RE-DUAL PCI
Study in NVAF patients undergoing PCI

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

Christopher P. Cannon

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On behalf of the steering committee and RE-DUAL PCI investigators

Thank you to all the RE-DUAL PCI investigators

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Country	No. patients	National co-ordinator
Argentina	49	Dr Jose Navarro Estrada
Australia	28	Prof. Steve Nicholls
Austria	18	Prof. Kurt Huber
Belgium	44	Prof. Danny Schoors
Brazil	34	Dr Jose Nicolau
Bulgaria	77	Prof. Dimitar Raev
Canada	48	Dr Shamir Mehta
Chile	12	Dr Fernando Lanas Zanetti
Colombia	11	Dr Efrain Gomez
Croatia	40	Dr Darko Pocanic
Czech Republic	49	MUDr Petr Jansky
Denmark	57	Dr Michael Mæng
Finland	43	Prof. Juhani Airaksinen
France	97	Prof. Gilles Montalescot
Germany	470	Prof. Uwe Zeymer
		Prof. Georg Nickenig
Greece	100	Prof. Panagiotis Vardas
Hong Kong	14	Prof Stephen Lee
Hungary	115	Prof. Robert Gabor Kiss
India	35	Dr Upendra Kaul
Ireland	14	Dr Peter Crean
Israel	35	Prof. Ran Kornowski

Country	No. patients	National co-ordinator
Italy	88	Prof. Raffaele De Caterina
Japan	111	Prof. Takeshi Kimura
Korea	81	Prof. Ki-Bae Seung
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Netherlands	50	Dr Ton Oude Ophuis
New Zealand	5	Prof. Harvey White
Norway	57	Dr Sigrun Halvorsen
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Portugal	41	Prof. Joao Morais
Russia	129	Prof. Dmitry Aleksandrovich Zateyshchikov
Singapore	9	Prof. Ru San Tan
Slovakia	39	Prof. Robert Hatala
Slovenia	14	Dr Dragan Kovacic
Spain	114	Prof. Jose Luis Lopez Sendon
Sweden	46	Prof. David Erlinge
Taiwan	34	Dr Juey-Jen Hwang
Thailand	29	Prof. Rungroj Krittayaphong
Turkey	157	Prof. Zeki Ongen
United Kingdom	69	Dr Mick Ozkor
United States	151	Dr Laura Mauri

Antithrombotic therapy for atrial fibrillation and PCI

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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

?

ASA, acetylsalicylic acid; PCI, percutaneous coronary intervention

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

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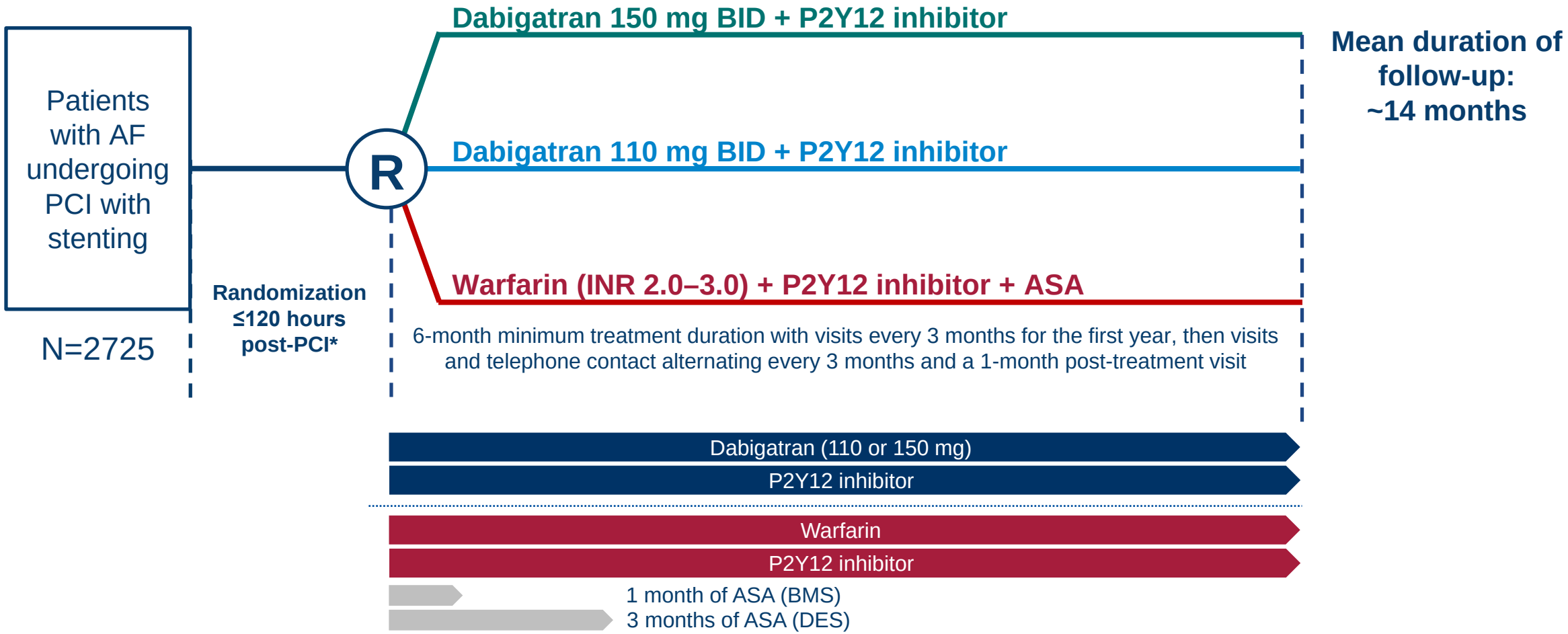

***Study drug should be administered 6 hours after sheath removal and no later than ≤120 hrs post-PCI (≤72 hrs is preferable).** PROBE, prospective, randomized, open, blinded end-point; R, randomization; BMS, bare metal stent; DES, drug-eluting stent. ClinicalTrials.gov: NCT02164864; Cannon et al. Clin Cardiol 2016

Patients were randomized based on age group and location

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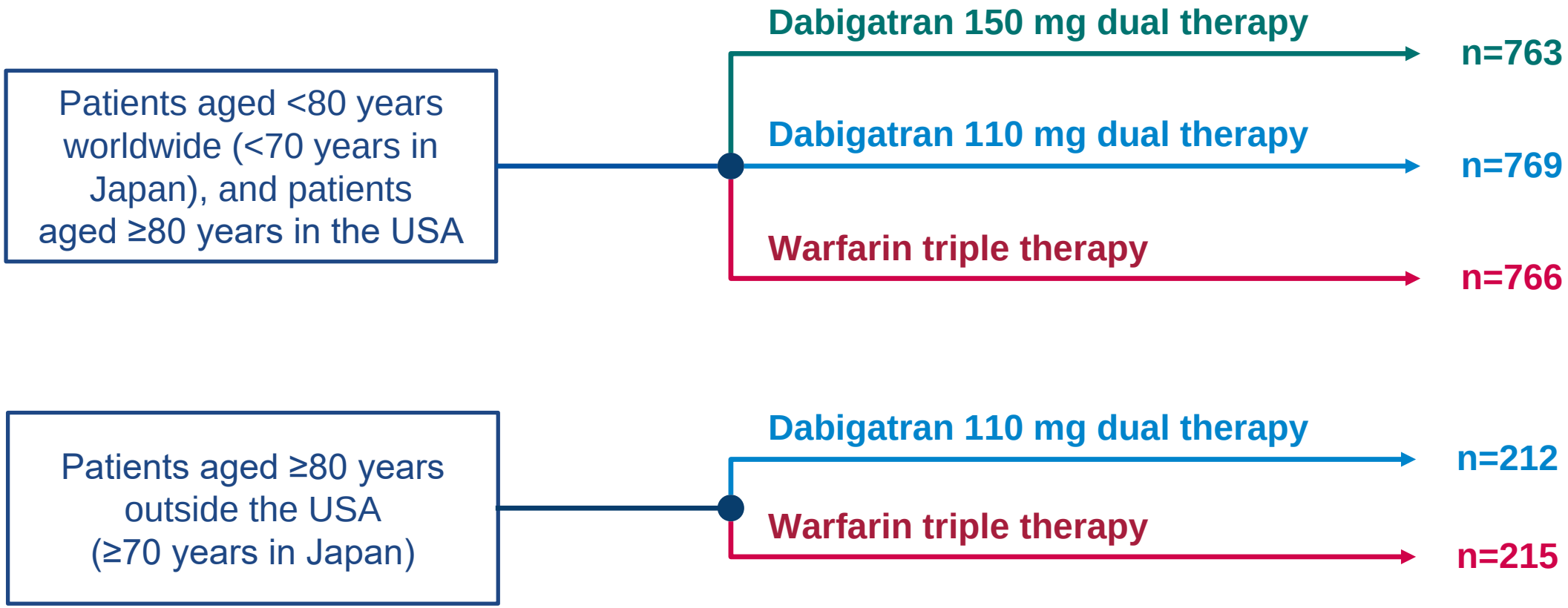

Inclusion and exclusion criteria

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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 <30mL/min)

ACS, acute coronary syndrome; CAD, coronary artery disease; CrCl, creatinine clearance

Study objective and design

RE-DUAL PCI
Study in NVAF patients undergoing PCI

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

ISTH, International Society of Thrombosis and Haemostasis; MI, myocardial infarction Non-inferiority testing (margin 1.38)

Summary of patient disposition

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	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

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	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
CHA_2DS_2–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

ROW, rest of world

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

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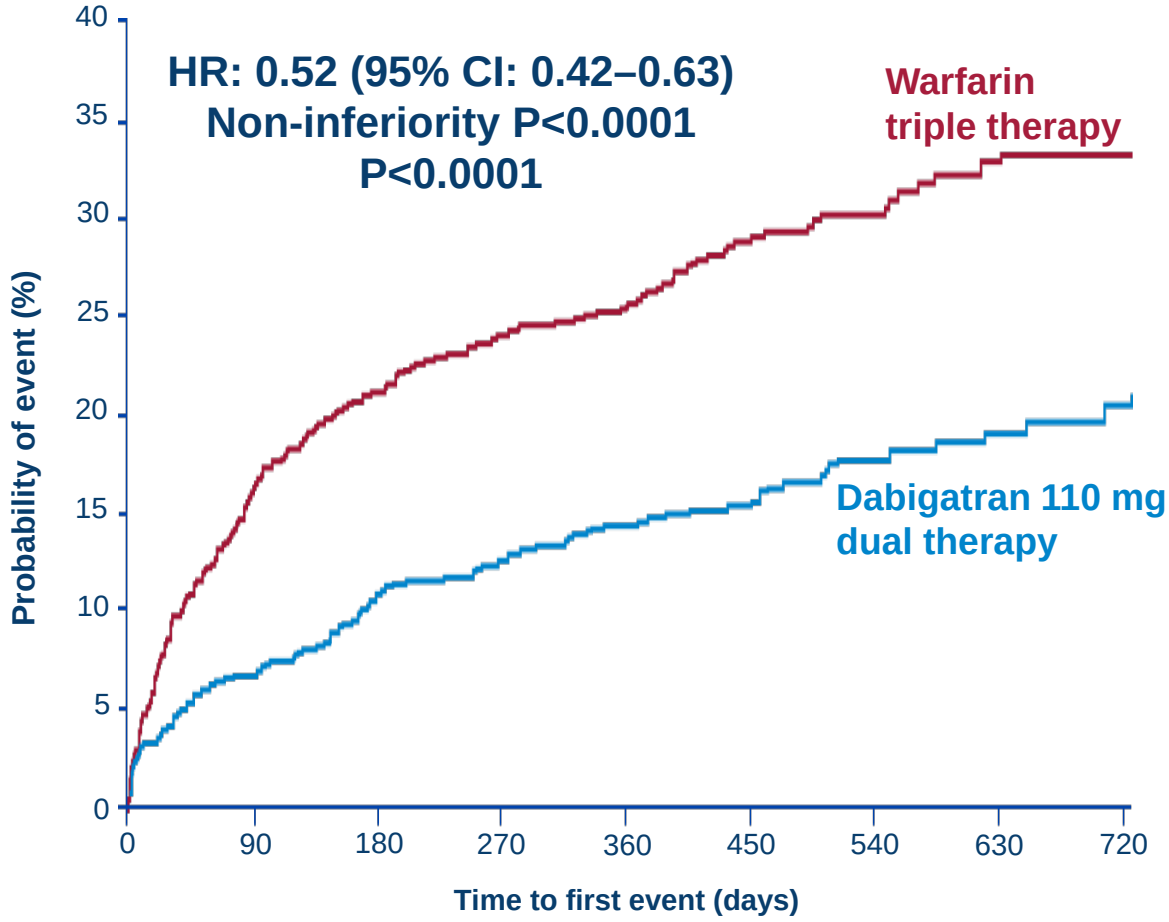

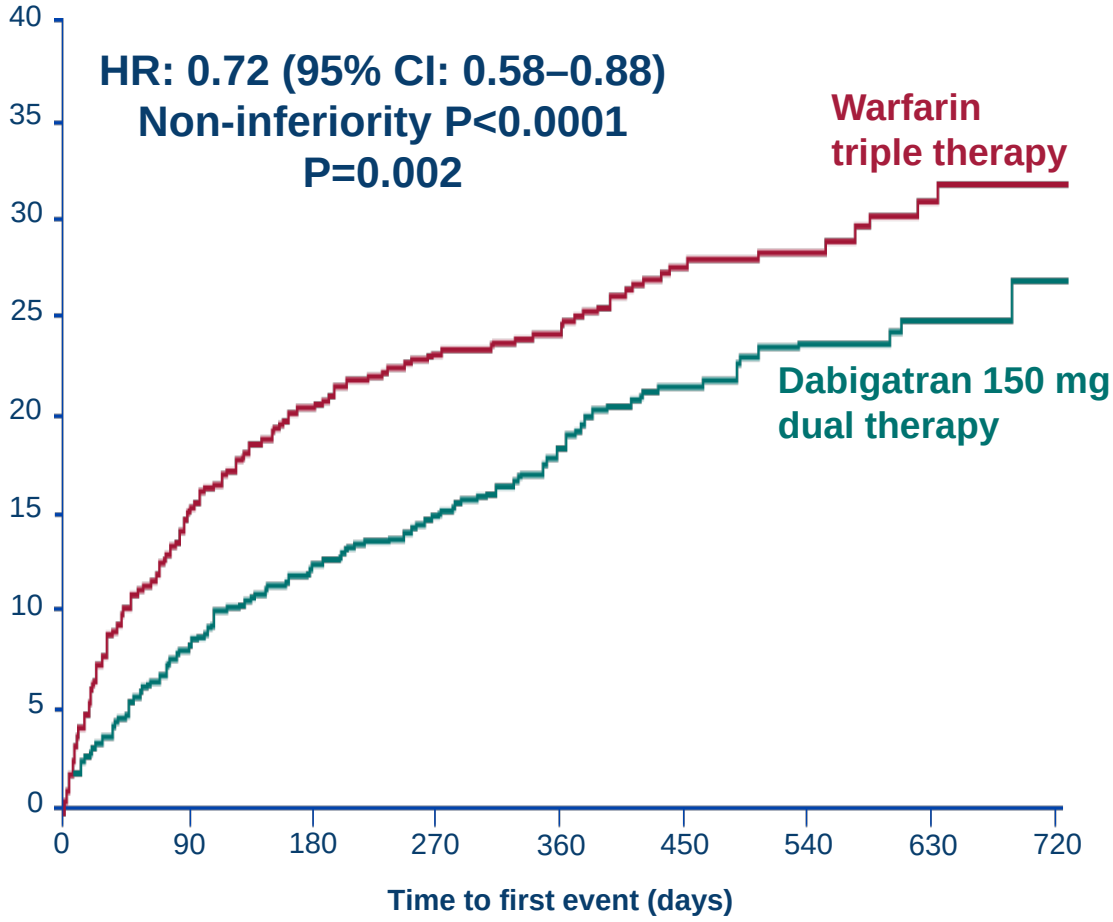

Full analysis set presented. HRs and Wald CIs from Cox proportional-hazard model. For the dabigatran 110 mg vs warfarin comparison, the model is stratified by age, non-elderly vs elderly (<70 or ≥70 in Japan and <80 or ≥80 years old elsewhere). For the dabigatran 150 mg vs warfarin comparison, an unstratified 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

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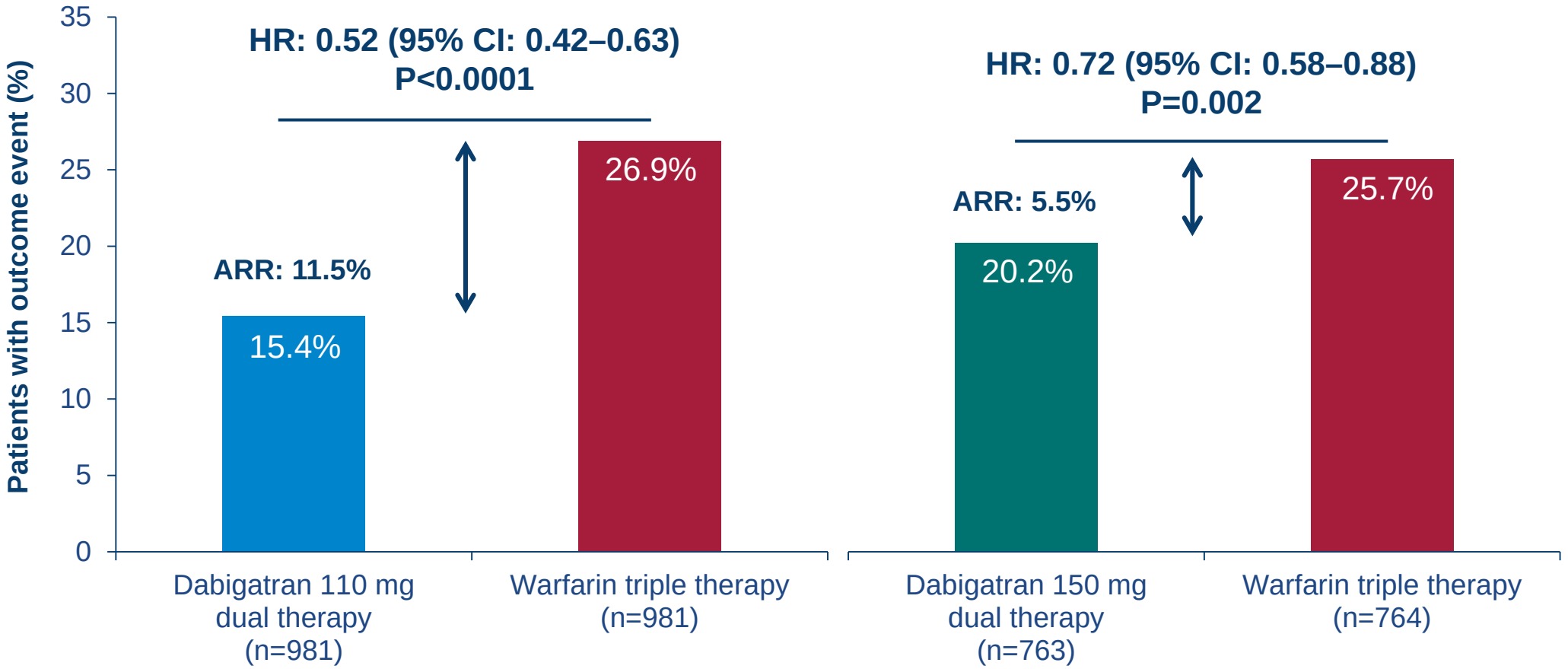

Wald two-sided P value from (stratified) Cox proportional-hazard model (alpha=0.05). ARR, absolute risk reduction

Rates of ISTH major bleeding

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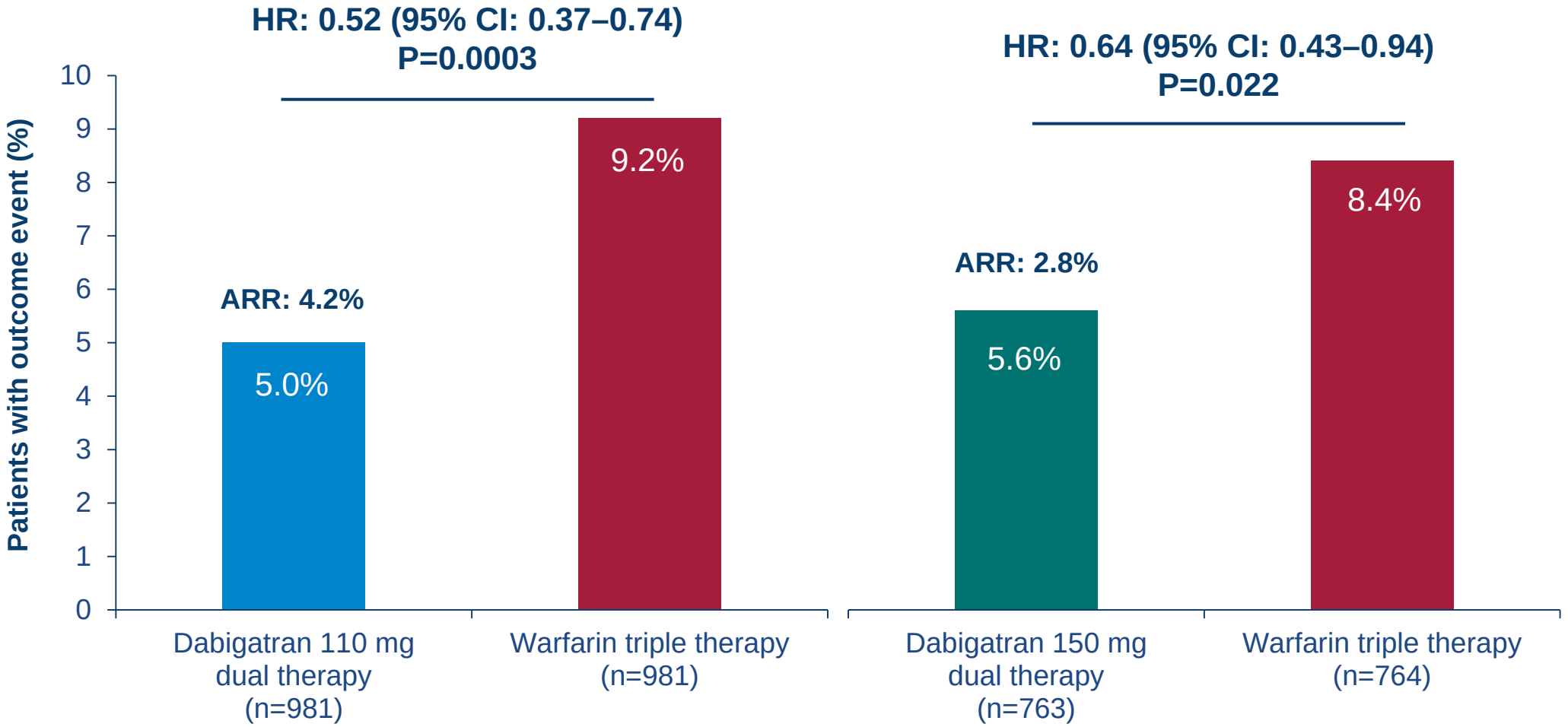

Wald two-sided P value from (stratified) Cox proportional-hazard model (alpha=0.05). ISTH major bleeding definition: fatal, critical organ (including intracranial haemorrhage), clinically overt bleeding with fall in Hb ≥2 g/dL. Hb, haemoglobin

Rates of TIMI major or minor bleeding

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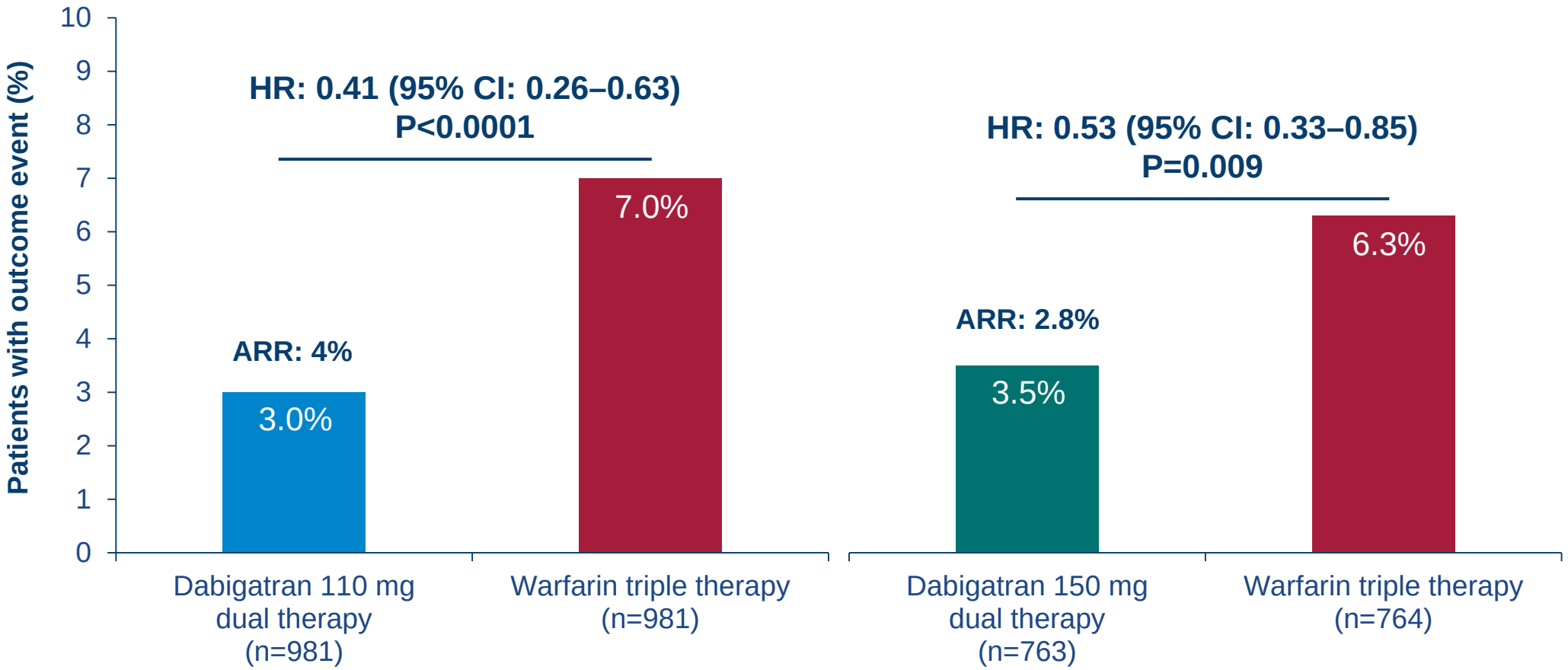

Wald two-sided P value from (stratified) Cox proportional-hazard model (alpha=0.05). TIMI major bleeding definition: fatal, intracranial haemorrhage, clinically overt bleeding with fall in Hb ≥5 g/dL; TIMI minor bleeding definition: clinically overt bleeding (including imaging), resulting in Hb drop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

Rates of TIMI major bleeding

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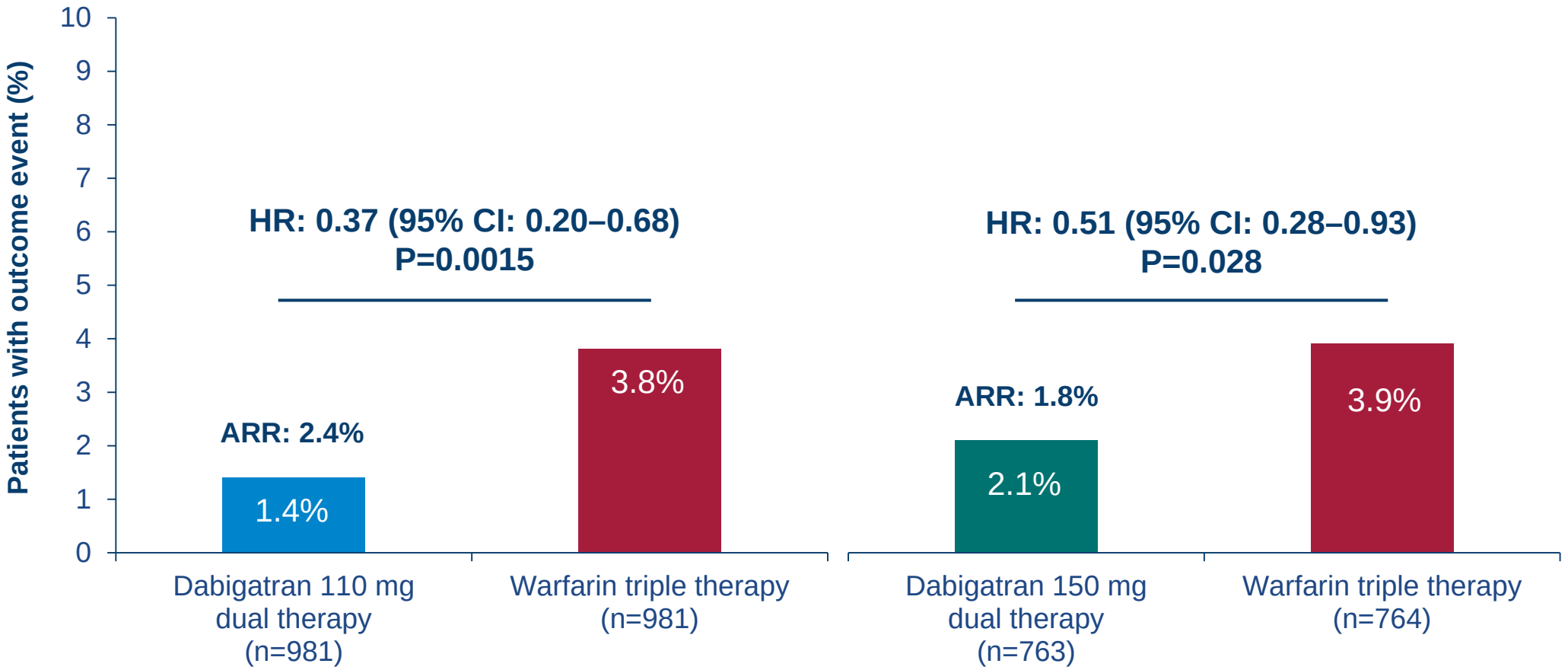

Wald two-sided P value from (stratified) Cox proportional-hazard model (alpha=0.05). TIMI major bleeding definition: fatal, intracranial haemorrhage, clinically overt bleeding with fall in Hb ≥5 g/dL.

Rate of intracranial haemorrhage

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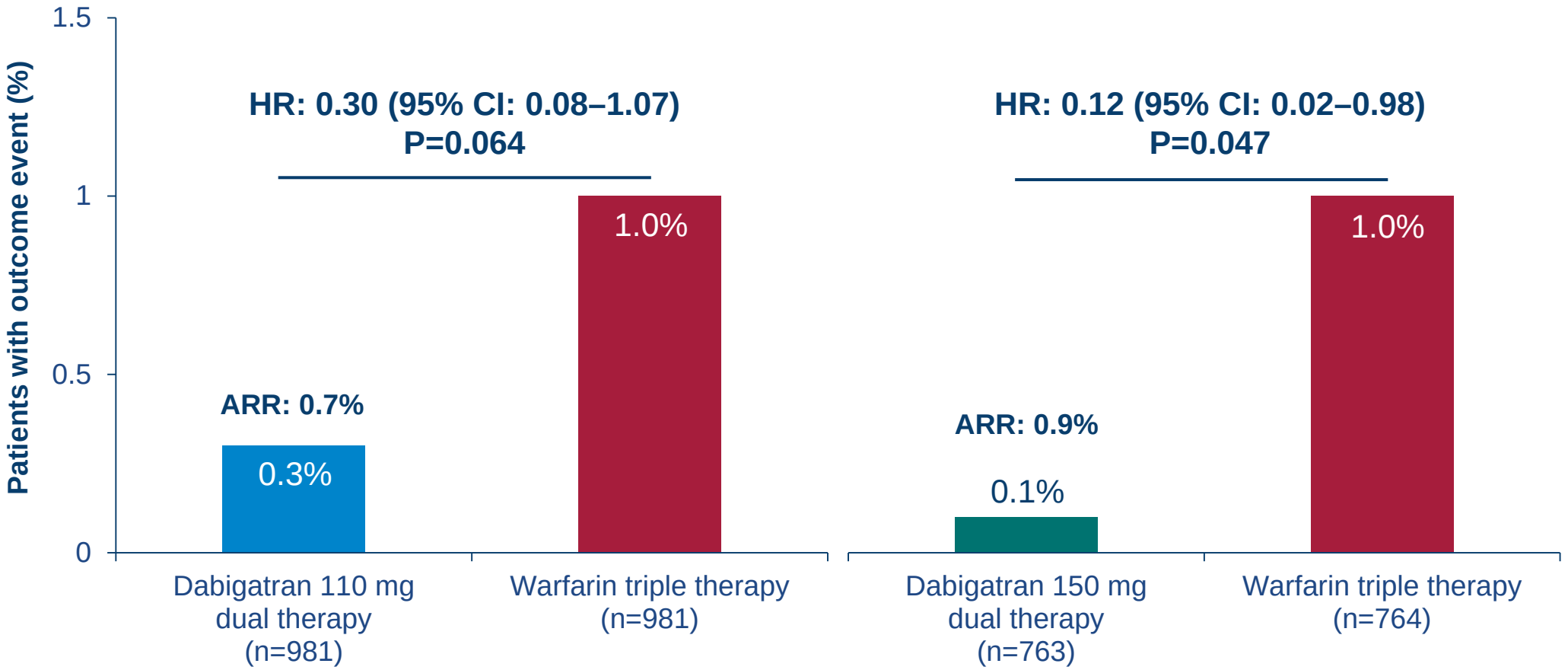

Wald two-sided P value from (stratified) Cox proportional-hazard model (alpha=0.05)

Time to death or thromboembolic event, or unplanned revascularization

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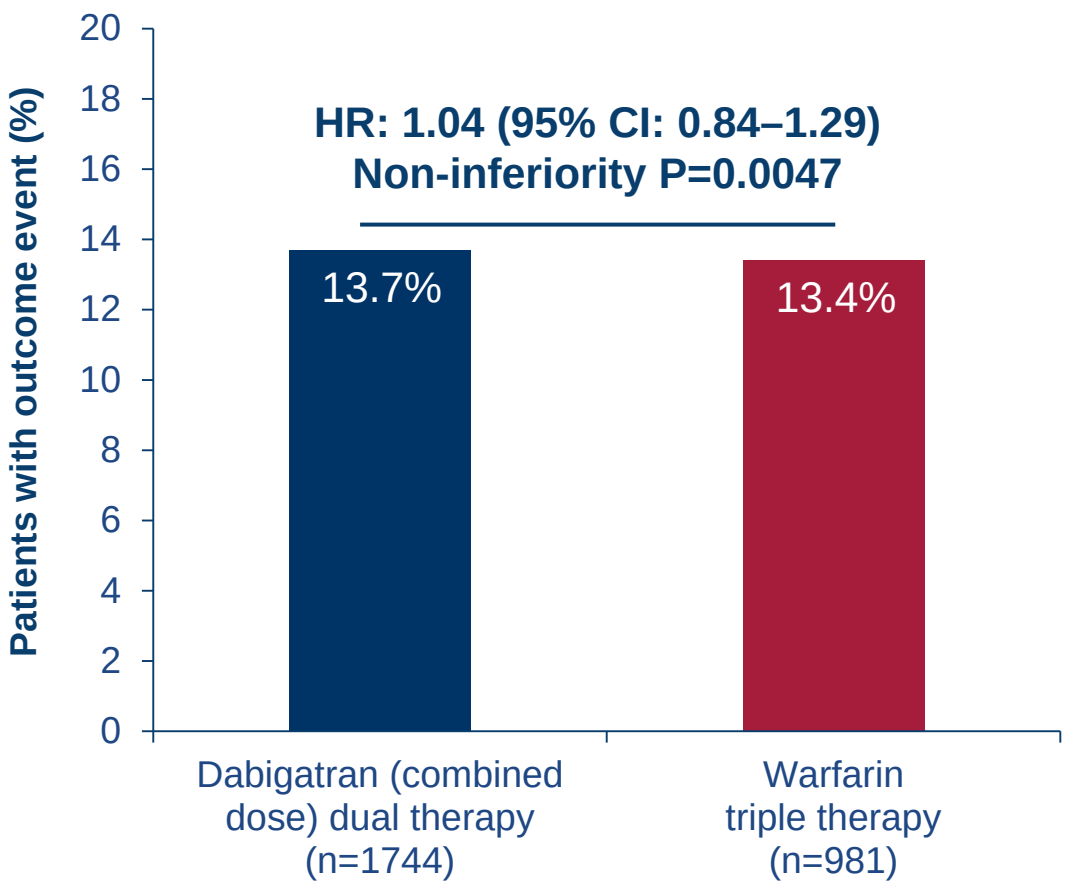

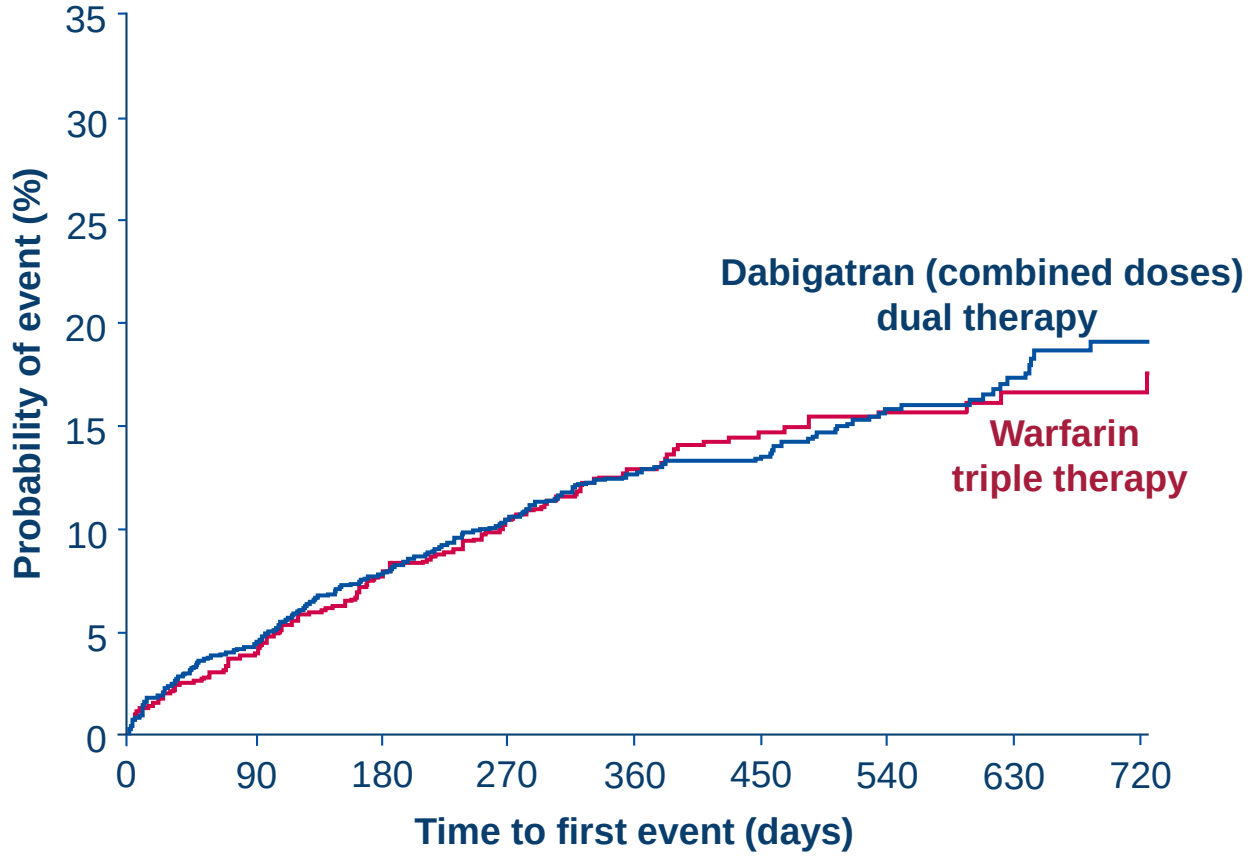

Non-inferiority P value is one sided (alpha=0.025). Results presented are Step 3 of hierarchical testing procedure, testing non-inferiority of dabigatran dual therapy (combined doses) to warfarin triple therapy in death or thromboembolic event and unplanned revascularization

Additional individual thromboembolic endpoints

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	Dabigatran 110 mg dual therapy (n=981) n (%)	Warfarin triple therapy (n=981) n (%)	D110 DT vs warfarin TT HR (95% CI)	D110 DT vs warfarin TT P value	Dabigatran 150 mg dual therapy (n=763) n (%)	Warfarin triple therapy (n=764) n (%)	D150 DT vs warfarin TT HR (95% CI)	D150 DT vs warfarin TT 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

Results presented are times to event. Stent thrombosis is time to definite stent thrombosis

Subgroup analysis: age and ticagrelor use at baseline

Time to first ISTH MBE or CRNMBE

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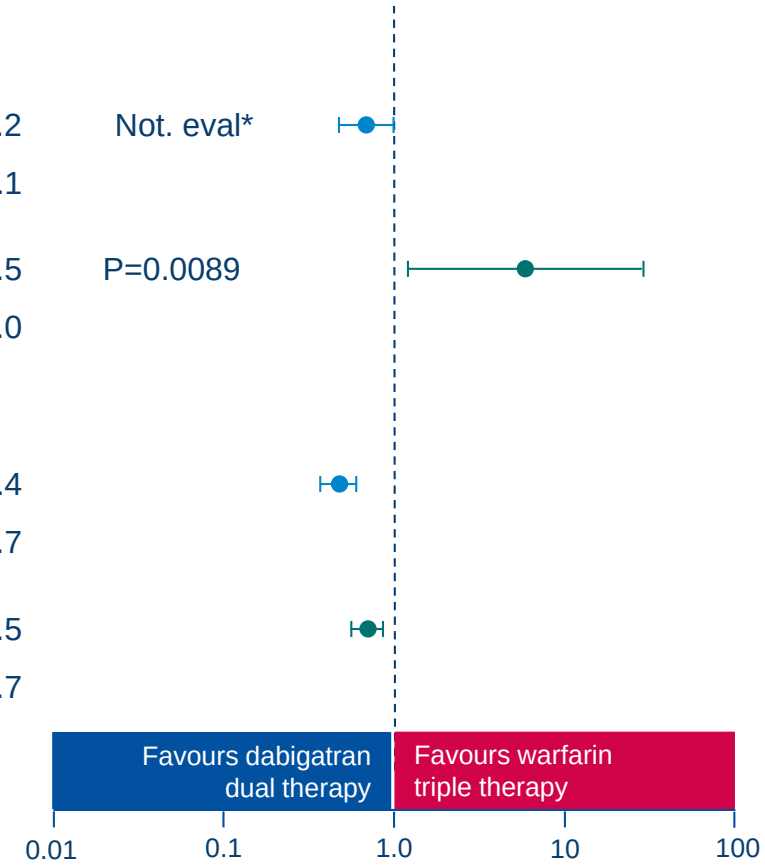
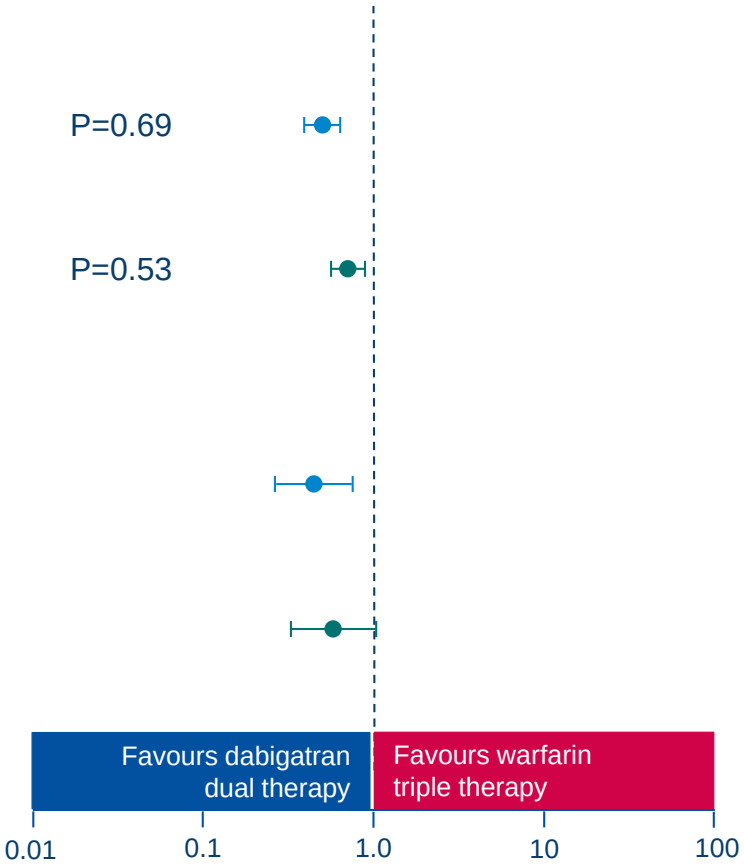
Age

	Pts (n)	Pts with event (%)	Interaction P value	HR (95% CI)
Elderly				
D110-DT	225	22.2	Not. eval*	
Warfarin-TT	225	31.1		
D150-DT	8	87.5	P=0.0089	
Warfarin-TT†	8	25.0		
Non-elderly				
D110-DT	756	13.4		
Warfarin-TT	756	25.7		
D150-DT	755	19.5		
Warfarin-TT†	756	25.7		



Ticagrelor use at baseline (12% Pts)

	Pts (n)	Pts with event (n)	Interaction P value	HR (95% CI)
No				
849	14.5	P=0.69		
890	25.8			
659	19.7	P=0.53		
691	24.7			
Yes				
132	21.2			
91	37.4			
104	23.1			
73	34.2			



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

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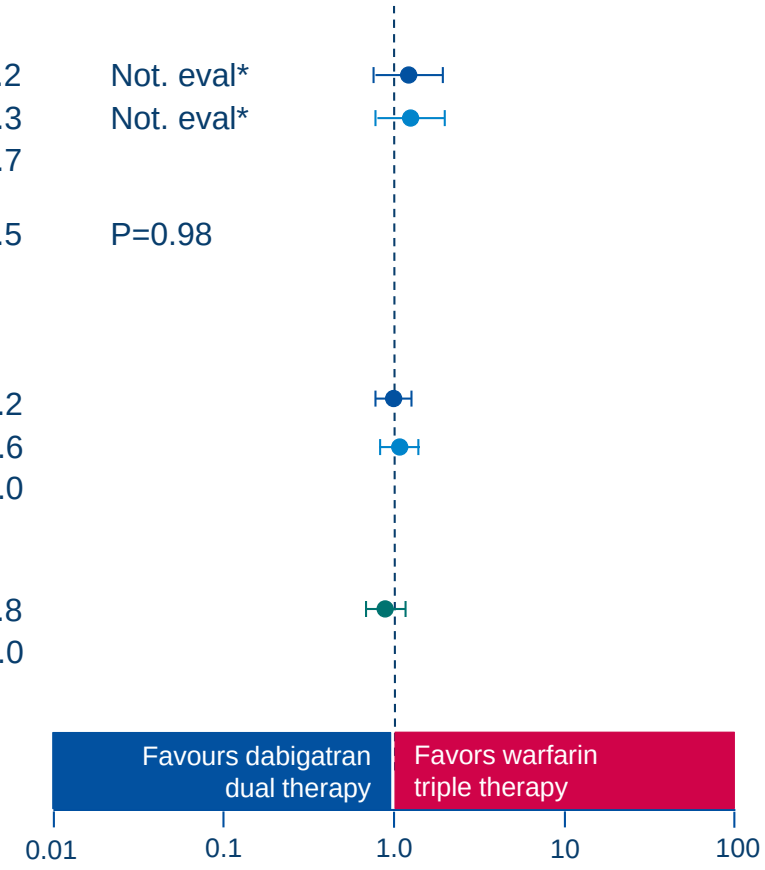
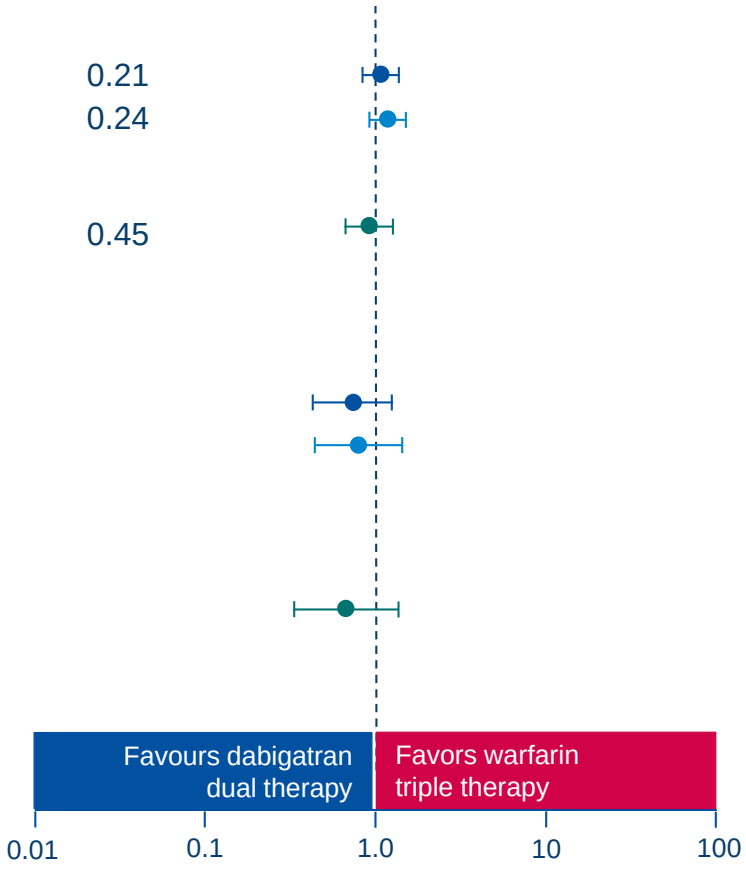
Age

	Pts (n)	Pts with event (%)	Interaction P value
Elderly			
All dabigatran	233	17.2	Not. eval*
D110-DT	225	17.3	Not. eval*
Warfarin-TT	225	14.7	
D150-DT	8	12.5	P=0.98
Warfarin-TT†	8	0	
Non-elderly			
All dabigatran	1511	13.2	
D110-DT	756	14.6	
Warfarin-TT	756	13.0	
D150-DT	755	11.8	
Warfarin-TT†	756	13.0	



Ticagrelor use at baseline (12% Pts)

	Pts (n)	Pts with event (%)	Interaction P value
No			
1508	13.1	0.21	
849	14.6	0.24	
890	12.5		
659	11.2	0.45	
691	12.0		
Yes			
236	17.4		
132	18.9		
91	22.0		
104	15.4		
73	20.5		



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Conclusions

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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

RE-DUAL PCI
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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dual Antithrombotic Therapy with Dabigatran after PCI in Atrial Fibrillation

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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.