

RE-DUAL PCI: dual antithrombotic therapy with dabigatran after percutaneous coronary intervention in patients with atrial fibrillation

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Antithrombotic therapy for atrial fibrillation and PCI



Anticoagulant therapy

Low shear stress thrombosis in left atrium

Anticoagulation superior to antiplatelet therapy



Antiplatelet therapy

High shear stress thrombosis – platelet mediated in the arteries

Dual antiplatelet therapy superior to ASA alone



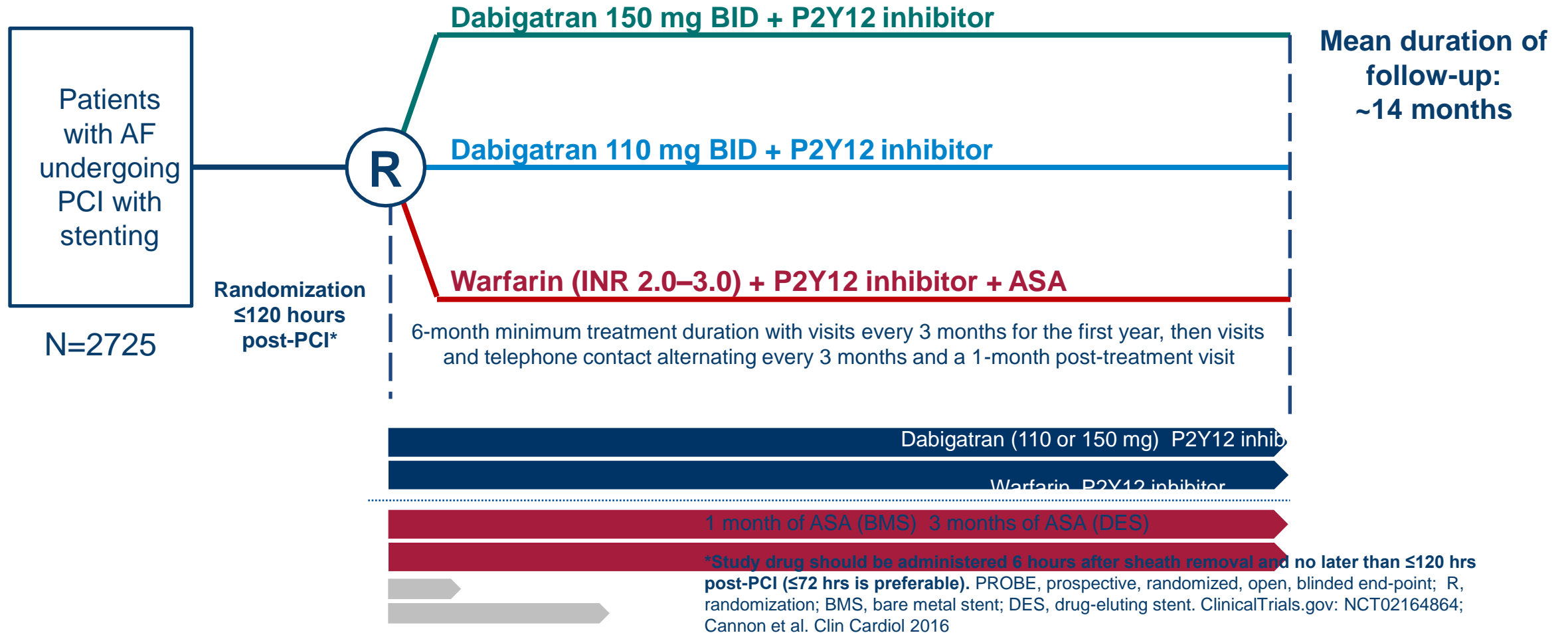
BOTH anticoagulant and dual antiplatelet therapy =

'triple therapy'

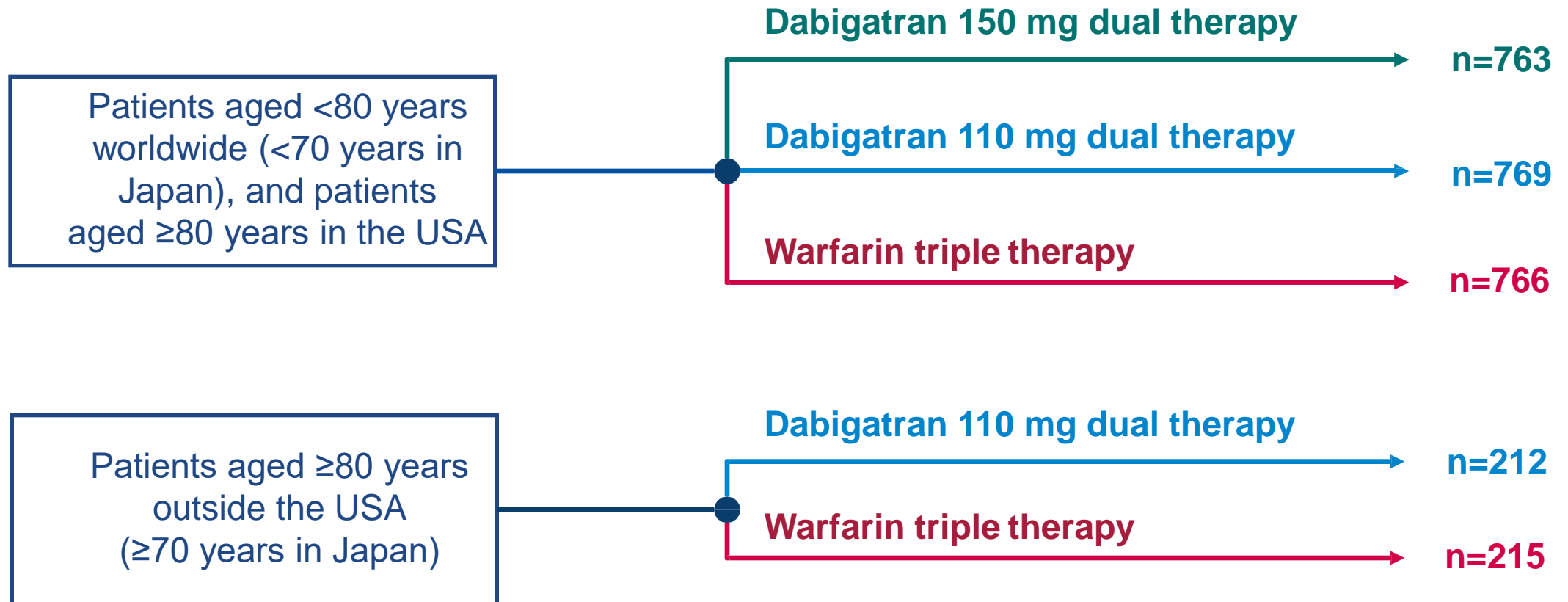
High bleeding risk



Study Design: Multicenter, randomized, open-label trial following a PROBE design



Patients were randomized based on age group and location



Inclusion and exclusion criteria

Key inclusion criteria

- Patients aged ≥ 18 years with paroxysmal, persistent or permanent NVAF
- ACS successfully treated by PCI and stenting (BMS or DES)
- Stable CAD with ≥ 1 lesion eligible for PCI that was successfully treated by elective PCI and stenting (BMS or DES)

Key exclusion criteria

- Cardiogenic shock during current hospitalization
- Use of fibrinolytics within 24 hrs of randomization that, in the investigator's opinion, will put patient at high risk of bleeding
- Stroke or major bleeding event within 1 month prior to screening visit
- Severe renal impairment (CrCl < 30 mL/min)

Study objective and design

RE-DUAL PCI tests the safety and efficacy of two regimens of dual therapy with dabigatran without aspirin vs triple therapy with warfarin

- The primary endpoint was time to first ISTH major or clinically relevant non-major bleeding
- Formally tested and powered endpoints included:
 - Non-inferiority of 110 mg and 150 mg dual therapy groups on time to first ISTH major or clinically relevant non-major bleeding event.
 - Non-inferiority of both dual therapy groups combined on time to first event of death, thromboembolic event (MI, stroke, systemic embolism) or unplanned revascularization
 - Superiority testing of the bleeding endpoints
- 100% of outcome events were independently adjudicated by blinded external committee

Summary of patient disposition

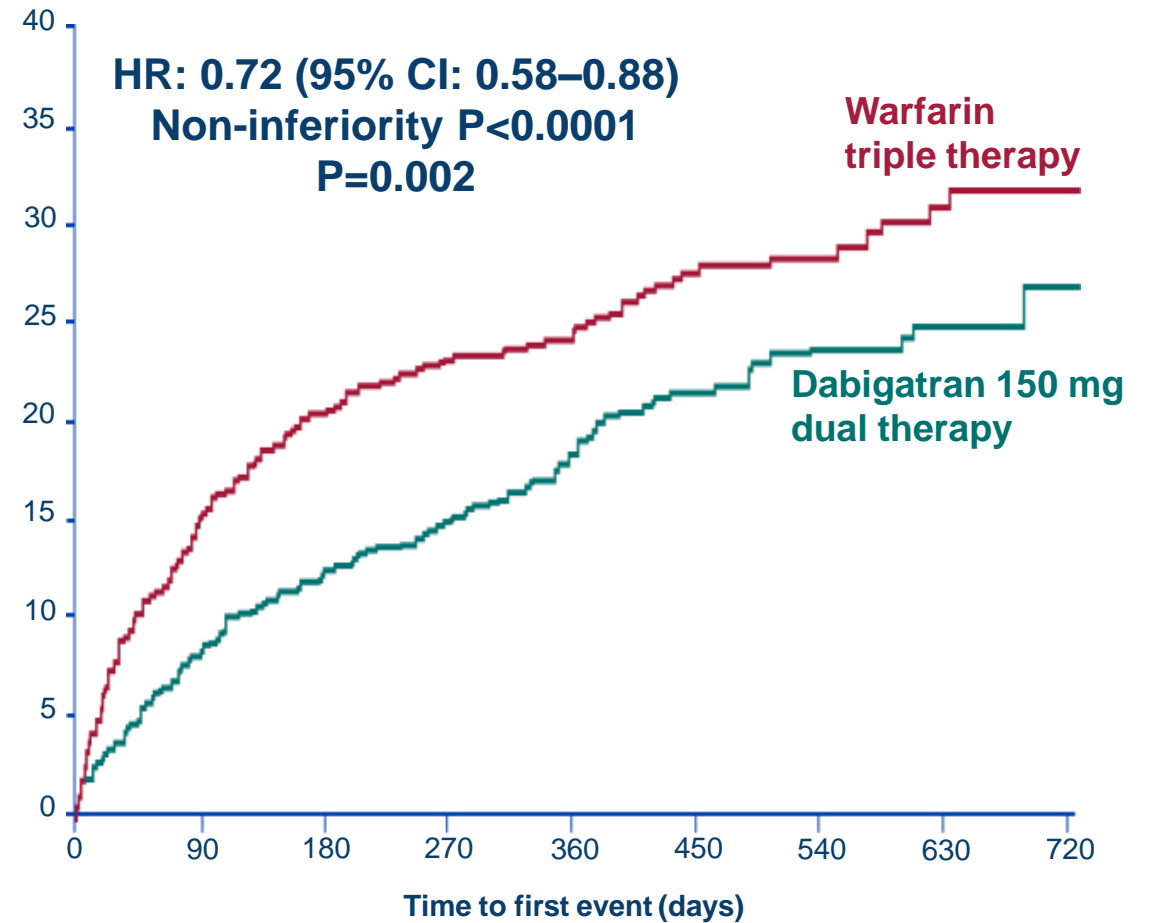
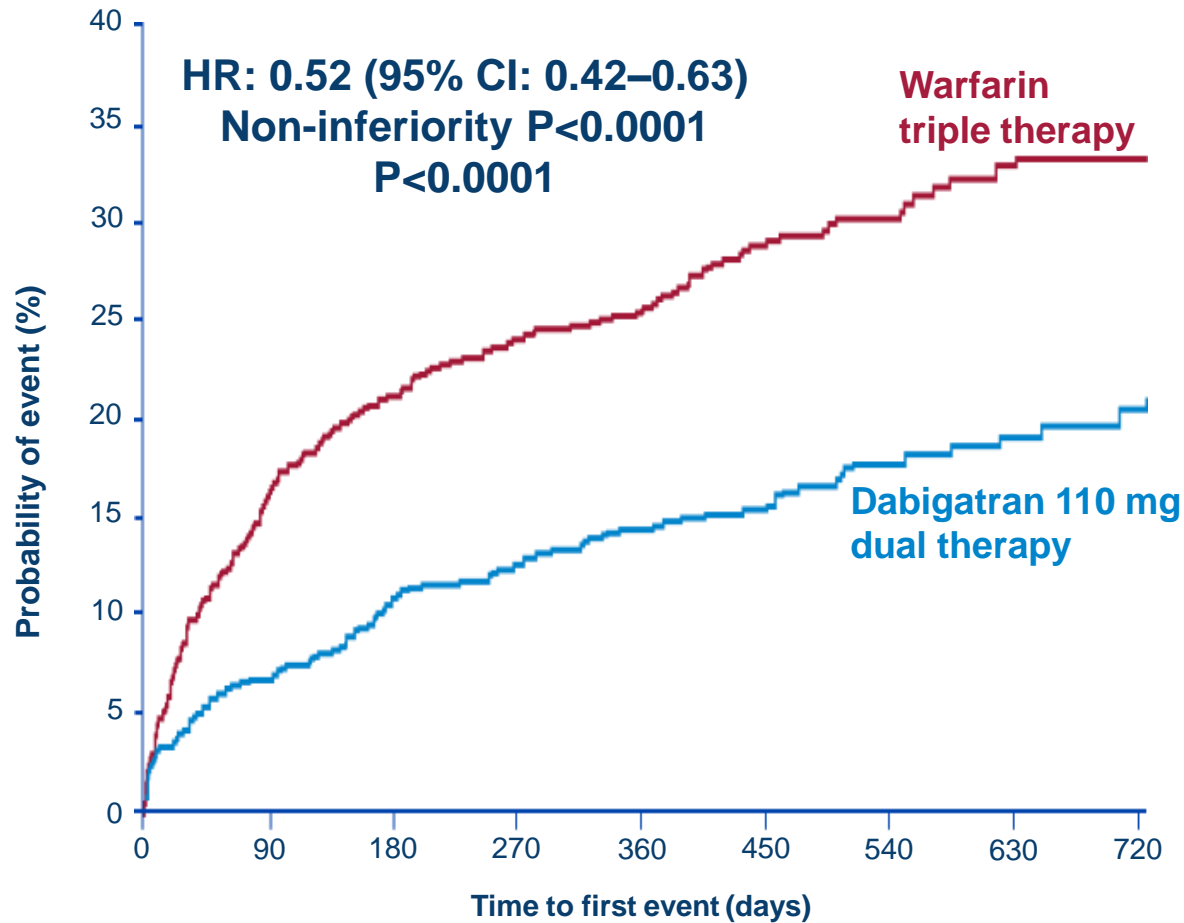
	Dabigatran 110 mg dual therapy	Dabigatran 150 mg dual therapy	Warfarin triple therapy
Randomized patients, n	981	763	981
Patients completing study			
on study medication	756	604	686
with premature medication discontinuation	130	99	163
Premature study discontinuation	95	60	132
Adverse event	65	41	59
Protocol violation	2	4	1
Loss to follow-up	4	3	2
Consent withdrawn	21	8	56
Missing/other	3	4	14
Mean duration of follow-up, months	14.1	14.3	13.8
Total patient-years	1013	803	933
Time in target INR range 2.0–3.0,* mean	n/a	n/a	64%

*First valid INR measurement is defined as the first on-treatment INR measurement taken >90 days after randomization. At each specified time point, patients who had INR data up to that time point were evaluated and all valid INR data up to that time point were used. The target INR range was 2–3; an exception were patients in Japan who were ≥70 years old – for these patients, the target INR was 2–2.6. 58 patients had no valid INR measurement throughout the trial and are therefore excluded from the display

Baseline characteristics

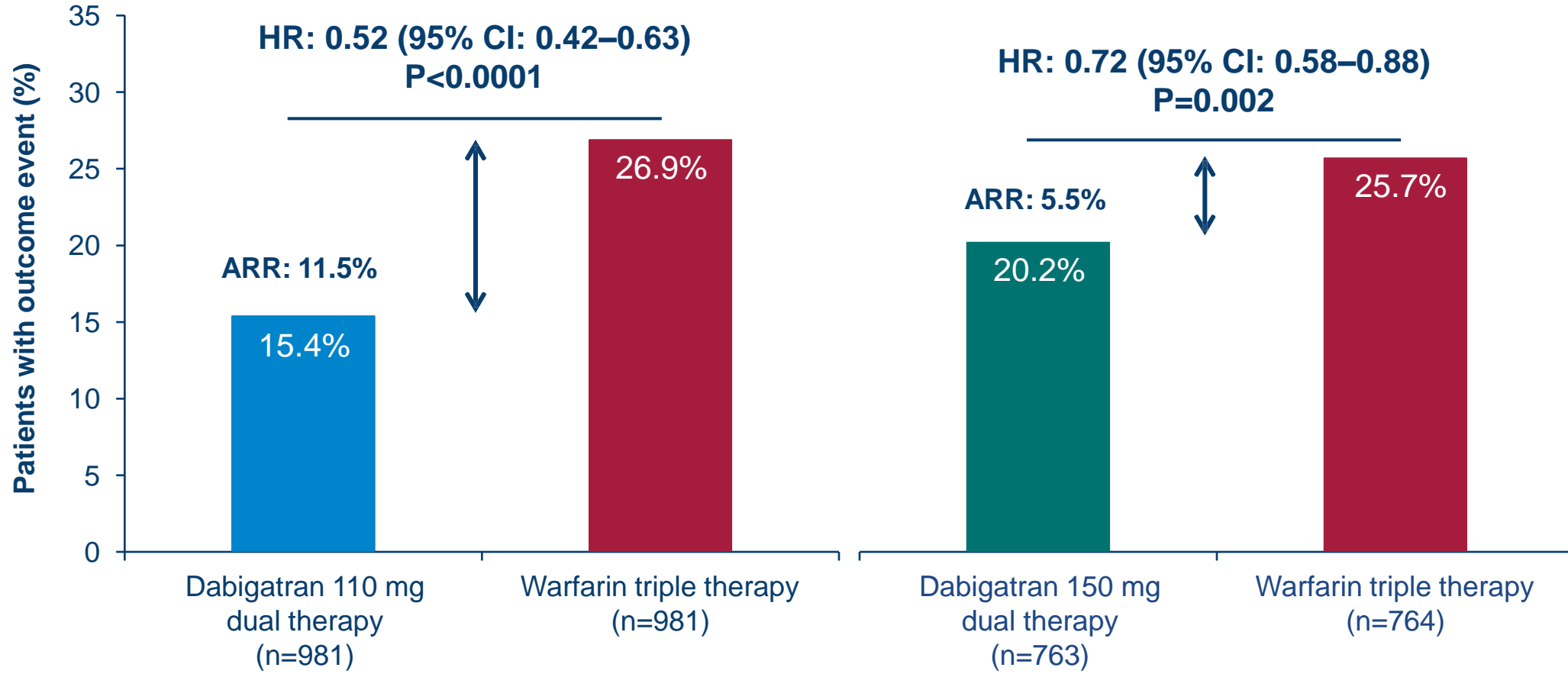
	Dabigatran 110 mg dual therapy (n=981)	Warfarin triple therapy (n=981)	Dabigatran 150 mg dual therapy (n=763)	Corresponding Warfarin triple therapy (n=764)
Age, years, mean	71.5	71.7	68.6	68.8
≥80 (US, ROW), ≥70 (Japan), %	22.9	22.9	1.0	1.0
<80 (US, ROW), <70 (Japan), %	77.1	77.1	99.0	99.0
Male, %	74.2	76.5	77.6	77.7
Baseline CrCl, mL/min, mean	76.3	75.4	83.7	81.3
Diabetes mellitus, %	36.9	37.8	34.1	39.7
CHA₂DS₂-VASc score (mean)	3.7	3.8	3.3	3.6
Modified HAS-BLED score at baseline (mean)	2.7	2.8	2.6	2.7
ACS indication for PCI, %	51.9	48.4	51.2	48.3
DES only, %	82.0	84.2	81.4	83.5

Primary Endpoint: Time to first ISTH major or clinically relevant non-major bleeding event

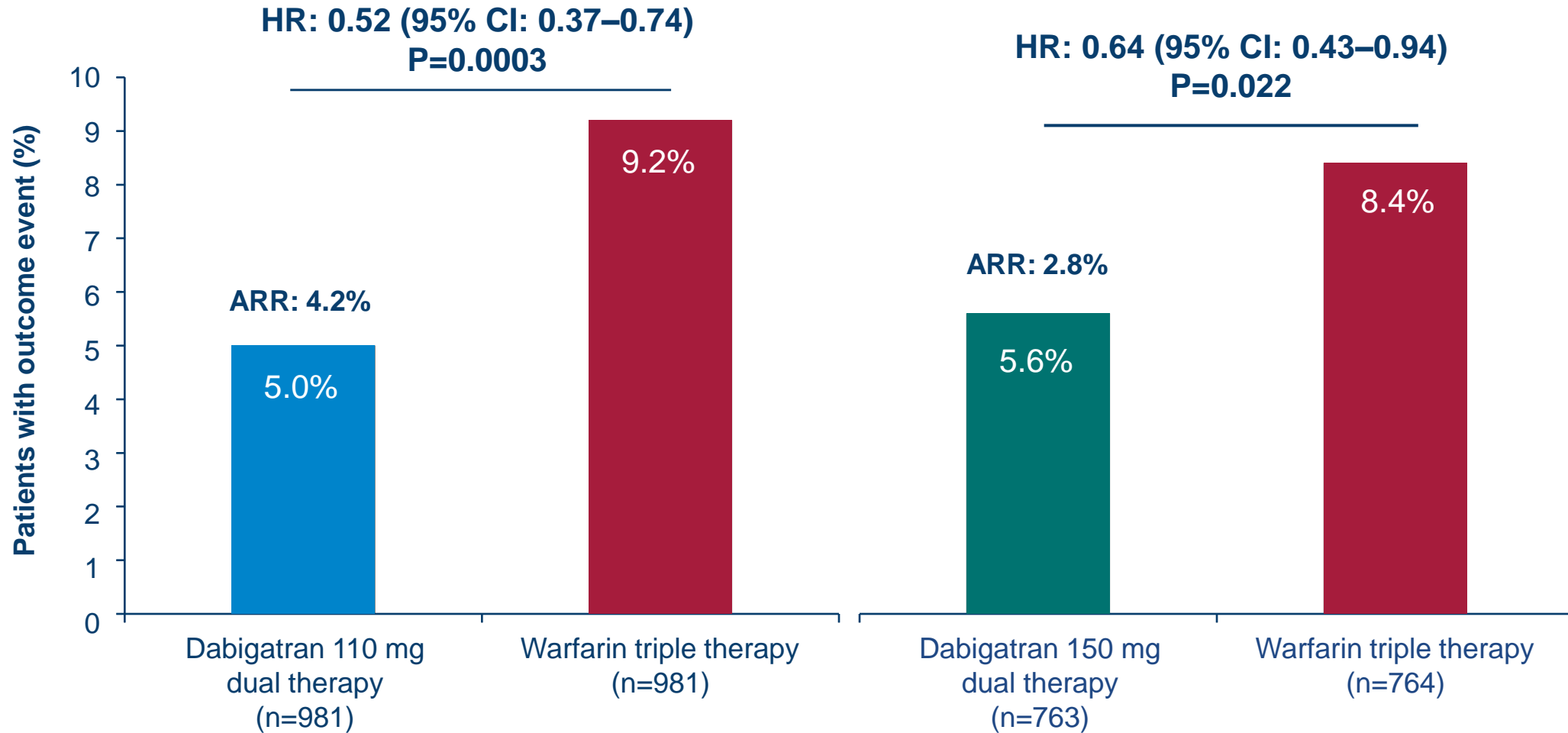


Full analysis set presented. HRs and Wald CIs from Cox proportional-hazard model. For the dabigatran 110 mg vs warfarin comparison, the model is stratified by age, non-elderly vs elderly (<70 or ≥70 in Japan and <80 or ≥80 years old elsewhere). For the dabigatran 150 mg vs warfarin comparison, an unstratified model is used, elderly patients outside the USA are excluded. Non-inferiority P value is one sided (alpha=0.025). Wald two-sided P value from (stratified) Cox proportional-hazard model (alpha=0.05)

Primary endpoint: ISTH major or clinically relevant non-major bleeding event

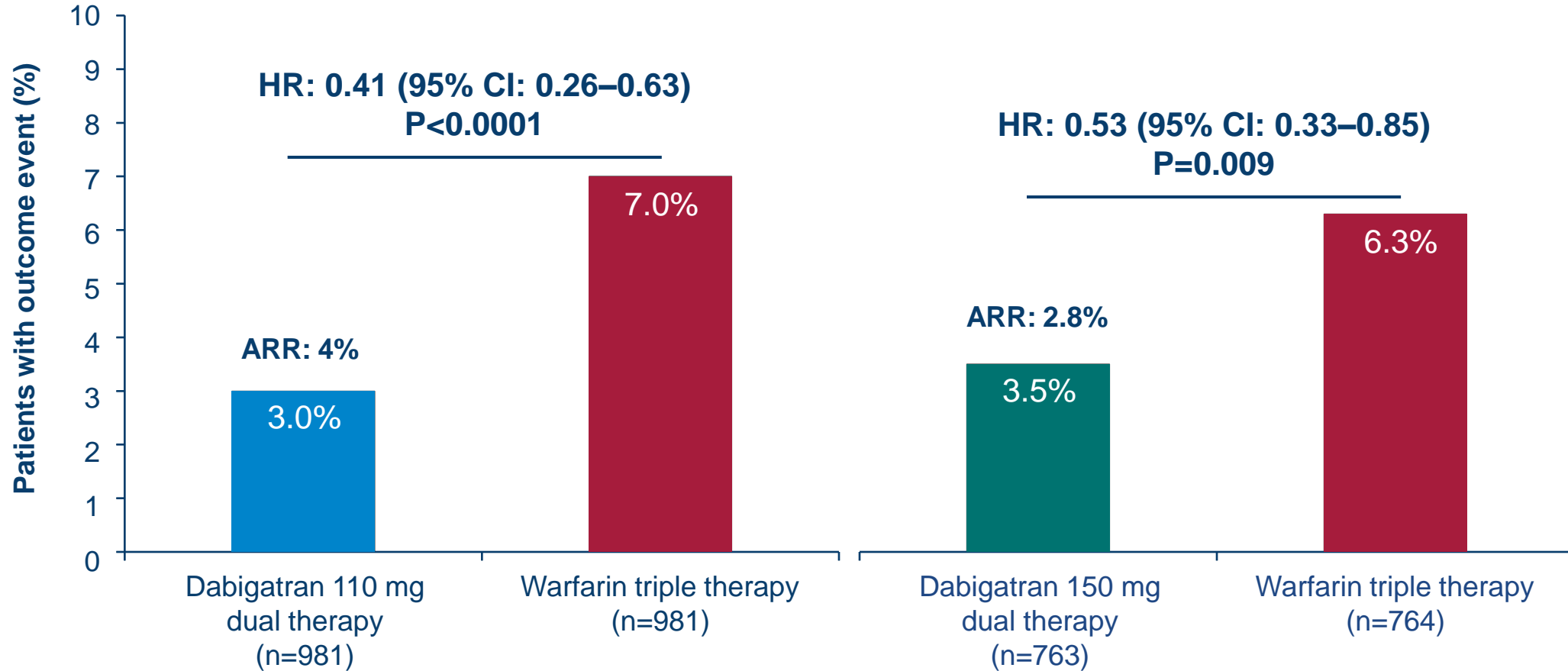


Rates of ISTH major bleeding



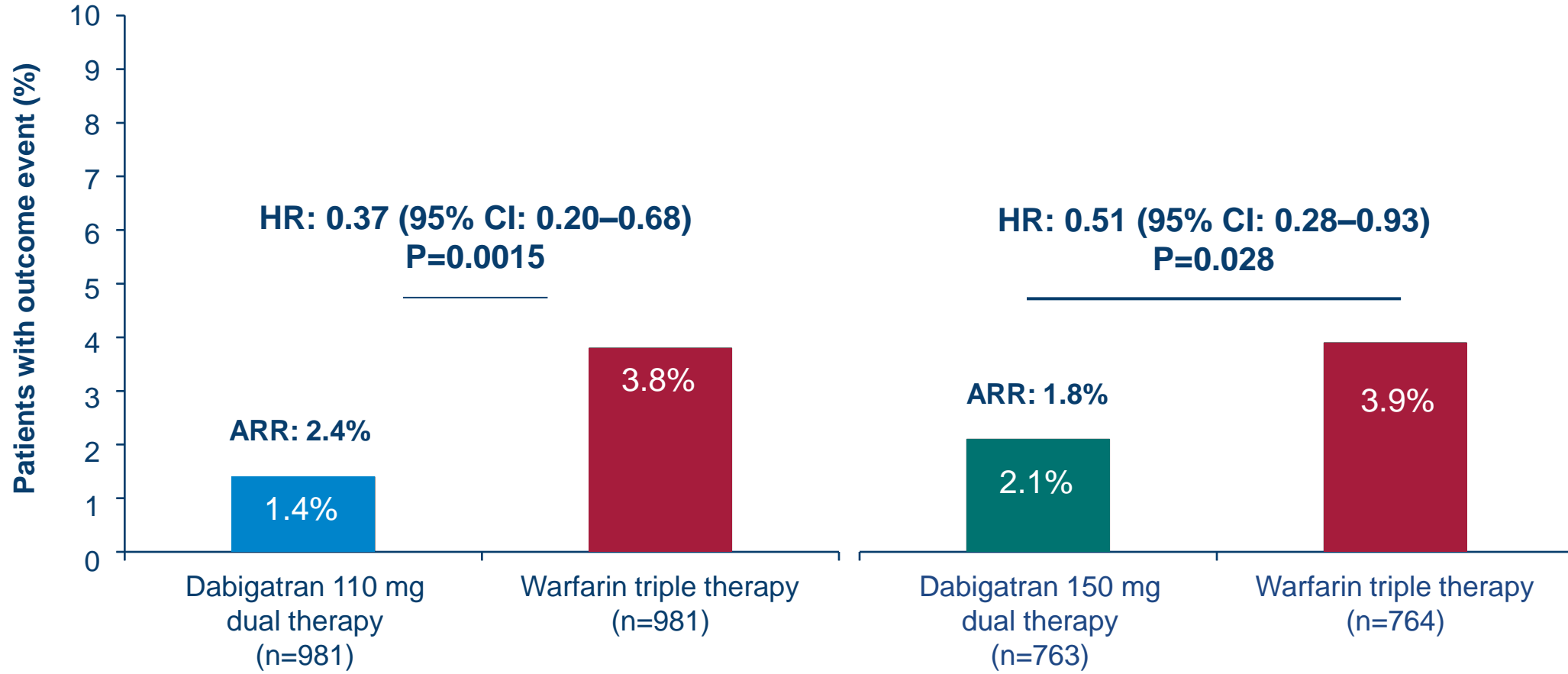
Wald two-sided P value from (stratified) Cox proportional-hazard model (alpha=0.05). ISTH major bleeding definition: fatal, critical organ (including intracranial haemorrhage), clinically overt bleeding with fall in Hb ≥ 2 g/dL. Hb, haemoglobin

Rates of TIMI major or minor bleeding



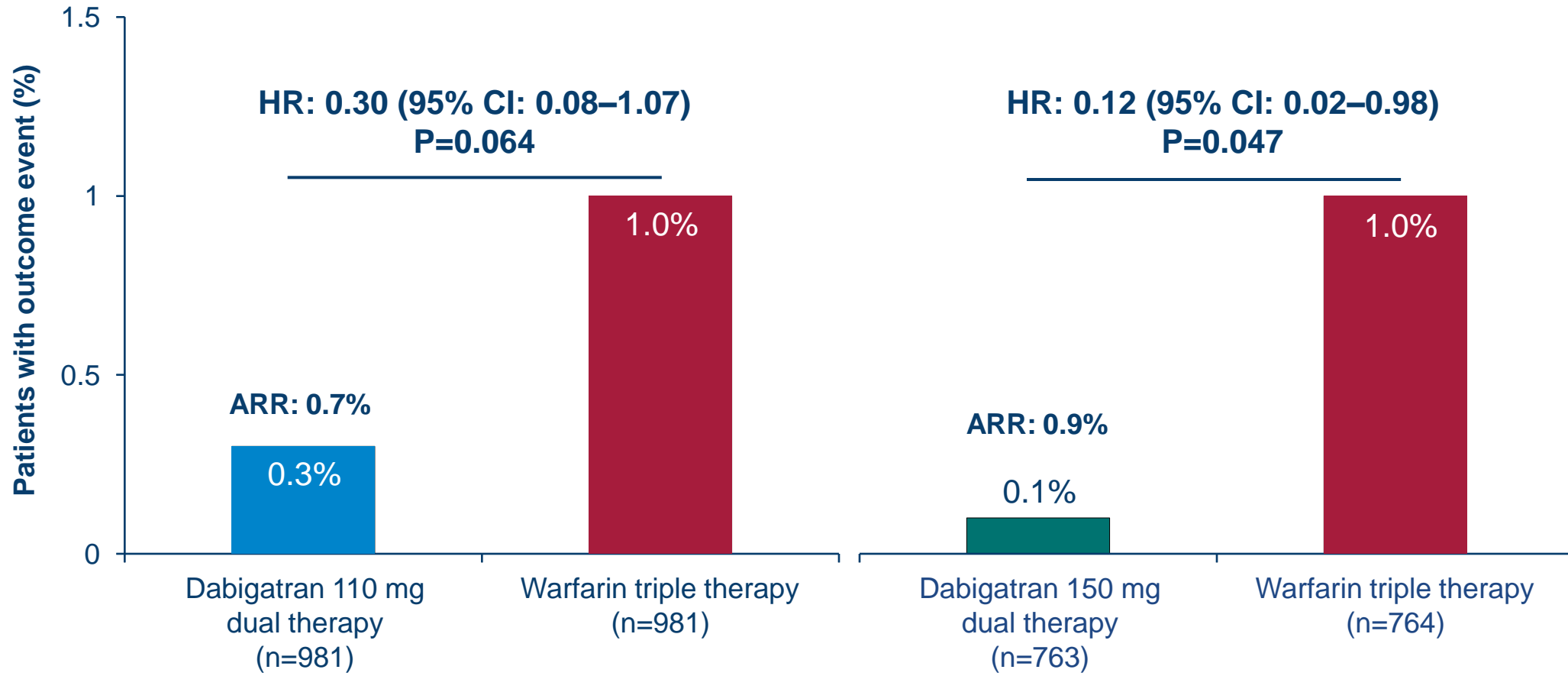
Wald two-sided P value from (stratified) Cox proportional-hazard model (alpha=0.05). TIMI major bleeding definition: fatal, intracranial haemorrhage, clinically overt bleeding with fall in Hb ≥ 5 g/dL; TIMI minor bleeding definition: clinically overt bleeding (including imaging), resulting in Hb drop of 3 to >5 g/dL. TIMI, thrombolysis in myocardial infarction

Rates of TIMI major bleeding

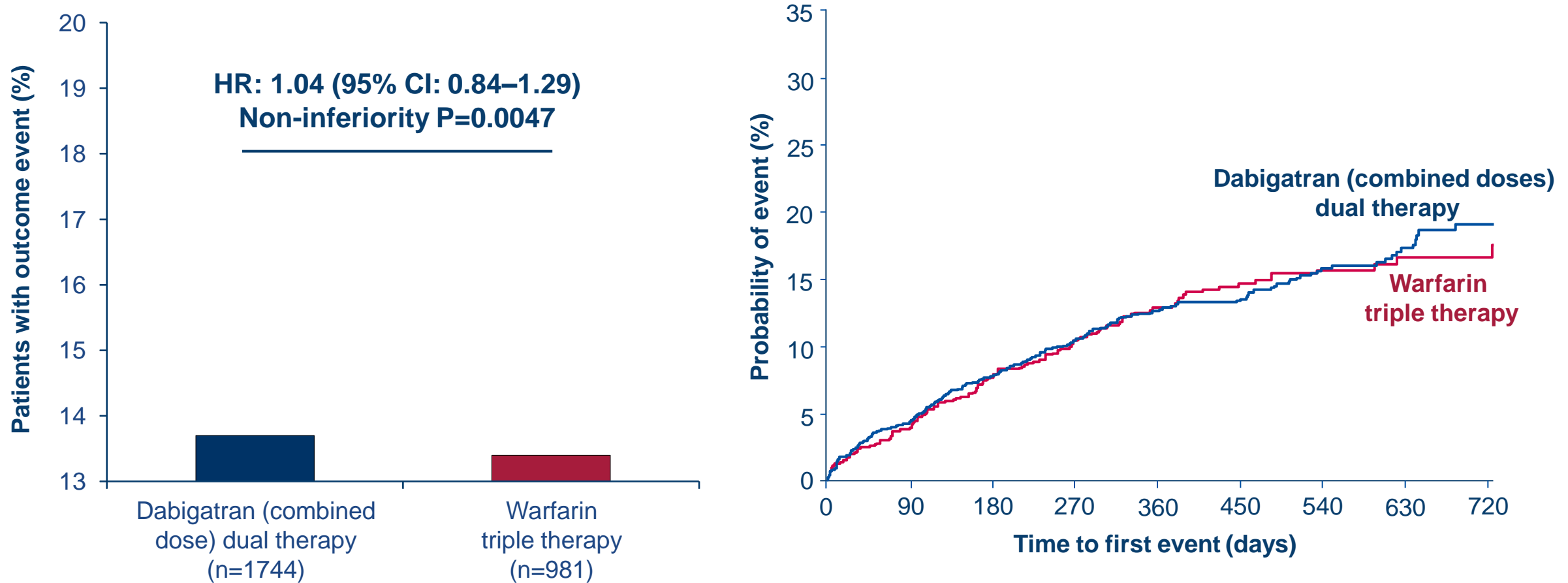


Wald two-sided P value from (stratified) Cox proportional-hazard model (alpha=0.05). TIMI major bleeding definition: fatal, intracranial haemorrhage, clinically overt bleeding with fall in Hb \geq 5 g/dL.

Rate of intracranial haemorrhage



Time to death or thromboembolic event, or unplanned revascularization



Non-inferiority P value is one sided (alpha=0.025). Results presented are Step 3 of hierarchical testing procedure, testing non-inferiority of dabigatran dual therapy (combined doses) to warfarin triple therapy in death or thromboembolic event and unplanned revascularization

Additional individual thromboembolic endpoints

	Dual therapy	Warfarin triple therapy (n=981)	D110 DT vs warfarin TT		Dabigatran 150 mg dual therapy (n=763)	Warfarin triple therapy (n=764)	D150 DT vs warfarin TT	
	n (%)	n (%)	HR (95% CI)	P value	n (%)	n (%)	HR (95% CI)	P value
All-cause death	55 (5.6)	48 (4.9)	1.12 (0.76–1.65)	0.56	30 (3.9)	35 (4.6)	0.83 (0.51–1.34)	0.44
Stroke	17 (1.7)	13 (1.3)	1.30 (0.63–2.67)	0.48	9 (1.2)	8 (1.0)	1.09 (0.42–2.83)	0.85
Unplanned revascularization	76 (7.7)	69 (7.0)	1.09 (0.79–1.51)	0.61	51 (6.7)	52 (6.8)	0.96 (0.65–1.41)	0.83
MI	44 (4.5)	29 (3.0)	1.51 (0.94–2.41)	0.09	26 (3.4)	22 (2.9)	1.16 (0.66–2.04)	0.61
Stent thrombosis	15 (1.5)	8 (0.8)	1.86 (0.79–4.40)	0.15	7 (0.9)	7 (0.9)	0.99 (0.35–2.81)	0.98

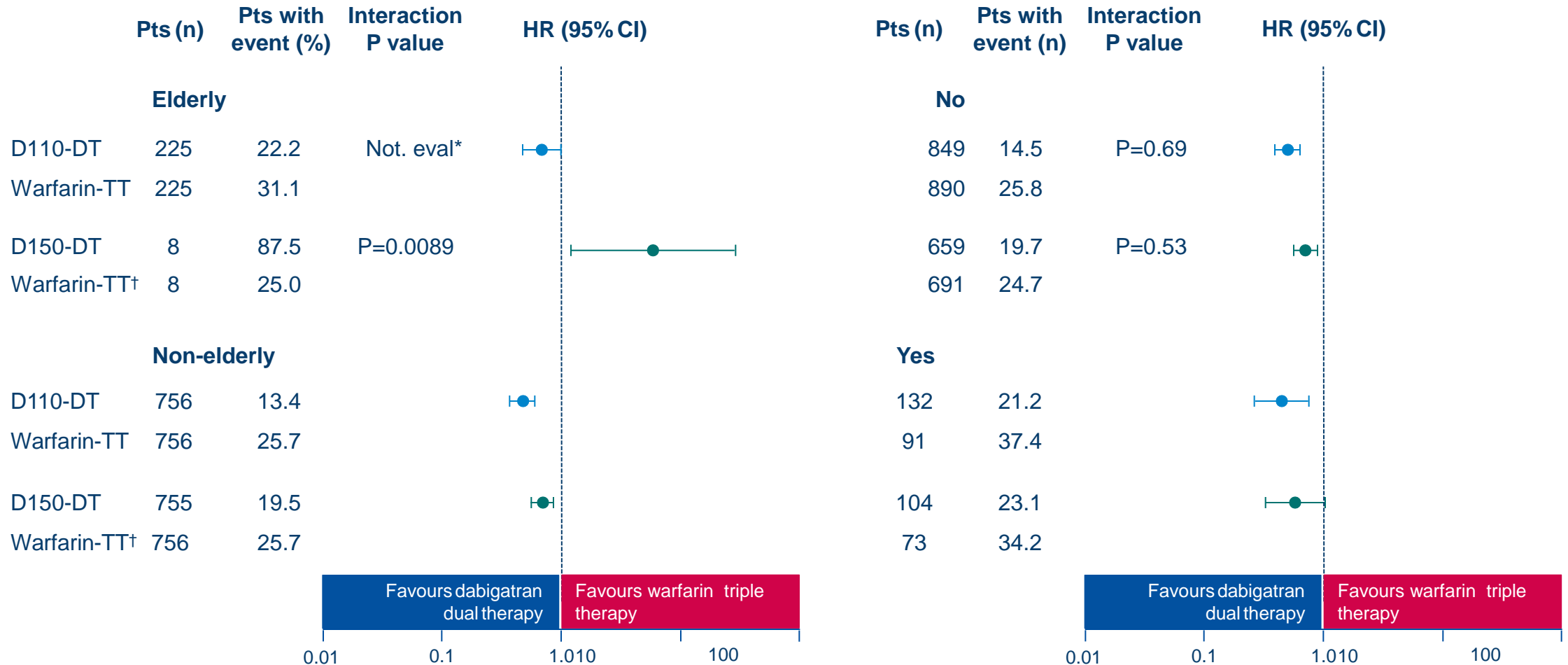
Subgroup analysis: age and ticagrelor use at baseline

Time to first ISTH MBE or CRNMBE



Age

Ticagrelor use at baseline (12% Pts)

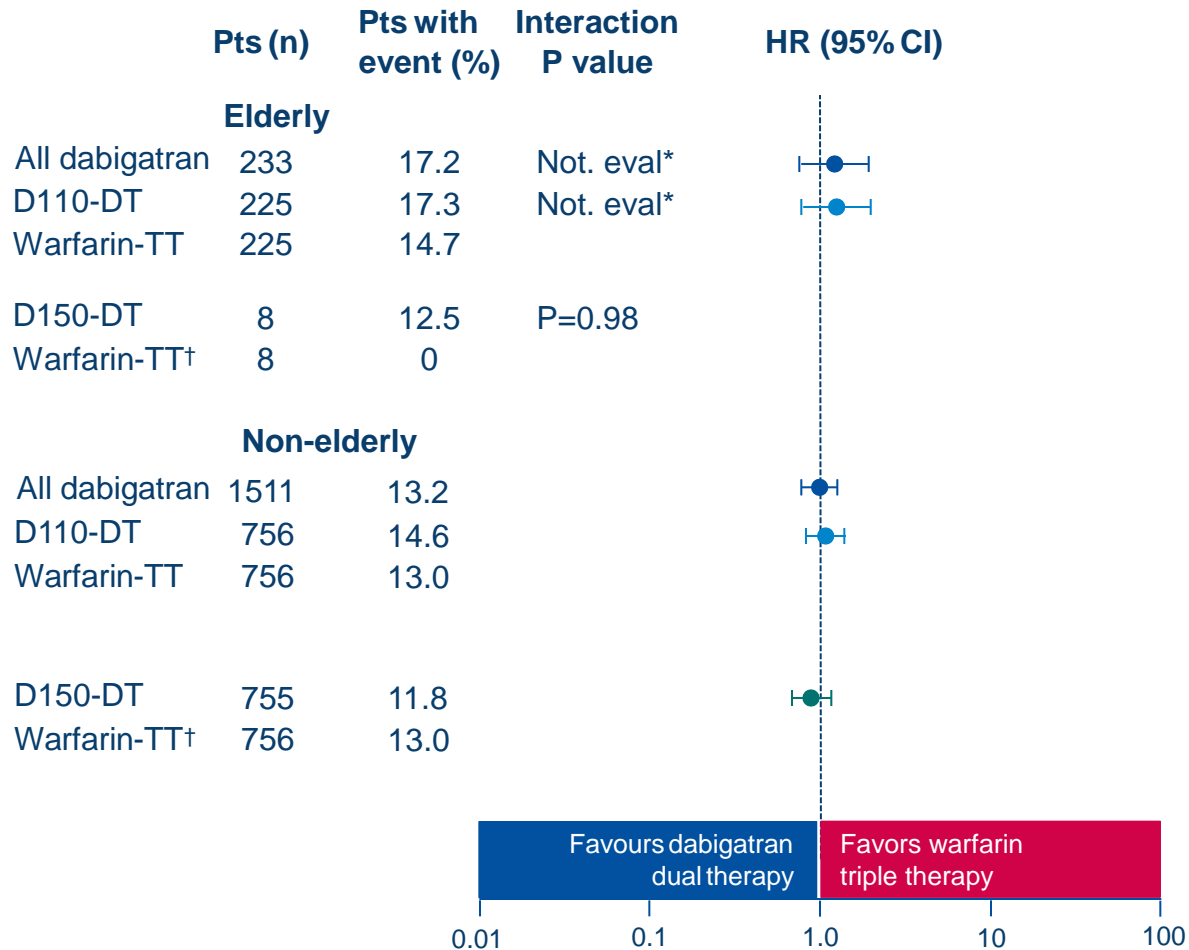


Missing/not applicable categories not shown and removed prior to calculation of interaction P values. *Not evaluable: for age-stratified model, the interaction P value is not derived. †For the comparison with D150-DT, elderly patients outside the USA are excluded. Age category is determined IVRS, interactive voice response system; MBE, major bleeding event; CRNMBE, clinically relevant non-major bleeding event; Pts, patients

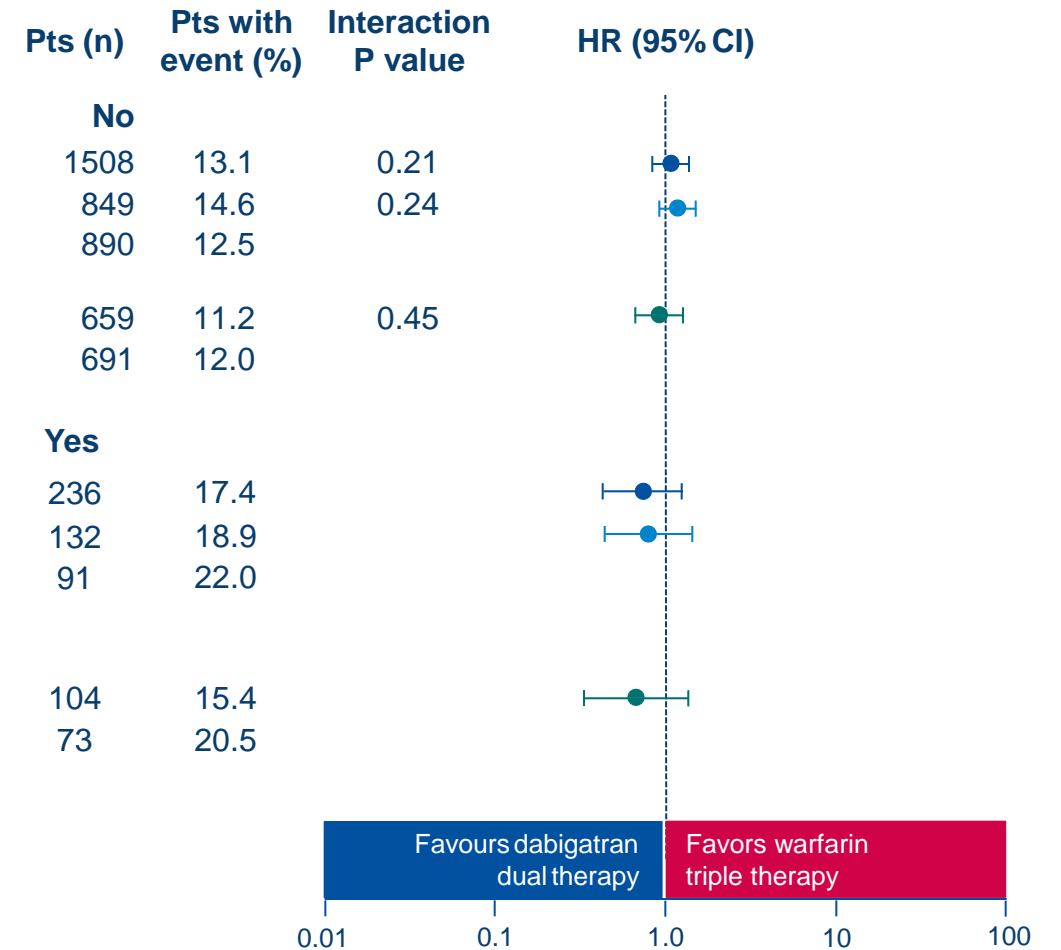
Subgroup analysis: age and ticagrelor use at baseline

Time to first DTE or unplanned revascularization

Age



Ticagrelor use at baseline (12% Pts)



Missing/not applicable categories not shown and removed prior to calculation of interaction P values. Age category is determined IVRS, interactive voice response system; . *Not evaluable: for age-stratified model, the interaction P value is not derived. [†]For the comparison with D150-DT, elderly patients outside the USA are excluded. DTE, death or thrombotic event

Conclusions

In patients with AF who have undergone PCI:



Dual therapy with dabigatran and a P2Y12 antagonist **significantly reduced the risk of bleeding versus warfarin triple therapy**, with non-inferiority for overall thromboembolic events



Absolute risk reductions with dabigatran dual therapy were **11.5% and 5.5%** in ISTH major or clinically relevant non-major bleeding at the 110 mg and 150 mg doses, respectively, compared with warfarin triple therapy



These dabigatran dual therapy regimens, using doses approved worldwide for stroke prevention, offer clinicians two additional options for managing Afib patients post-PCI

RE-DUAL PCI results are now published



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ORIGINAL ARTICLE

Dual Antithrombotic Therapy with Dabigatran after PCI in Atrial Fibrillation

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Stefan H. Hohnloser, M.D., for the RE-DUAL PCI Steering Committee and Investigators*

CONCLUSIONS

Among patients with atrial fibrillation who had undergone PCI, the risk of bleeding was lower among those who received dual therapy with dabigatran and a P2Y12 inhibitor than among those who received triple therapy with warfarin, a P2Y12 inhibitor, and aspirin. Dual therapy was noninferior to triple therapy with respect to the risk of thromboembolic events.

