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Comparison of Dabigatran Plus a $P2Y_{12}$ Inhibitor With Warfarin-Based Triple Therapy Across Body Mass Index in RE-DUAL PCI

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ABSTRACT

BACKGROUND: Body mass index (BMI) affects drug levels of nonvitamin K antagonist oral anticoagulants. We sought to assess whether BMI affected outcomes in the RE-DUAL PCI trial.

METHODS: RE-DUAL PCI (NCT02164864) evaluated the safety and efficacy of a dual-antithrombotic-therapy regimen using dabigatran (110 mg or 150 mg twice daily and a $P2Y_{12}$ platelet antagonist) in comparison with triple therapy of warfarin, aspirin, and a $P2Y_{12}$ platelet inhibitor in 2725 patients with atrial fibrillation who had undergone percutaneous coronary intervention (PCI). We compared the risk of first International Society on Thrombosis and Haemostasis (ISTH)-defined major or clinically relevant nonmajor bleeding events (primary endpoint) and the composite of death, myocardial infarction, stroke, systemic embolism, or unplanned revascularization (main efficacy endpoint) in relation to baseline BMI.

RESULTS: Median (range) BMI was 28.1 (14-66) kg/m^2. Dabigatran dual therapy versus warfarin triple therapy had relevantly and similarly lower rates of bleeding at both 110 mg and 150 mg twice-daily doses, irrespective of BMI. Thromboembolic event rates appeared consistent across categories of BMI, including those <25 and ≥35 kg/m^2 (*P* for interaction: 0.806 and 0.279, respectively).

CONCLUSIONS: The reduction in bleeding with dabigatran dual therapy compared with warfarin triple therapy in patients here evaluated appears consistent across BMI categories.

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KEYWORDS: Bleeding; Body mass index (BMI); Dabigatran etexilate; Ischemic event; Nonvitamin K antagonist oral anticoagulants (NOACs)

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INTRODUCTION

The four nonvitamin K antagonist oral anticoagulants (NOACs) currently available for long-term use in atrial fibrillation and venous thromboembolism—dabigatran etexilate (dabigatran), rivaroxaban, apixaban, and edoxaban[1,2]—exert anticoagulant effects related to their plasma concentrations.[3-6] Because the distribution volume of NOACs is related—at least in part—to body weight (and its correlates, including body mass index [BMI]), extremes in BMI or body weight may affect their efficacy or safety.[7-10] Efficacy and safety of NOACs are also affected by concomitant antiplatelet therapy,[11] as in patients having both an indication to anticoagulation because of atrial fibrillation or venous thromboembolism and also requiring coronary stenting.[12-14] Patients are here exposed to a high risk of both thrombotic events for the possible occurrence of stent thrombosis or recurrent acute coronary syndrome and of bleeding due to the antithrombotic drug combination.[14,15] Data on efficacy and safety of the NOACs in such conditions, different from the setting of atrial fibrillation without recent stenting,[16] are limited, and even more so in extremes of BMI.[8]

CLINICAL SIGNIFICANCE

- The current subanalysis of the RE-DUAL PCI study assessed the impact of body mass index (BMI) on the treatment effects of dabigatran dual therapy compared with warfarin triple therapy.
- The benefit of dabigatran dual therapy compared with warfarin triple therapy in patients with atrial fibrillation after percutaneous coronary intervention was consistent regardless of BMI, including patients with low (<25 kg/m^2) and high (≥35 kg/m^2) BMI.

The Randomized Evaluation of Dual Antithrombotic Therapy with Dabigatran versus Triple Therapy with Warfarin in Patients with Nonvalvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention (RE-DUAL PCI) trial was a randomized controlled trial with main objectives of assessing safety and gathering preliminary efficacy data for 2 regimens of dual antithrombotic therapy with dabigatran twice daily (BID) plus a $P2Y_{12}$ inhibitor compared with the standard triple-antithrombotic therapy combination of warfarin plus a $P2Y_{12}$ inhibitor plus aspirin ≤100 mg once daily (warfarin triple therapy) in patients with atrial fibrillation and receiving coronary stenting.[17,18] This trial thus provides a unique opportunity to explore efficacy or safety of dabigatran dual therapy across classes of BMI in conditions with a high risk of thrombotic and bleeding events.

Here we report on the safety and efficacy of the dabigatran dual-therapy regimens examined against warfarin triple therapy in the classes of BMI of patients included in the trial.

METHODS

RE-DUAL PCI Study Population and Design

The RE-DUAL PCI trial design has been previously published.[17] Here men and women ≥18 years of age were eligible for inclusion in the trial if they had atrial fibrillation potentially treatable long-term with one of the NOACs and had successfully undergone PCI in acute coronary syndrome or stable coronary artery disease with a bare-metal or drug-eluting stent implantation within the previous 120 hours. Patients had received standard an antithrombotic treatment for the PCI procedure. After PCI, eligible patients were randomly assigned in a 1:1:1 ratio to receive 1 of 3 treatments: dual therapy with dabigatran 110 mg BID plus either clopidogrel or ticagrelor (dabigatran 110 mg dual-therapy group), dual therapy with dabigatran 150 mg BID plus either clopidogrel or ticagrelor (dabigatran 150 mg dual-therapy group), or triple therapy with warfarin plus aspirin (≤100 mg once daily) and either clopidogrel or ticagrelor (warfarin triple therapy). Patients' follow-up was performed every 3 months. The trial continued until all the patients had a minimum of 6 months of follow-up and the target number of endpoint events was anticipated to be reached.

Endpoints

As in the trial,[17,18] the primary endpoint here was the first major bleeding event or clinically relevant nonmajor bleeding event as defined by the International Society on Thrombosis and Haemostasis (ISTH) criteria in a time-to-event analysis. A main secondary—efficacy—endpoint was a composite of time-to-death or time-to-first thromboembolic event (death and thromboembolic event: myocardial infarction, stroke, or systemic embolism) or unplanned revascularization (PCI or coronary artery bypass grafting). Other secondary endpoints included the combination of death and thromboembolic event alone, as well as individual thromboembolic events and definite stent thrombosis. Clinical endpoint events were adjudicated by an independent committee unaware of treatment assignments.

Clustering of Patients According to BMI

We divided the patient population into 4 prespecified discrete accepted categories of BMI:[19] <25 kg/m^2 body surface area (BSA; normal weight and underweight); 25 to <30 kg/m^2 BSA (overweight); 30 to <35 kg/m^2 BSA (Class I moderate obesity); and ≥35 kg/m^2 BSA (severe obesity). BMI categories were not based on equal numbers of patients per category.

Statistical Analyses

We summarized baseline characteristics descriptively by BMI subgroup. For the comparison of dabigatran 110 mg dual therapy versus warfarin triple therapy within the BMI subgroups, we applied Cox proportional hazard regression models stratified by age (nonelderly vs elderly [<80 years vs ≥80 years; <70 years vs ≥70 years in Japan]). We calculated hazard ratios (HRs) and 2-sided 95% Wald confidence intervals (CIs) for HRs resulting from Cox proportional

hazard models. For the comparison of dabigatran 150 mg dual therapy compared with warfarin triple therapy, we applied unstratified Cox proportional hazard regression models. We provide exploratory treatment-by-subgroup interaction *P* values resulting from Cox proportional hazard regression models.

To further investigate BMI effects on outcomes, we compared the risk of the primary safety endpoint and of the main composite efficacy endpoint with a multivariable Cox proportional hazard regression model that included treatment and BMI as a continuous variable, as well as the interaction between treatment and BMI. The resulting HRs and CIs comparing dabigatran dual therapy with warfarin triple therapy for varying values of BMI were visualized via interaction plots. For the comparison of dabigatran 110 mg versus warfarin triple therapy, we stratified the multivariable model by age.

RESULTS

Patient Distribution According to Classes of BMI

Distributions of patients enrolled in the trial according to classes of BMI are reported in Table 1. Most patients were in the middle categories, with the class of BMI 25 to <30 kg/m^2 BSA being the most represented (n = 677 dabigatran dual-therapy patients). Patient distribution in the extreme classes was clearly skewed toward the overall mean values, but there were extreme values of either very low (16 kg/m^2) or very high (66 kg/m^2) BMI. There were trends to lower age and higher creatinine clearance in classes of higher BMI.

Safety and Efficacy Outcomes According to Classes of BMI

Safety outcomes in terms of the primary safety endpoint by BMI categories are shown in Figure 1.

With regard to the primary safety endpoint, there was no evidence of interaction between BMI and treatment for either 110 mg dabigatran dual therapy versus warfarin triple therapy or 150 mg dabigatran dual therapy versus warfarin triple therapy. In particular, the risk of a major bleeding event or clinically relevant nonmajor bleeding event was similar in the critical category of BMI <25 kg/m^2 (**Figure 1**). The total number of patients in the lowest BMI category was small, and we therefore refrained from any interpretation of data in this category.

Efficacy outcomes according to BMI categories are shown in **Figure 2**. Outcomes for the other secondary efficacy endpoints of death and thromboembolic event, as well as for the one combining the individual thromboembolic events and definite stent thrombosis, are shown in **Tables 2** and **3**.

Table 1 Baseline Characteristics of Patients by BMI Category

Characteristic	BMI Category (kg/m^2)			
	<25 n = 618	25 to <30 n = 1113	30 to <35 n = 664	≥35 n = 326
Age (years)	73.3 ± 8.2	71.3 ± 8.6	69.6 ± 8.4	66.7 ± 8.3
Age ≥80 (years), n (%)	145 (23.5)	176 (15.8)	75 (11.3)	17 (5.2)
Female sex, n (%)	171 (27.7)	235 (21.1)	141 (21.2)	106 (32.5)
Creatinine clearance,[a] mL/min	61.7 ± 19.4	73.2 ± 22.9	87.6 ± 29.4	107.1 ± 39.7
BMI (kg/m^2)	22.9 ± 1.8	27.3 ± 1.4	32.1 ± 1.4	38.9 ± 4.3
Weight, kg	66.0 ± 9.3	80.1 ± 9.7	94.4 ± 11.0	111.2 ± 17.3
Prior MI, n (%)	144 (23.3)	289 (26.0)	180 (27.1)	86 (26.4)
Prior PCI,[b] n (%)	198 (32.0)	373 (33.5)	227 (34.2)	113 (34.7)
Indication for PCI,[b] n (%)				
ACS	331 (53.6)	566 (50.9)	330 (49.7)	146 (44.8)
Elective PCI (non-ACS)	287 (46.4)	546 (49.1)	334 (50.3)	180 (55.2)
Type of atrial fibrillation,[b] n (%)				
Paroxysmal	335 (54.2)	562 (50.5)	310 (46.7)	141 (43.3)
Persistent	119 (19.3)	174 (15.6)	128 (19.3)	63 (19.3)
Permanent	164 (26.5)	376 (33.8)	225 (33.9)	122 (37.4)
Previous stroke,[b] n (%)	55 (8.9)	94 (8.4)	59 (8.9)	18 (5.5)
CHA_2DS_2–VASc score	3.7 ± 1.5	3.6 ± 1.6	3.6 ± 1.6	3.6 ± 1.5
CHA_2DS_2–VASc score >2, n (%)	468 (75.7)	838 (75.3)	497 (74.8)	248 (76.1)
Modified HAS–BLED score	2.7 ± 0.7	2.7 ± 0.7	2.7 ± 0.7	2.6 ± 0.7
Modified HAS–BLED score ≥3, n (%)	409 (66.2)	753 (67.7)	433 (65.2)	184 (56.4)

All values are means ± SD unless stated otherwise.

[a]Data missing from 50 patients in BMI <25 kg/m^2; 89 patients in BMI 25 to <30 kg/m^2; 58 patients in BMI 30 to <35 kg/m^2; 34 patients in BMI ≥35 kg/m^2.

[b]Data missing from 1 patient in BMI 25 to <30 kg/m^2. BMI data were missing from 4 patients.

ACS = acute coronary syndrome; BMI = body mass index; MI = myocardial infarction; PCI = percutaneous coronary intervention; SD = standard deviation.

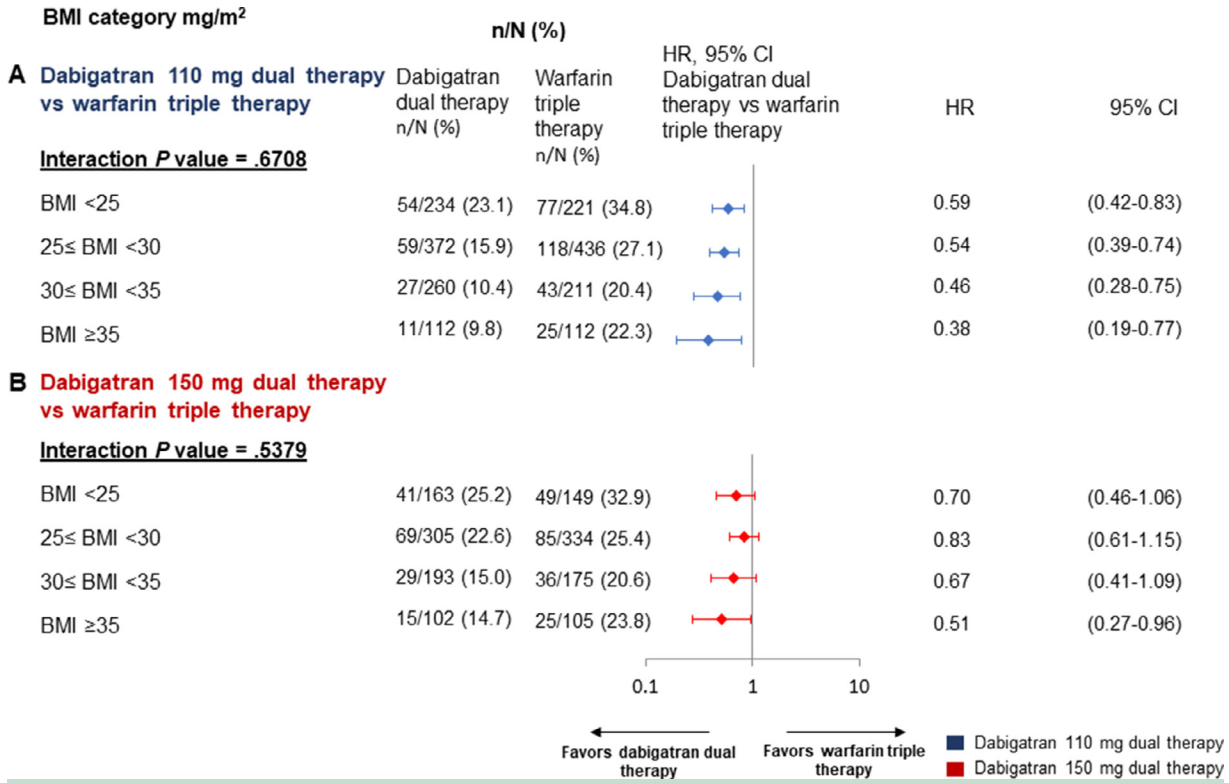

Figure 1 Primary safety endpoint (ISTH MBEs or CRNMBEs according to the study charter definitions) by BMI discrete categories. HRs and 95% CIs from Cox proportional hazard models; **(A)** stratified by age (elderly vs nonelderly) are plotted for the comparison of dabigatran 110-mg dual therapy versus warfarin triple therapy in the upper panel, and **(B)** from unstratified Cox proportional hazard models for the comparison of dabigatran 150-mg dual therapy versus warfarin triple therapy in the lower panel (excluding elderly patients outside the United States ≥80 years of age [≥70 years of age in Japan]).
BMI = body mass index; CI = confidence interval; CRNMBE = clinically relevant nonmajor bleeding event; HR = hazard ratio; ISTH = International Society on Thrombosis and Haemostasis; MBE = major bleeding event.

With regard to the main efficacy endpoint, we found no evidence of interaction between BMI and treatment with either 110 mg dabigatran dual therapy versus warfarin triple therapy or 150 mg dabigatran dual therapy versus warfarin triple therapy.

Safety and Efficacy Outcomes According to BMI Treated as a Continuous Variable

Interaction plots for BMI and primary safety and main efficacy endpoints, displaying the HRs and 95% CIs in the comparison of dabigatran 110 mg dual therapy versus warfarin triple therapy and dabigatran 150 mg dual therapy versus warfarin triple therapy are shown in Figures 3 and 4, respectively. As to the primary safety endpoint, the line of the HR was here always below the warfarin triple therapy reference line throughout all values of BMI for dabigatran 110 mg dual therapy, although with wider CIs for the extreme BMI values (interaction P value = 0.2370), and below the reference line down to approximately 20 kg/m^2, with CIs not overlapping the warfarin triple-therapy reference line down to approximately 25 kg/m^2 for the dabigatran 150 mg dual-therapy dose (interaction P value = 0.1491). As to the main efficacy endpoint, CIs included the warfarin triple-therapy reference line throughout all BMI values for the dabigatran 110 mg dual-therapy dose; and the HR line was below the warfarin triple-therapy reference line for the dabigatran 150 mg dual-therapy dose for most BMI values, suggesting at least consistent efficacy across BMI groups (interaction P values = 0.6578 and 0.3434, respectively).

DISCUSSION

This analysis of RE-DUAL PCI shows that the relative safety and efficacy of dabigatran 150 mg or 110 mg dual therapy compared with warfarin triple therapy are largely preserved in different categories of BMI. These data are quite reassuring for the possible use of the dual-therapy combination in most categories of patients with an indication for anticoagulation because of atrial fibrillation and a recent stenting demanding antiplatelet therapy to prevent stent thrombosis.[14]

Safety and efficacy of the NOACs in lower and higher levels of BMI are, in general, of concern, because of the standard dosing of the NOACs without titration, contrary to

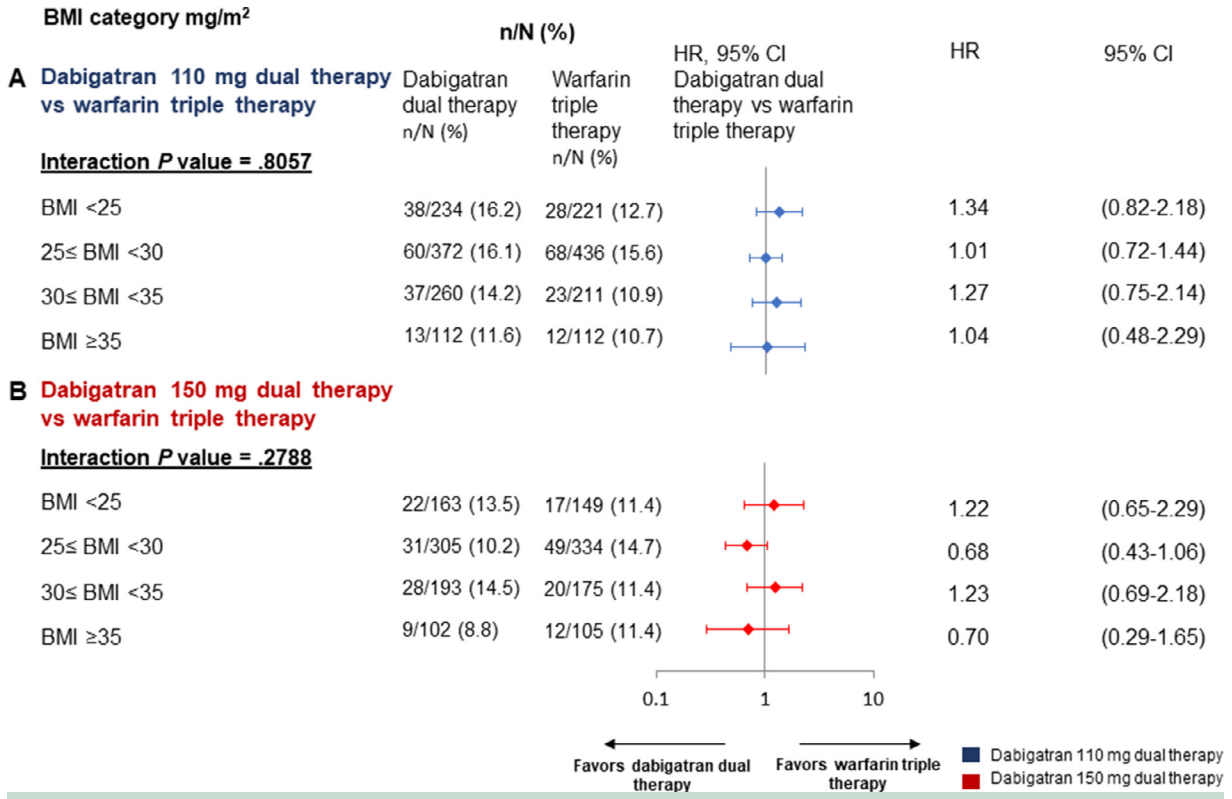

Figure 2 Main efficacy endpoint (DTE or unplanned revascularization according to the study charter definitions) by BMI discrete categories. Thromboembolic events were myocardial infarction, stroke, or systemic embolism (acute vascular occlusion of the extremities or any organ). Unplanned revascularization was percutaneous coronary intervention or coronary artery bypass grafting. Statistics as in Figure 1.
BMI = body mass index; CI = confidence interval; DTE = death and thromboembolic event; HR = hazard ratio.

what occurs in the case of warfarin. This potentially implies excess bleeding in patients with low BMI and lack of efficacy (ie, an excess of thromboembolic events) in patients with high BMI.[8,9] By dividing patient categories according to classes of BMI, we did not find evidence of any significant interactions between BMI subgroup and treatment with regard to any of the evaluated safety or efficacy endpoints. We devoted particular attention to safety (bleeding events) in patients with low to normal BMI (<25 kg/m^2) and to efficacy (thromboembolic events, including stent thrombosis) in patients with very high BMI (≥35 kg/m^2). We found largely similar results when treating BMI as a continuous variable.

In the absence of more robust evidence deriving from much larger—but not forthcoming—trials, the similar occurrence of ischemic events in RE-DUAL PCI (especially with dabigatran 150 mg dual therapy), together with the superior safety on bleeding with dabigatran dual therapy compared with warfarin triple therapy, are strong arguments for preferring a dual-therapy regimen including dabigatran and a P2Y$_{12}$ inhibitor over the classical triple-therapy arm with warfarin, aspirin, and clopidogrel. We now extend these findings in observing consistent results for both safety and efficacy in even lower and higher levels of BMI, with reduced bleeding risk preserved also with BMI <25 kg/m^2; similar efficacy was also shown for a BMI ≥35 kg/m^2 class. This latter patient category also had a higher value of creatinine clearance compared with lower BMI categories. Because dabigatran is largely excreted through the kidneys,[20] one could fear a dangerous decrease in plasma concentrations of the active drug in such patient categories, through a combination of increased distribution volume and higher renal excretion. This was apparently not the case in the light of our data. This would support the possibility of adopting the dual-therapy regimens with dabigatran and a P2Y$_{12}$ inhibitor especially in situations in which bleeding is the major concern, such as low BMI, or where lack of protection from ischemic events is the major concern, such as in the setting of very obese patients. In this latter setting, a dabigatran 150 mg dual-therapy regimen appears a reasonable alternative to warfarin triple therapy.

We have limited data on outcomes in patients with extreme BMIs; therefore, our data cannot change any recommendations on use in those with BMI >40.[8]

DATA-SHARING STATEMENT

To ensure independent interpretation of clinical study results, Boehringer Ingelheim grants all external authors

Table 2 Safety and Efficacy Outcomes According to BMI Categories in the Dabigatran 110-mg Dual Therapy Versus Warfarin Triple Therapy Comparisons

	BMI Category (kg/m^2)							
	<25		25 to <30		30 to <35		≥35	
	Dabigatran 110-mg dual therapy n = 234	Warfarin triple therapy n = 221	Dabigatran 110-mg dual therapy n = 372	Warfarin triple therapy n = 436	Dabigatran 110-mg dual therapy n = 260	Warfarin triple therapy n = 211	Dabigatran 110-mg dual therapy n = 112	Warfarin triple therapy n = 112
Major bleeding event - Clinically relevant nonmajor bleeding								
Events, no. (%)	54 (23.1)	77 (34.8)	59 (15.9)	118 (27.1)	27 (10.4)	43 (20.4)	11 (9.8)	25 (22.3)
HR (95% CI)	0.59 (0.42-0.83)		0.54 (0.39-0.74)		0.46 (0.28-0.75)		0.38 (0.19-0.77)	
Interaction *P* value = 0.6708								
Death and thromboembolic event or unplanned revascularization								
Events, no. (%)	38 (16.2)	28 (12.7)	60 (16.1)	68 (15.6)	37(14.2)	23 (10.9)	13 (11.6)	12 (10.7)
HR (95% CI)	1.34 (0.82-2.18)		1.01 (0.72-1.44)		1.27 (0.75-2.14)		1.04 (0.48-2.29)	
Interaction *P* value = 0.8057								
Death and thromboembolic event								
Events, no. (%)	27 (11.5)	16 (7.2)	43 (11.6)	43 (9.9)	26 (10.0)	14 (6.6)	11 (9.8)	10 (8.9)
HR (95% CI)	1.66 (0.89-3.09)		1.16 (0.76-1.77)		1.50 (0.78-2.87)		1.06 (0.45-2.51)	
Interaction *P* value = 0.7674								
Unplanned revascularization								
Events, no. (%)	21 (9.0)	14 (6.3)	30 (8.1)	37 (8.5)	19 (7.3)	13 (6.2)	6 (5.4)	5 (4.5)
HR (95% CI)	1.45 (0.74-2.87)		0.93 (0.57-1.51)		1.11 (0.55-2.26)		1.14 (0.35-3.75)	
Interaction *P* value = 0.7608								
All-cause death - stroke - MI								
Events, no. (%)	26 (11.1)	16 (7.2)	43 (11.6)	40 (9.2)	26 (10.0)	14 (6.6)	11 (9.8)	10 (8.9)
HR (95% CI)	1.59 (0.85-2.96)		1.25 (0.81-1.93)		1.50 (0.78-2.89)		1.06 (0.45-2.51)	
Interaction *P* value = 0.8739								
MI								
Events, no. (%)	13 (5.6)	6 (2.7)	17 (4.6)	14 (3.2)	10 (3.8)	6 (2.8)	4 (3.6)	3 (2.7)
HR (95% CI)	2.08 (0.79-5.48)		1.41 (0.70-2.87)		1.27 (0.46-3.51)		1.26 (0.28-5.63)	
Interaction *P* value = 0.8996								
Stroke								
Events, no. (%)	3 (1.3)	6 (2.7)	3 (0.8)	5 (1.1)	8 (3.1)	2 (0.9)	2 (1.8)	0
HR (95% CI)	0.49 (0.12-1.95)		0.68 (0.16-2.83)		3.45 (0.73-16.35)		n.d.	
Interaction *P* value = 0.2889								
Definite stent thrombosis								
Events, no. (%)	5 (2.1)	3 (1.4)	5 (1.3)	3 (0.7)	4 (1.5)	1 (0.5)	1 (0.9)	1 (0.9)
HR (95% CI)	1.61 (0.38-6.74)		1.91 (0.46-8.01)		3.44 (0.38-30.91)		0.98 (0.06-15.74)	
Interaction *P* value = 0.9216								

HRs and 95% CIs from Cox proportional hazard models; stratified by age (elderly vs nonelderly). n.d.: at least 1 treatment group has 0 events and HR is not given. BMI data were missing from 4 patients. Interaction *P* value between treatment and subgroup.

BMI = body mass index; CI = confidence interval; HR = hazard ratio; MI = myocardial infarction.

Table 3 Safety and Efficacy Outcomes According to BMI Categories in the Dabigatran 150-mg Dual Therapy Versus Warfarin Triple Therapy Comparisons

	BMI Category (kg/m^2)							
	<25		25 to <30		30 to <35		≥35	
	Dabigatran 150-mg dual therapy n = 163	Warfarin triple therapy n = 149	Dabigatran 150-mg dual therapy n = 305	Warfarin triple therapy n = 334	Dabigatran 150-mg dual therapy n = 193	Warfarin triple therapy n = 175	Dabigatran 150-mg dual therapy n = 102	Warfarin triple therapy n = 105
Major bleeding event - Clinically relevant nonmajor bleeding								
Events, no. (%)	41 (25.2)	49 (32.9)	69 (22.6)	85 (25.4)	29 (15.0)	36 (20.6)	15 (14.7)	25 (23.8)
HR (95% CI)	0.70 (0.46-1.06)		0.83 (0.61-1.15)		0.67 (0.41-1.09)		0.51 (0.27-0.96)	
Interaction *P* value = 0.5379								
Death and thromboembolic event or unplanned revascularization								
Events, no. (%)	22 (13.5)	17 (11.4)	31 (10.2)	49 (14.7)	28 (14.5)	20 (11.4)	9 (8.8)	12 (11.4)
HR (95% CI)	1.22 (0.65-2.29)		0.68 (0.43-1.06)		1.23 (0.69-2.18)		0.70 (0.29-1.65)	
Interaction *P* value = 0.2788								
Death and thromboembolic event								
Events, no. (%)	15 (9.2)	9 (6.0)	19 (6.2)	29 (8.7)	20 (10.4)	12 (6.9)	6 (5.9)	10 (9.5)
HR (95% CI)	1.56 (0.68-3.56)		0.70 (0.39-1.26)		1.47 (0.72-3.00)		0.56 (0.20-1.54)	
Interaction *P* value = 0.1925								
Unplanned revascularization								
Events, no. (%)	12 (7.4)	8 (5.4)	20 (6.6)	27 (8.1)	15 (7.8)	12 (6.9)	4 (3.9)	5 (4.8)
HR (95% CI)	1.43 (0.58-3.50)		0.79 (0.45-1.42)		1.11 (0.52-2.37)		0.75 (0.20-2.78)	
Interaction *P* value = 0.7005								
All-cause death - stroke - MI								
Events, no. (%)	15 (9.2)	9 (6.0)	19 (6.2)	26 (7.8)	20 (10.4)	12 (6.9)	6 (5.9)	10 (9.5)
HR (95% CI)	1.56 (0.68-3.56)		0.79 (0.44-1.43)		1.47 (0.72-3.00)		0.56 (0.20-1-54)	
Interaction *P* value = 0.2623								
MI								
Events, no. (%)	6 (3.7)	4 (2.7)	11 (3.6)	9 (2.7)	7 (3.6)	6 (3.4)	2 (2.0)	3 (2.9)
HR (95% CI)	1.38 (0.39-4.90)		1.32 (0.55-3.18)		1.04 (0.35-3.08)		0.64 (0.11-3.84)	
Interaction *P* value =0 .8912								
Stroke								
Events, no. (%)	2 (1.2)	5 (3.4)	2 (0.7)	2 (0.6)	5 (2.6)	1 (0.6)	0	0
HR (95% CI)	0.38 (0.07-1.96)		1.07 (0.15-7.57)		4.32 (0.50-36.97)		n.d.	
Interaction *P* value = .03620								
Definite stent thrombosis								
Events, no. (%)	1 (0.6)	3 (2.0)	3 (1.0)	2 (0.6)	3 (1.6)	1 (0.6)	0	1 (1.0)
HR (95% CI)	0.30 (0.03-2.90)		1.62 (0.27-9.68)		2.71 (0.28-26.01)		n.d.	
Interaction *P* value = 0.5673								

For the comparison with dabigatran 150-mg dual therapy, elderly patients outside the United States ≥80 years of age (≥70 years of age in Japan) are excluded. HRs and 95% CIs from unstratified Cox proportional hazard models. n.d.: at least 1 treatment group has 0 events and HR is not given. BMI data were missing from 1 patient. Interaction *P* value between treatment and subgroup.

BMI = body mass index; CI = confidence interval; HR = hazard ratio; MI = myocardial infarction.

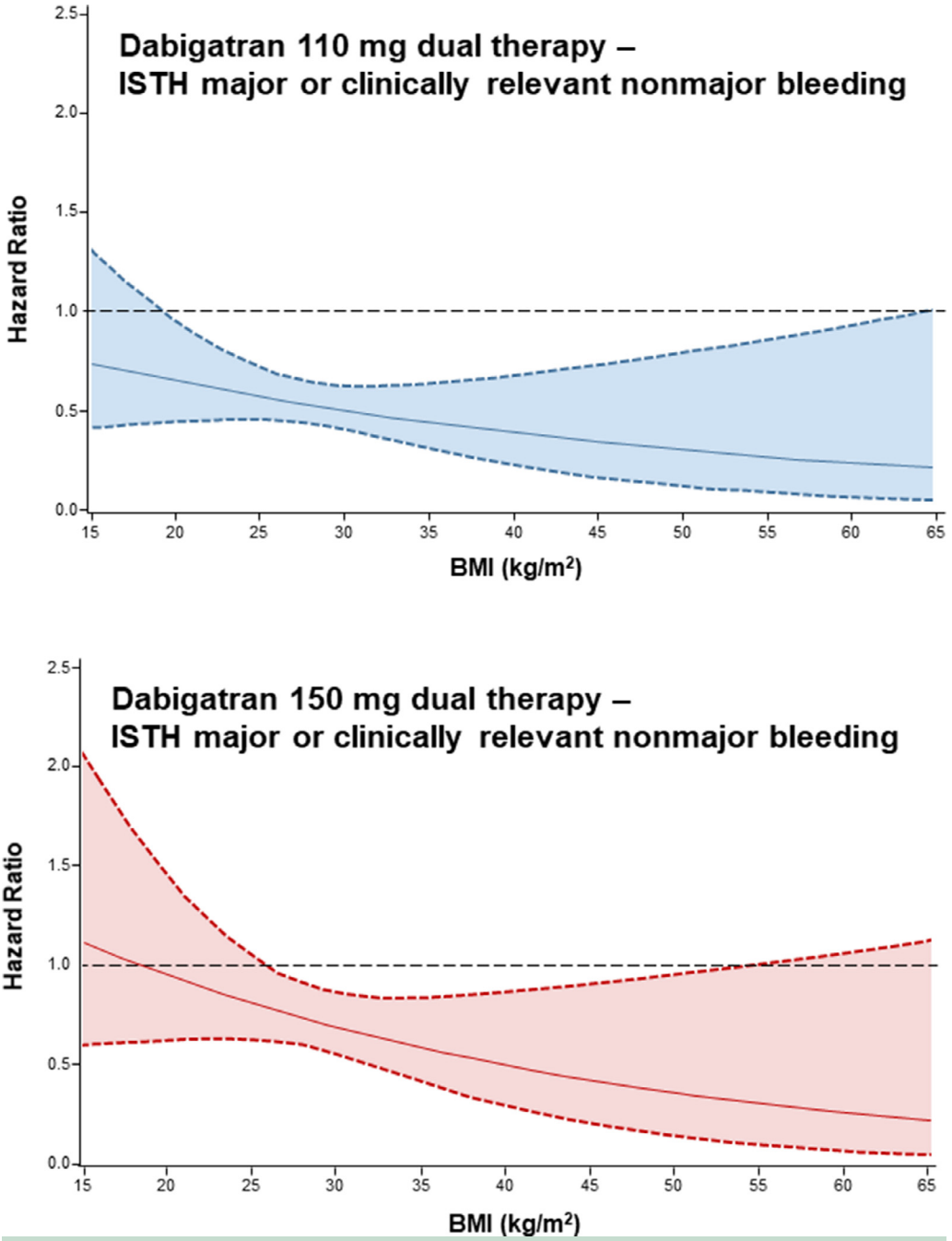

Figure 3 Primary safety endpoint (ISTH MBE and CRNMBE): interaction plot for varying values of BMI as a continuous variable. Interaction plot showing the HRs and corresponding 95% CI comparing the risk of adjudicated MBEs or CRNMBEs (RE-DUAL PCI primary safety endpoint) in patients treated with dabigatran 110 mg twice daily plus the $P2Y_{12}$ inhibitor (dabigatran dual therapy) versus triple antithrombotic therapy with aspirin, the $P2Y_{12}$ inhibitor, and warfarin (warfarin triple therapy) for varying values of BMI. HRs (solid lines) and Wald 95% CIs from stratified Cox proportional hazard model including treatment, continuous variable BMI, and the interaction term of treatment by BMI (upper panel); and comparing dabigatran 150-mg dual therapy versus warfarin triple therapy (lower panel). For the comparison with dabigatran 150-mg dual therapy, elderly patients outside the United States ≥80 years of age (≥70 years of age in Japan) are excluded and HRs and 95% CIs are from an unstratified Cox proportional hazard model (lower panel). For each panel the horizontal dashed line depicts the reference line for a HR of 1.

BMI = body mass index; CI = confidence interval; CRNMBE = clinically relevant nonmajor bleeding event; HR = hazard ratio; ISTH = International Society on Thrombosis and Haemostasis; MBE = major bleeding event; 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.

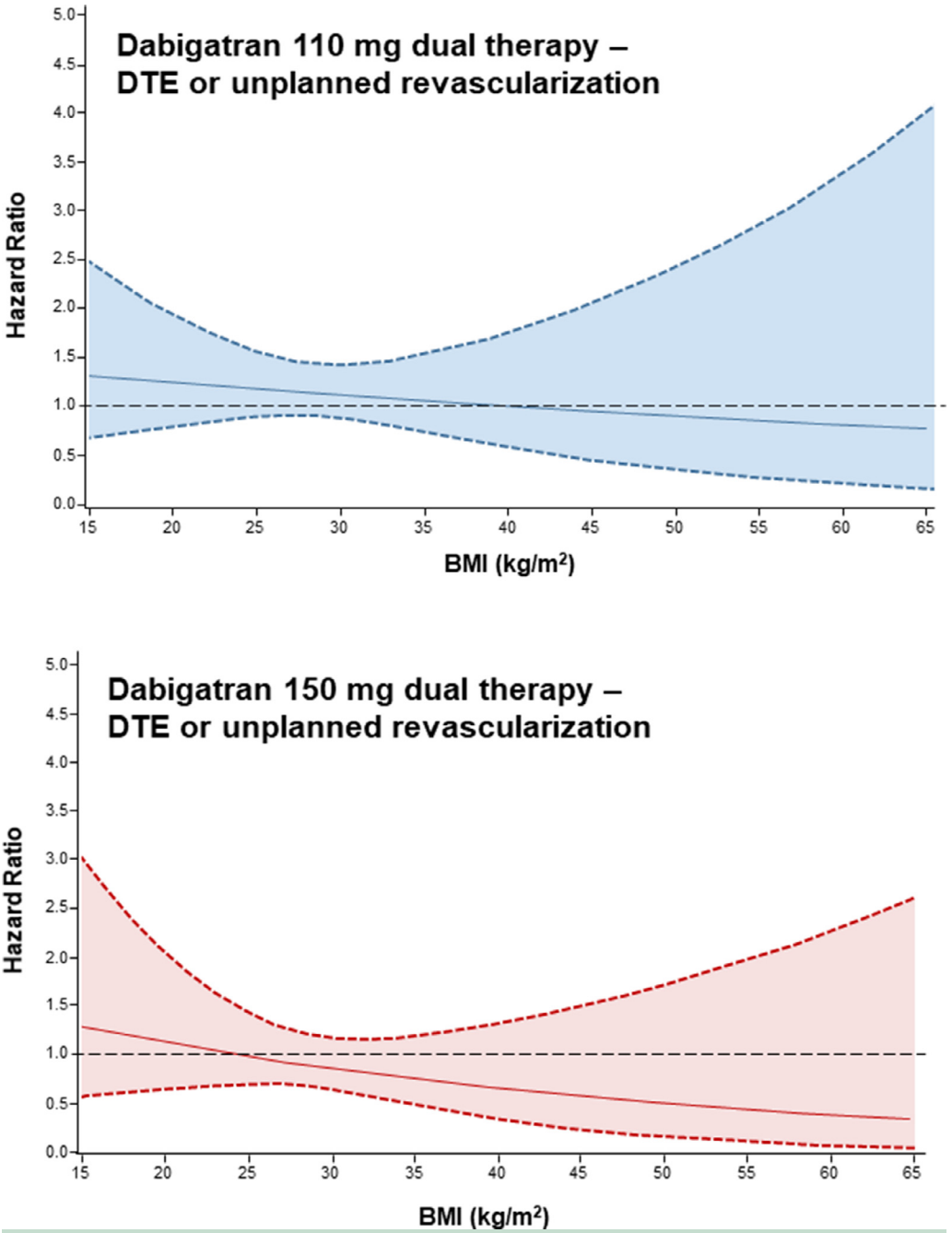

Figure 4 Main efficacy endpoint (DTE and unplanned revascularization): interaction plot for varying values of BMI as a continuous variable. Interaction plot showing the HRs and corresponding 95% CI comparing the risk of adjudicated death and thrombotic events/unplanned revascularization (REDUAL PCI main efficacy endpoint) in patients treated with dabigatran 110 mg twice daily plus the $P2Y_{12}$ inhibitor (dabigatran dual therapy) versus triple antithrombotic therapy with aspirin, the $P2Y_{12}$ inhibitor and warfarin (warfarin triple therapy) for varying values of BMI. HRs (solid lines) and Wald 95% CIs from stratified Cox proportional hazard model including treatment, continuous variable BMI, and the interaction term of treatment by BMI (upper panel); and comparing dabigatran 150-mg dual therapy versus warfarin triple therapy (lower panel). For the comparison with dabigatran 150-mg dual therapy, elderly patients outside the United States ≥80 years of age (≥70 years of age in Japan) are excluded, and HRs and 95% CIs are from an unstratified Cox proportional hazard model (lower panel). For each panel the horizontal dashed line depicts the reference line for a HR of 1.

BMI = body mass index; CI = confidence interval; DTE = death and thromboembolic event; HR = hazard ratio; 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.

access to all relevant material, including participant-level clinical study data, and relevant material as needed by them to fulfill their role and obligations as authors under the ICMJE criteria.

Furthermore, clinical study documents (e.g. study report, study protocol, statistical analysis plan) and participant clinical study data are available to be shared after publication of the primary manuscript in a peer-reviewed journal and if regulatory activities are complete and other criteria met per the BI Policy on Transparency and Publication of Clinical Study Data: https://trials.boehringer-ingelheim.com/

Prior to providing access, documents will be examined, and, if necessary, redacted and the data will be de-identified, to protect the personal data of study participants and personnel, and to respect the boundaries of the informed consent of the study participants.

Clinical Study Reports and Related Clinical Documents can be requested via this link: https://trials.boehringer-ingelheim.com/

All such requests will be governed by a Document Sharing Agreement.

Bona fide, qualified scientific and medical researchers may request access to de-identified, analyzable participant clinical study data with corresponding documentation describing the structure and content of the datasets. Upon approval, and governed by a Data Sharing Agreement, data are shared in a secured data-access system for a limited period of 1 year, which may be extended upon request.

Researchers should use https://trials.boehringer-ingelheim.com/ to request access to study data.

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