 110 mg dual therapy reduces bleeding events and by showing comparable outcomes for the main composite efficacy endpoint, this diabetes subgroup analysis confirms the main conclusions reported in the primary RE-DUAL PCI publication. The results are also in accordance with the RE-LY trial, in which the rate of major bleeding was 3.4% per year in the warfarin group, compared with 2.7% per year in the group receiving 110 mg of dabigatran ($p = 0.003$) and 3.1% per year in the group receiving 150 mg of dabigatran ($p = 0.31$) (6). A RE-LY subgroup analysis suggested that concomitant antiplatelet use increased major bleeds by approximately 60% with a single antiplatelet agent, and major bleeds were more than doubled when dual-antiplatelet therapy was used (18). The relative increase in bleeding risk in case of antiplatelet use was similar between the 2 dabigatran doses and warfarin, but the absolute rates of bleeding were lowest in patients treated with dabigatran 110 mg (18). This information is important to tailor the treatment to the individual patient. In 2 recently updated consensus documents from both a European and a North American perspective, it was recommended that when dabigatran is used as part of dual therapy, the 150-mg dose should be used in patients considered to be at higher thrombotic risk, while the 110-mg dose can be considered in elderly patients and those with high bleeding risk (10,19). Our data support this strategy for patients without diabetes. Among those with diabetes, however, dabigatran 110 mg dual therapy seems to reduce bleeding events to a greater extent than dabigatran 150 mg dual therapy compared with warfarin triple therapy, although the interaction p value was >0.05. Thus, because of the limitations of this subgroup analysis (see also the "Study Limitations" section), it is not fully clear if the results from the dabigatran 150 mg dual therapy versus warfarin comparison in the diabetic subgroup indicate a signal or are just a chance finding. Furthermore, the point estimates of the HR suggested comparable risk for the composite efficacy endpoint compared with warfarin triple therapy with the caveat that the RE-DUAL PCI study was not powered for subgroup analyses.

STUDY LIMITATIONS. First, this was a subgroup analysis and consequently was powered neither for statistical comparisons between treatment groups nor for statistical interaction terms. Therefore, this subgroup analysis is generally to be regarded as an exploratory analysis, and observed results serve for signal detection and hypothesis generation. Thus, the absence of a statistically significant interaction between treatment and the diabetes subgroup does not necessarily imply consistency with the results obtained in the overall population. In contrast, no conclusions can be drawn purely on the results from the single subgroup categories.

Second, because of multiple statistical testing, it is possible that nominally statistically significant results may be a play of chance.

Third, intracranial hemorrhage and stent thrombosis were both rare events, and this subgroup analysis, as well as the main study, was not powered for individual endpoints. Nevertheless, we decided to report these events because of their major influence on clinical decision making.

Fourth, patients were randomized within 120 h after successful PCI and received open-label treatment, which according to guidelines included triple therapy and therefore aspirin from PCI to randomization (10,19). Periprocedural aspirin treatment is therefore still recommended.

Finally, our study included predominantly patients of male sex, and the outcomes may differ between men and women.

CONCLUSIONS

Dabigatran dual therapy had a lower risk for bleeding than warfarin triple therapy in patients with AF with or without diabetes following PCI. The point estimates of the HR also suggest a similar risk for the main composite efficacy endpoint, but one must keep in mind that the RE-DUAL PCI study was not powered for this efficacy endpoint in individual dose groups.

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ADDRESS FOR CORRESPONDENCE: Dr. Michael Maeng, Department of Cardiology, Aarhus University Hospital, Palle Juul-Jensens Boulevard 99, 8200 Aarhus N, Denmark. E-mail: michael.maeng@ki.au.dk.

PERSPECTIVES

WHAT IS KNOWN? In the RE-DUAL PCI trial, dual therapy with dabigatran 110 mg or 150 mg plus clopidogrel or ticagrelor was superior for reducing risk for bleeding events compared with triple therapy with warfarin, aspirin, and clopidogrel or ticagrelor while being noninferior regarding ischemic events. Diabetes mellitus is a risk factor for adverse cardiovascular events in patients with AF as well as following coronary stent implantation.

WHAT IS NEW? Following coronary stent implantation in patients with AF, patients with diabetes seem to have a higher risk for DTE but not a higher risk for bleeding compared with patients without diabetes. Consistent with the main RE-DUAL PCI trial results, dual therapy with dabigatran had a lower risk for bleeding and was as efficacious as triple therapy with warfarin in patients with AF with and without diabetes following PCI.

WHAT IS NEXT? These results with dabigatran dual therapy following coronary stent implantation in patients with diabetes should be confirmed by dual therapy with other direct oral anticoagulant agents and with a study sufficiently powered for the investigation of patients with diabetes.

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KEY WORDS dabigatran, percutaneous coronary intervention, RE-DUAL PCI, warfarin