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Comparison of the Effect of Age (< 75 Versus ≥ 75) on the Efficacy and Safety of Dual Therapy (Dabigatran + Clopidogrel or Ticagrelor) Versus Triple Therapy (Warfarin + Aspirin + Clopidogrel or Ticagrelor) in Patients With Atrial Fibrillation After Percutaneous Coronary Intervention (from the RE-DUAL PCI Trial)

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Jurrien M. ten Berg, MD, PhD[a,*], Philippe Gabriel Steg, MD[b,c,d,e], Deepak L. Bhatt, MD, MPH[f], Stefan H. Hohnloser, MD[g], Anne de Veer, MD[a], 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], and Christopher P. Cannon, MD[f], on behalf of the RE-DUAL PCI Steering Committee and Investigators

The RE-DUAL PCI trial reported that dabigatran dual therapy (110/150 mg twice daily, plus clopidogrel or ticagrelor) reduced bleeding events versus warfarin triple therapy (warfarin plus aspirin and clopidogrel or ticagrelor) in patients with atrial fibrillation who underwent percutaneous coronary intervention, with noninferiority in composite thromboembolic events. In this prespecified analysis, risks of first major or clinically relevant nonmajor bleeding event and composite end point of death, thromboembolic events, or unplanned revascularization were compared between dabigatran dual therapy and warfarin triple therapy in older (≥ 75 years) and younger (< 75 years) patients, using Cox proportional hazard regression. Of 2,725 patients randomized to treatment, 1,026 (37.7%) were categorized into older and 1,699 (62.3%) into younger age groups. Dabigatran 110 mg dual therapy lowered bleeding risk versus warfarin triple therapy in older (hazard ratio [HR] 0.67; 95% confidence interval [CI] 0.51 to 0.89) and younger patients (HR 0.40; 95% CI 0.30 to 0.54); interaction p value: 0.0125. Dabigatran 150 mg dual therapy lowered bleeding risk versus warfarin triple therapy in younger patients (HR 0.57; 95% CI 0.44 to 0.74), whereas no benefit could be observed in older patients (HR 1.21; 95% CI 0.83 to 1.77); interaction p value: 0.0013. For the thromboembolic end point, there was a trend for a higher risk with dabigatran 110 mg dual therapy in older patients, compared with warfarin triple therapy, whereas the risk was similar in younger patients. For dabigatran 150 mg dual therapy, the thromboembolic risk versus warfarin triple therapy was similar in older and younger patients. In conclusion, the benefits of dabigatran dual therapy differed in the 2 age groups, which may help dose selection when using dabigatran dual therapy.

Older patients (≥ 75 yrs)					Younger patients (< 75 yrs)			
DE 110 mg dual therapy (n = 417)	Warfarin triple therapy (n = 410)	DE 150 mg dual therapy (n = 199)	Warfarin triple therapy (n = 208*)		DE 110 mg dual therapy (n = 564)	Warfarin triple therapy (n = 571)	DE 150 mg dual therapy (n = 564)	Warfarin triple therapy (n = 556*)
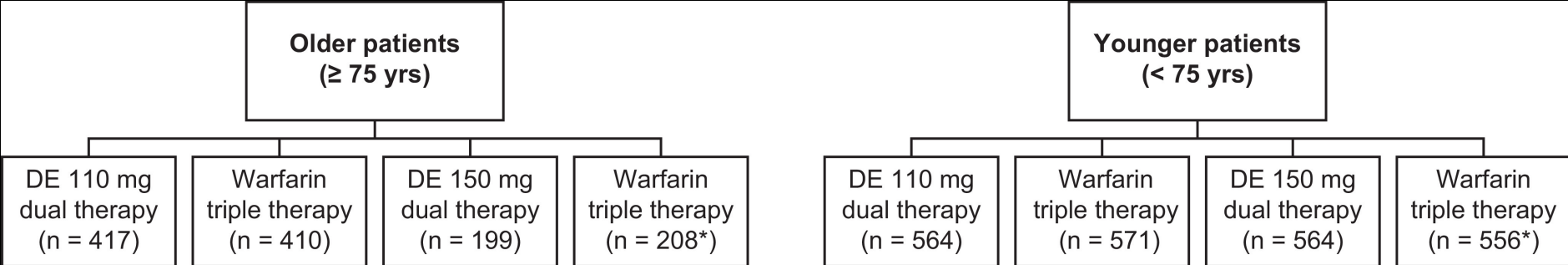
Figure 1. Patient randomization according to age group.

*For the comparison with dabigatran 150 mg dual therapy, elderly patients outside the United States aged ≥ 80 years (≥ 70 years in Japan) were excluded. DE=dabigatran.
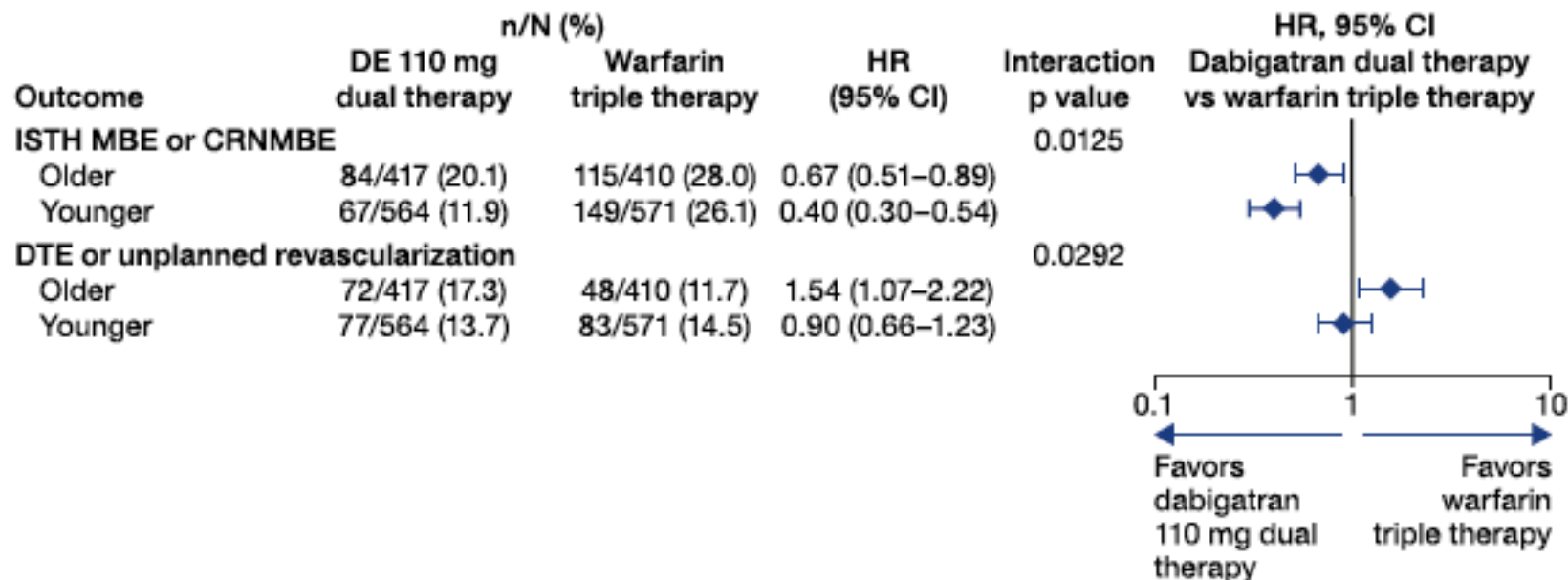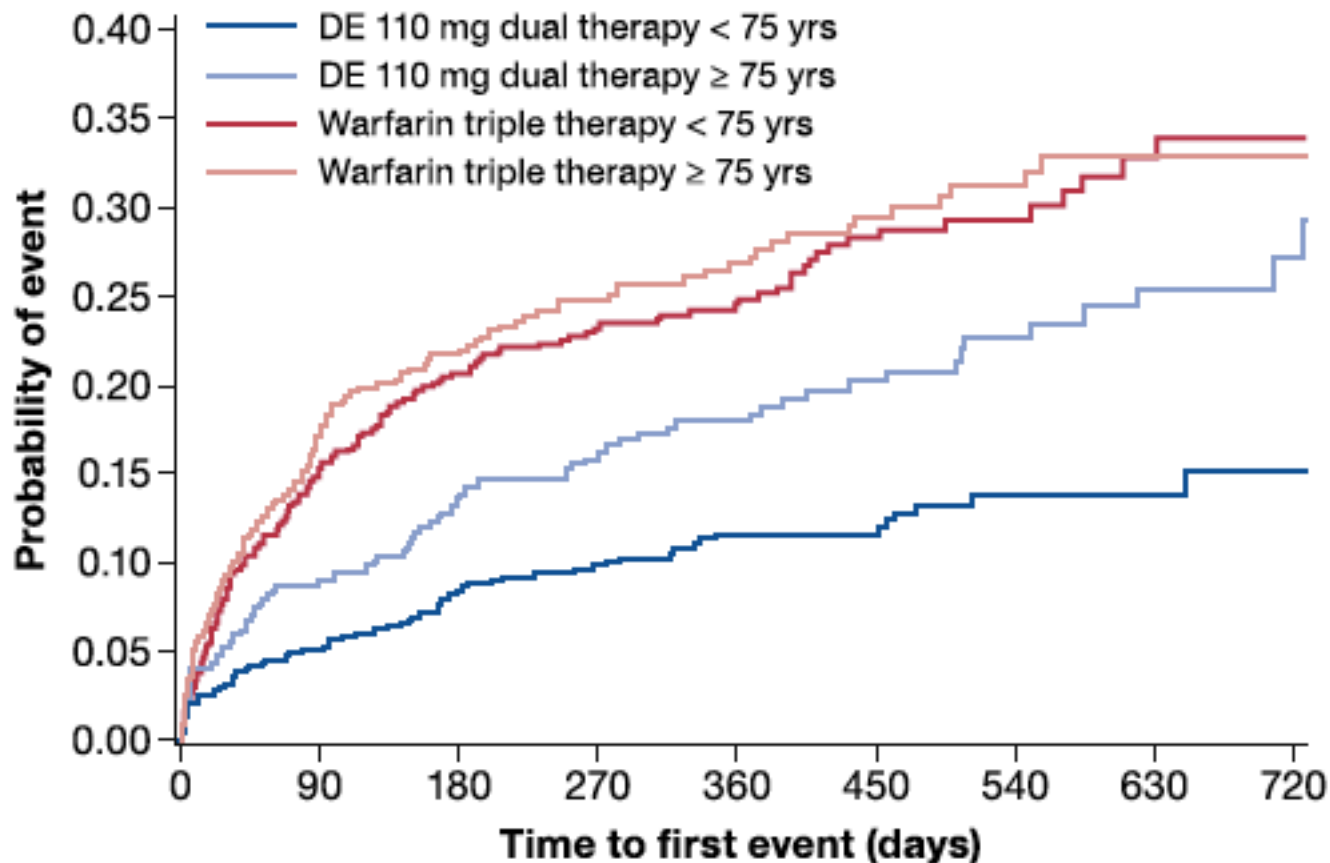
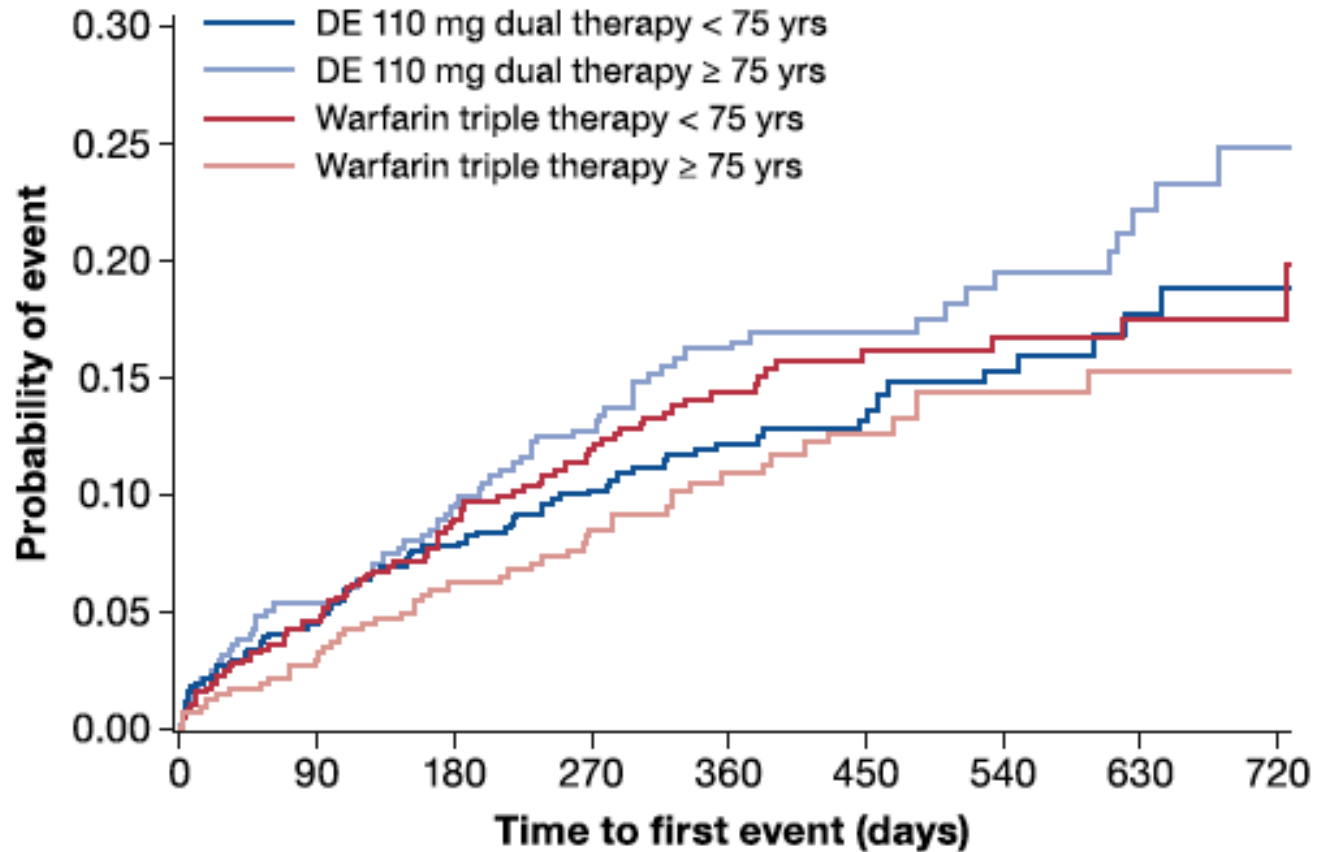Figure 2. Outcomes in older and younger patients according to treatment: dabigatran 110 mg dual therapy.
Patients aged ≥ 80 years outside the United States and patients aged ≥ 70 years from Japan were assigned to either DE 110 mg or warfarin in a 1:1 ratio; all other patients are randomized to all 3 treatment groups in a 1:1:1 ratio. HRs and 95% CIs from Cox proportional hazard models. CI = confidence interval; CRNMBE = clinically relevant nonmajor bleeding event; DE = dabigatran etexilate; DTE = death or thromboembolic event; HR = hazard ratio; ISTH = International Society on Thrombosis and Haemostasis; MBE = major bleeding event.

A

Legend:
- DE 110 mg dual therapy < 75 yrs
- DE 110 mg dual therapy ≥ 75 yrs
- Warfarin triple therapy < 75 yrs
- Warfarin triple therapy ≥ 75 yrs

Y-axis: Probability of event (0.00 – 0.40)

X-axis: Time to first event (days) (0 – 720)

Patients at risk

	0	90	180	270	360	450	540	630	720
DE 110 mg dual therapy < 75 yrs	564	525	493	405	325	228	148	89	48
DE 110 mg dual therapy ≥ 75 yrs	417	373	341	266	213	156	110	73	38
Warfarin triple therapy < 75 yrs	571	470	414	334	261	163	107	61	31
Warfarin triple therapy ≥ 75 yrs	410	330	305	246	192	139	98	63	32

Figure 3. Kaplan-Meier analysis for (*A*) time to first adjudicated ISTH MBE or CRNMBE and (*B*) DTE or unplanned revascularization (intent to treat period) by age group: dabigatran 110 mg dual therapy.

CRNMBE = clinically relevant nonmajor bleeding event; DE = dabigatran etexilate; DTE = death or thromboembolic event; ISTH = International Society on Thrombosis and Haemostasis; MBE = major bleeding event.

B

Figure 3. Kaplan-Meier analysis for (*A*) time to first adjudicated ISTH MBE or CRNMBE and (*B*) DTE or unplanned revascularization (intent to treat period) by age group: dabigatran 110 mg dual therapy.

CRNMBE = clinically relevant nonmajor bleeding event; DE = dabigatran etexilate; DTE = death or thromboembolic event; ISTH = International Society on Thrombosis and Haemostasis; MBE = major bleeding event.
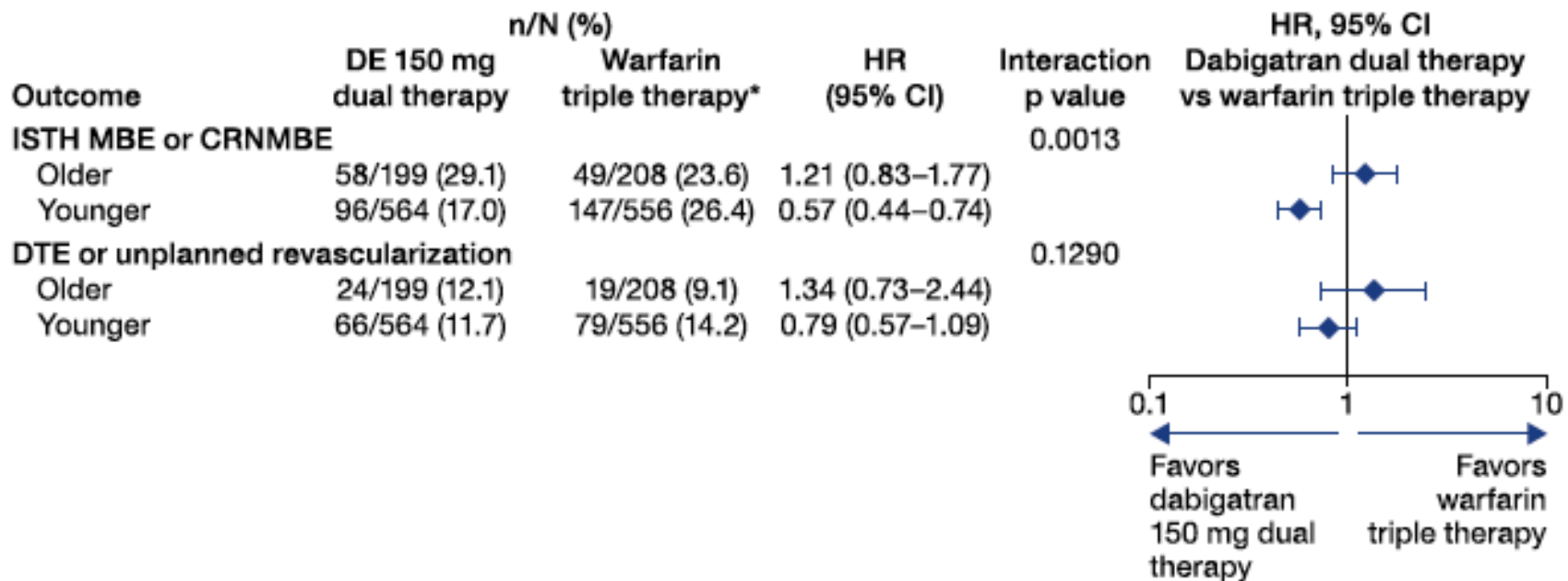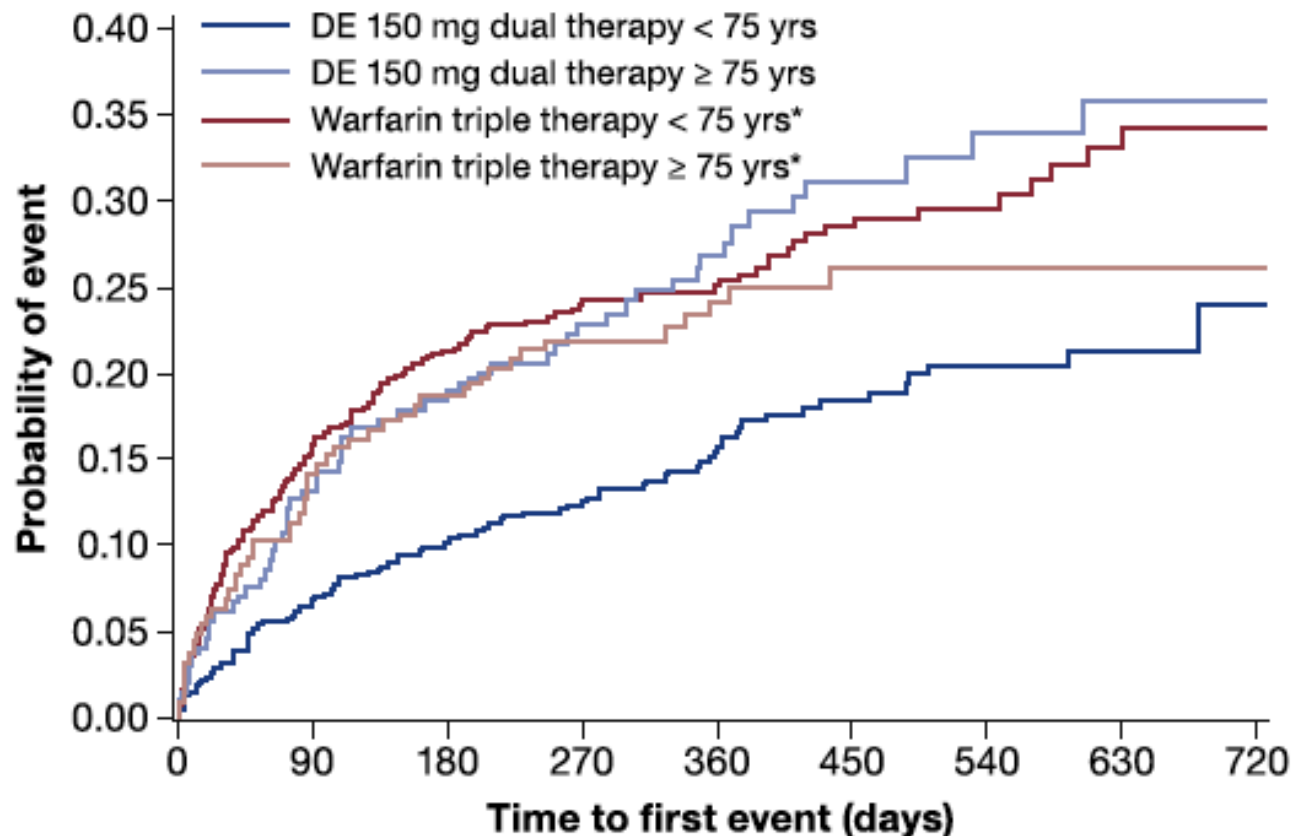
| | n/N (%) | | | | HR, 95% CI |
Outcome	DE 150 mg dual therapy	Warfarin triple therapy*	HR (95% CI)	Interaction p value	Dabigatran dual therapy vs warfarin triple therapy
ISTH MBE or CRNMBE				0.0013	
Older	58/199 (29.1)	49/208 (23.6)	1.21 (0.83–1.77)		
Younger	96/564 (17.0)	147/556 (26.4)	0.57 (0.44–0.74)		
DTE or unplanned revascularization				0.1290	
Older	24/199 (12.1)	19/208 (9.1)	1.34 (0.73–2.44)		
Younger	66/564 (11.7)	79/556 (14.2)	0.79 (0.57–1.09)		

Figure 4. Outcomes in older and younger patients according to treatment: dabigatran 150 mg dual therapy.
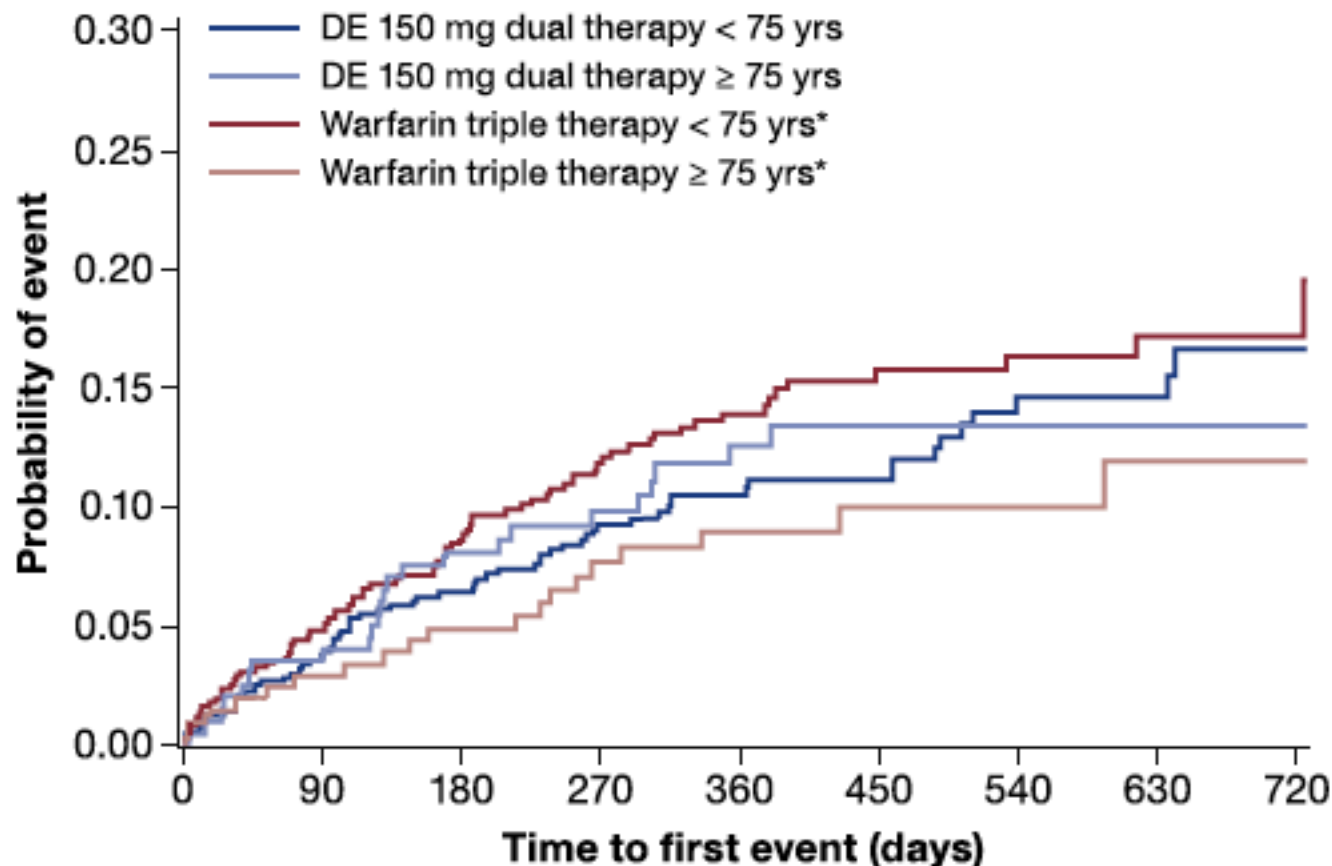
Patients aged ≥ 80 years outside the United States and patients aged ≥ 70 years from Japan were assigned to either DE 110 mg or warfarin in a 1:1 ratio; all other patients are randomized to all 3 treatment groups in a 1:1:1 ratio. *For the comparison with dabigatran 150 mg dual therapy, elderly patients outside the United States aged ≥ 80 years (≥ 70 years in Japan) are excluded. HRs and 95% CIs from Cox proportional hazard models. CI = confidence interval; CRNMBE = clinically relevant nonmajor bleeding event; DE = dabigatran etexilate; DTE = death or thromboembolic event; HR = hazard ratio; ISTH = International Society on Thrombosis and Haemostasis; MBE = major bleeding event.

Figure 5. Kaplan-Meier analysis for (A) time to first adjudicated ISTH MBE or CRNMBE and (B) DTE or unplanned revascularization (intent to treat period) by age group: dabigatran 150 mg dual therapy.
*For the comparison with dabigatran 150 mg dual therapy, elderly patients outside the United States aged ≥ 80 years (≥ 70 years in Japan) are excluded.
CRNMBE = clinically relevant nonmajor bleeding event; DE = dabigatran etexilate; DTE = death or thromboembolic event; ISTH = International Society on Thrombosis and Haemostasis; MBE = major bleeding event.

Figure 5. Kaplan-Meier analysis for (A) time to first adjudicated ISTH MBE or CRNMBE and (B) DTE or unplanned revascularization (intent to treat period) by age group: dabigatran 150 mg dual therapy.

*For the comparison with dabigatran 150 mg dual therapy, elderly patients outside the United States aged ≥ 80 years (≥ 70 years in Japan) are excluded. CRNMBE = clinically relevant nonmajor bleeding event; DE = dabigatran etexilate; DTE = death or thromboembolic event; ISTH = International Society on Thrombosis and Haemostasis; MBE = major bleeding event.
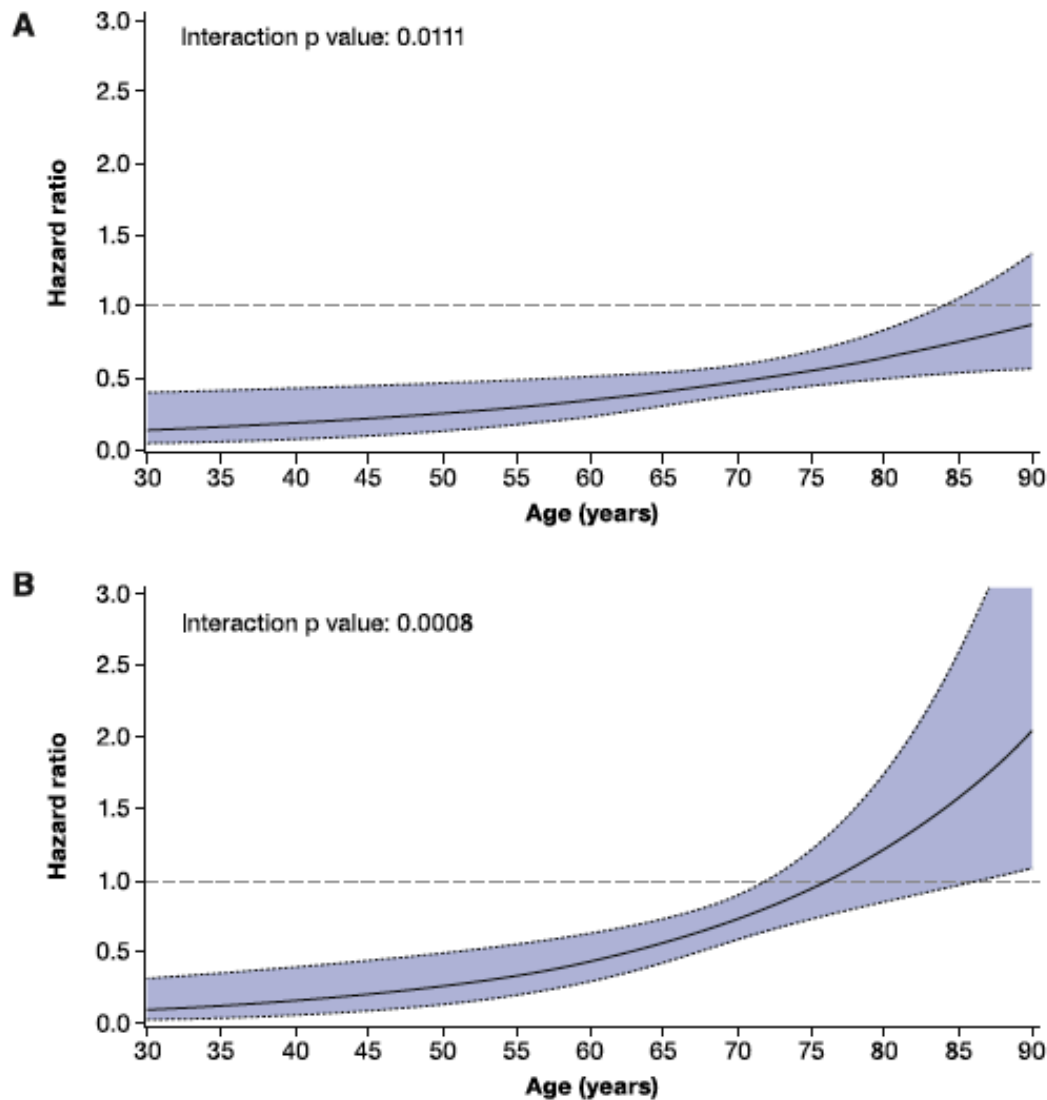
Figure 6. ISTH MBE and CRNMBE—interaction plot for varying values of age as a continuous variable: (*A*) dabigatran 110 mg dual therapy; (*B*) dabigatran 150 mg dual therapy.

HRs (solid lines) and Wald 95% CIs from Cox proportional hazard model including treatment, age, and interaction between treatment and age. For the comparison with dabigatran 150 mg dual therapy, elderly patients outside the United States aged ≥ 80 years (≥ 70 years in Japan) are excluded. CI = confidence interval; CRNMBE = clinically relevant nonmajor bleeding event; HR = hazard ratio; ISTH = International Society on Thrombosis and Haemostasis; MBE = major bleeding event.
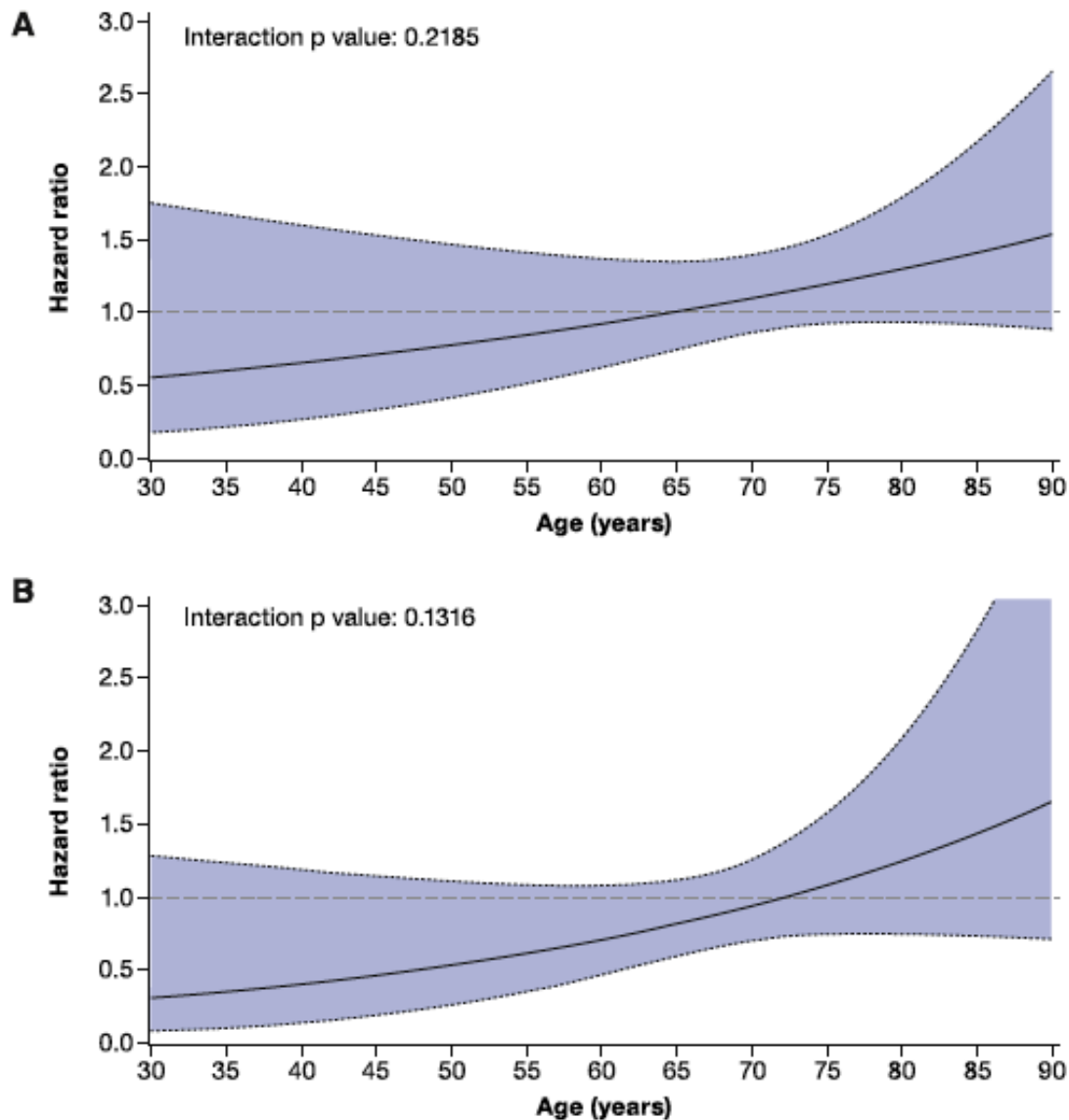
Figure 7. DTE and unplanned revascularization—interaction plot for varying values of age as a continuous variable: (*A*) dabigatran 110 mg dual therapy; (*B*) dabigatran 150 mg dual therapy.

HRs (solid lines) and Wald 95% CIs from Cox proportional hazard model including treatment, age, and interaction between treatment and age. For the comparison with dabigatran 150 mg dual therapy, elderly patients outside the United States aged ≥ 80 years (≥ 70 years in Japan) are excluded. CI = confidence interval; DTE = death or thromboembolic event; HR = hazard ratio.