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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Published in:
The American Journal of Cardiology

DOI (link to publication from Publisher):
10.1016/j.amjcard.2019.11.029

Publication date:
2020

Document Version
Publisher's PDF, also known as Version of record

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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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. **(Am J Cardiol 2020;125:735−743)**

Dabigatran is approved at 110 or 150 mg twice daily doses for the prevention of stroke in atrial fibrillation (AF).[1] The RE-DUAL PCI trial compared dabigatran dual therapy (110 or 150 mg twice daily, plus clopidogrel or ticagrelor) versus warfarin triple therapy (warfarin with aspirin plus clopidogrel or ticagrelor) in patients with AF who underwent percutaneous coronary intervention (PCI).[2] Dabigatran dual therapy at both doses reduced the risk of bleeding—assessed by International Society on Thrombosis and Haemostasis (ISTH) major bleeding events (MBEs) or clinically relevant

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Funding: This work was supported by Boehringer Ingelheim International GmbH.

See page 739 for disclosure information.

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https://doi.org/10.1016/j.amjcard.2019.11.029

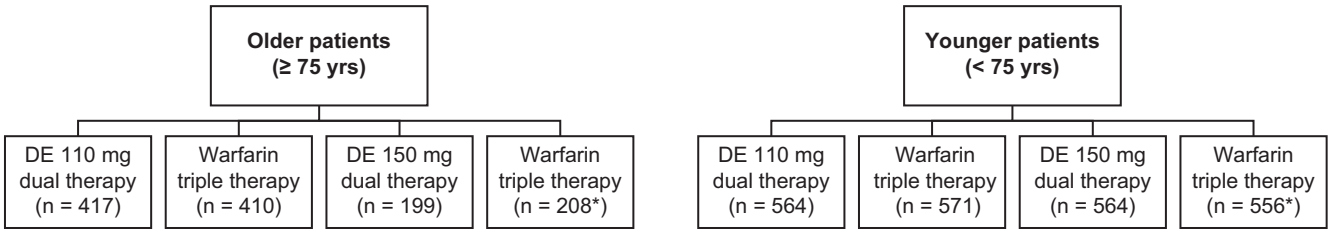


Figure 1. Patient randomization according to age group.
*For the comparison with dabigatran 150 mg dual therapy, elderly patients outside the United States aged ≥ 80 years (≥ 70 years in Japan) were excluded. DE = dabigatran.

nonmajor bleeding events (CRNMBEs)—compared with warfarin triple therapy, and was noninferior for the composite efficacy end point of thromboembolic events (myocardial infarction, stroke, or systemic embolism), death, or unplanned revascularization. The prevalence of AF is increased in older patients due to aging and common predisposing co-morbidities. In this prespecified analysis, we evaluated the influence of patient age on the outcomes in the RE-DUAL PCI trial, using age group as an exploratory variable in an unstratified model, whereas in the main RE-DUAL PCI trial, age was used as a stratifying factor.

Methods

The design of the RE-DUAL PCI trial (NCT02164864) has been reported previously.[3] In brief, 2,725 patients aged ≥ 18 years with nonvalvular AF who underwent PCI for acute coronary syndrome or stable coronary artery disease were randomly assigned to dabigatran dual or warfarin triple therapy, with a mean follow-up of 14 months. Aspirin was used for 1 month when a bare-metal stent was used, and for 3 months when a drug-eluting stent was used.

Dabigatran 150 mg is not licensed in patients aged ≥ 80 years in Europe or ≥ 70 years in Japan, whereas dabigatran at both 110- and 150-mg doses is approved in the United States regardless of age. Elderly patients in non-US countries (≥ 80 years) or Japan (≥ 70 years) were randomized in RE-DUAL PCI to receive dabigatran 110 mg dual or warfarin triple therapy in a 1:1 ratio, whereas younger patients in non-US countries (< 80 years) and Japan (< 70 years), and all US patients irrespective of age, were randomized to dabigatran 110 mg dual, dabigatran 150 mg dual, or warfarin triple therapy in a 1:1:1 ratio.

The primary safety end point in RE-DUAL PCI was the time to first ISTH MBE/CRNMBE. Key efficacy end point was a composite of the time to death, first thromboembolic event, or unplanned revascularization. The current analysis assessed these end points in patients categorized into older (≥ 75 years) and younger (< 75 years) age groups.

Cox proportional hazard regression models were used to compare dabigatran 110 or 150 mg dual versus warfarin triple therapy in older and younger age groups. Exploratory treatment-by-subgroup interaction p values were provided from the Cox proportional hazard regression models ($p < 0.05$ was considered statistically significant). Furthermore, the effect of age on the risk of the primary safety end point and of the key composite efficacy end point was investigated with a multivariable Cox proportional hazard regression model that included treatment and age as a continuous variable, as well as the interaction between treatment and age. The resulting hazard ratios (HRs) and confidence intervals (CIs) comparing dabigatran 110 or 150 mg dual versus warfarin triple therapy for varying values of age were visualized via interaction plots.

Results

Of the 2,725 patients randomized to treatment, 1,026 (37.7%) were categorized into older and 1,699 (62.3%) into younger age groups (Figure 1). Baseline characteristics of older and younger patients are shown in Table 1. Compared with younger patients, older patients were at higher risk of

Table 1
Baseline characteristics according to age groups

Variable	Age (yrs)	
	(≥ 75 years) Total (n = 1,026)	(< 75 years) Total (n = 1,699)
Mean age (yrs, ± SD)	79.3 ± 3.6	65.6 ± 6.5
Men	704 (68.6%)	1366 (80.4%)
CHA_2DS_2-VASc* score		
Mean ± SD	4.6 ± 1.3	3.0 ± 1.4
0	0	32 (1.9%)
1	0	171 (10.1%)
2	38 (3.7%)	429 (25.3%)
> 2	988 (96.3%)	1,067 (62.8%)
Modified HAS-BLED† score		
Mean ± SD	3.0 ± 0.6	2.5 ± 0.7
< 3	151 (14.7%)	792 (46.6%)
≥ 3	875 (85.3%)	907 (53.4%)
Diabetes mellitus‡	343 (33.4%)	650 (38.3%)
Previous stroke‡	103 (10.0%)	123 (7.2%)
Previous percutaneous coronary intervention‡	337 (32.8%)	575 (33.8%)
Previous stent thrombosis§	24 (2.3%)	44 (2.6%)
Previous coronary artery disease‡	692 (67.4%)	1136 (66.9%)
Previous myocardial infarction	247 (24.1%)	452 (26.6%)
Previous coronary artery bypass graft‡	117 (11.4%)	170 (10.0%)
Previous pulmonary embolism‖	16 (1.6%)	20 (1.2%)
Previous systemic embolism‡	7 (0.7%)	14 (0.8%)

SD = standard deviation.
* The CHA_2DS_2-VASc score reflects the risk of stroke, with values ranging from 0 to 9 and higher scores indicating greater risk.
† The HAS-BLED score reflects the risk of major bleeding in patients with atrial fibrillation who are receiving anticoagulant therapy, with values ranging from 0 to 9 and with higher scores indicating greater risk.
‡ Data missing from 1 younger patient.
§ Data missing from 15 older and 29 younger patients.
‖ Data missing from 3 older and 5 younger patients.

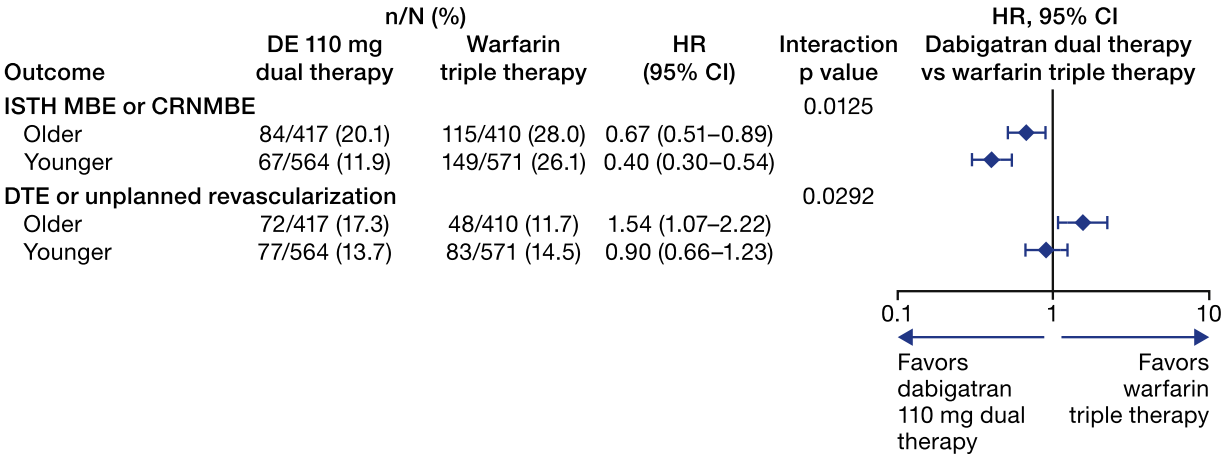


Figure 2. Outcomes in older and younger patients according to treatment: dabigatran 110 mg dual therapy.
Patients aged ≥ 80 years outside the United States and patients aged ≥ 70 years from Japan were assigned to either DE 110 mg or warfarin in a 1:1 ratio; all other patients are randomized to all 3 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.

bleeding and stroke, whereas previous medical history was broadly similar.

Dabigatran 110 mg dual therapy lowered the risk of MBE/CRNMBE versus warfarin triple therapy in older patients (HR 0.67; 95% CI 0.51 to 0.89) and younger patients (HR 0.40; 95% CI 0.30 to 0.54; Figures 2 and 3). Younger patients seem to be favored even more with respect to MBE/CRNMBE by the 110 mg dabigatran dose than older patients, as suggested by the significant interaction p value (0.013; Figure 2). Dabigatran 150 mg dual therapy lowered the risk of MBE/CRNMBE 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: 0.001; Figures 4 and 5). A reliable conclusion is however difficult, because the number of older patients with dabigatran 150 mg dual therapy is low.

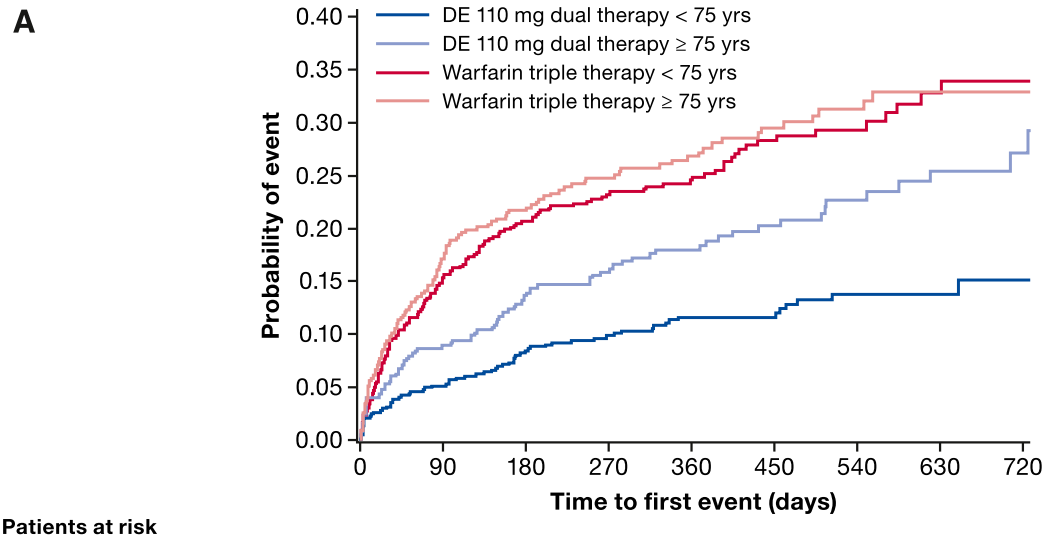
For the thromboembolic end point, there was a trend of a higher risk with dabigatran 110 mg dual therapy in older patients compared with warfarin triple therapy (HR 1.54; 95% CI 1.07 to 2.22), whereas the risk was similar to warfarin triple therapy in younger patients (HR 0.90; 95% CI 0.66 to 1.23; Figures 2 and 3). Thus, older patients seem to be less protected for thromboembolic events by the dabigatran 110 mg dose than younger patients, as is suggested by the significant interaction p value (0.029; Figure 2). For dabigatran 150 mg dual therapy, the thromboembolic risk versus warfarin triple therapy was similar in older (HR 1.34; 95% CI 0.73 to 2.44) and younger patients (HR 0.79; 95% CI 0.57 to 1.09; interaction p value: 0.129; Figures 4 and 5). A reliable conclusion is however difficult, because the number of older patients with dabigatran 150 mg dual therapy is low.

The interaction plots 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 6 and 7. They mainly support the results as obtained from the subgroup analysis. However, in contrast to the subgroup analysis with age as a categorical variable, the interaction p value from the model considering age as a continuous variable was statistically not significant (0.219) when comparing the efficacy between dabigatran 110 mg dual therapy and warfarin triple therapy.

Discussion

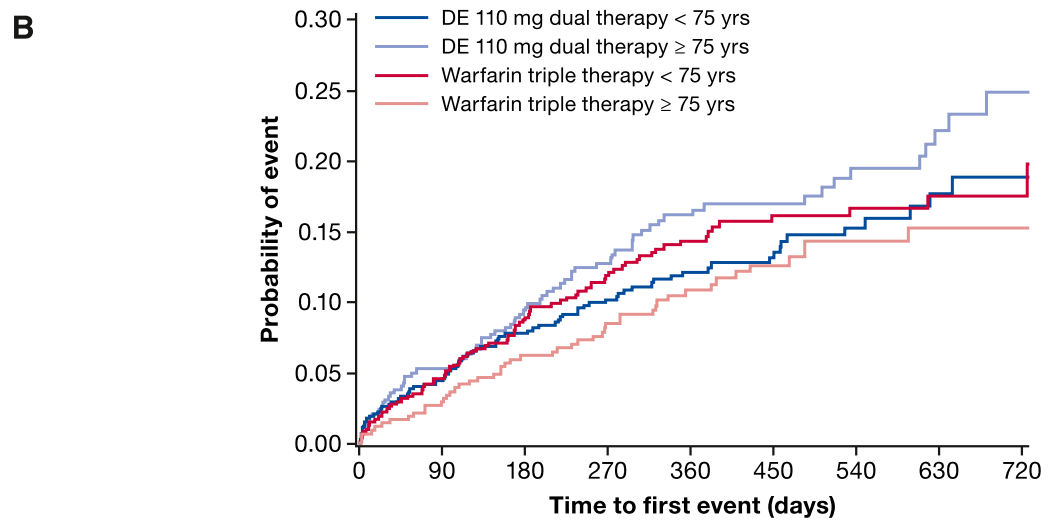
Because older patients have an increased risk both for bleeding and for thromboembolic events compared with younger patients, we analyzed whether the observed reduction of bleeding and similar thromboembolic risk with the use of dabigatran dual therapy compared with warfarin triple therapy observed in RE-DUAL PCI was the same in older (≥ 75 years of age) and in younger (< 75) patients. The most important findings of this analysis were: (1) both older and younger patients had a lower risk of bleeding with dabigatran 110 mg dual therapy than with warfarin triple therapy; (2) in younger patients treated with dabigatran 110 mg dual therapy, the risk of the thromboembolic end point was similar to that of patients treated with warfarin triple therapy, whereas in older patients, the risk tended to be higher for patients treated with dabigatran dual therapy; (3) the benefit of dabigatran 150 mg dual therapy with regard to bleeding risk was observed only in younger patients, whereas the results suggest no benefit in older patients; (4) the risk of the thromboembolic end point with dabigatran 150 mg dual versus warfarin triple therapy was similar in older and younger patients; (5) a reliable conclusion for older patients treated with dabigatran 150 mg dual versus warfarin triple therapy is difficult because of the low numbers.

There is a paucity of published data to guide anticoagulation regimens in older patients with AF who underwent PCI. Neither the WOEST, PIONEER-PCI, nor AUGUSTUS trials reported comparative outcomes in different age groups.[4–6] Subgroup analysis of the RE-LY trial based on age category showed that dabigatran at 110 and 150 mg twice daily doses was associated with lower risks of intracranial and extracranial bleeding compared with warfarin in younger patients (age <75 years), whereas older patients had a lower risk of intracranial bleeding and a similar or



Patients at risk

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



Patients at risk

DE 110 mg dual therapy < 75 yrs	564	537	507	413	333	229	152	85	48
DE 110 mg dual therapy ≥ 75 yrs	417	390	366	286	223	170	120	79	41
Warfarin triple therapy < 75 yrs	571	533	485	392	312	208	132	81	41
Warfarin triple therapy ≥ 75 yrs	410	388	369	308	236	175	127	80	40

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.

higher risk of extracranial bleeding with dabigatran than warfarin, the latter potentially attributable to a combination of age-related factors such as decreased renal excretion and increased prevalence of gastrointestinal pathology and pharmacokinetic interactions.[7] Our analysis also shows different outcomes in elderly patients compared with younger patients. For the 110-mg dabigatran dose (when combined with clopidogrel or ticagrelor), the results suggest that it is less effective in preventing thromboembolism in older patients compared with younger patients. For the 150-mg dabigatran dose (combined with clopidogrel or ticagrelor), the results suggest that there is no reduced bleeding risk in older patients compared with warfarin triple therapy which was observed in younger patients. The same factors observed in the RE-LY trial explaining the different effects of dabigatran in elderly patients may apply to this analysis.

A limitation of our current analysis is that, as a subgroup analysis of the RE-DUAL PCI trial, it was not powered for

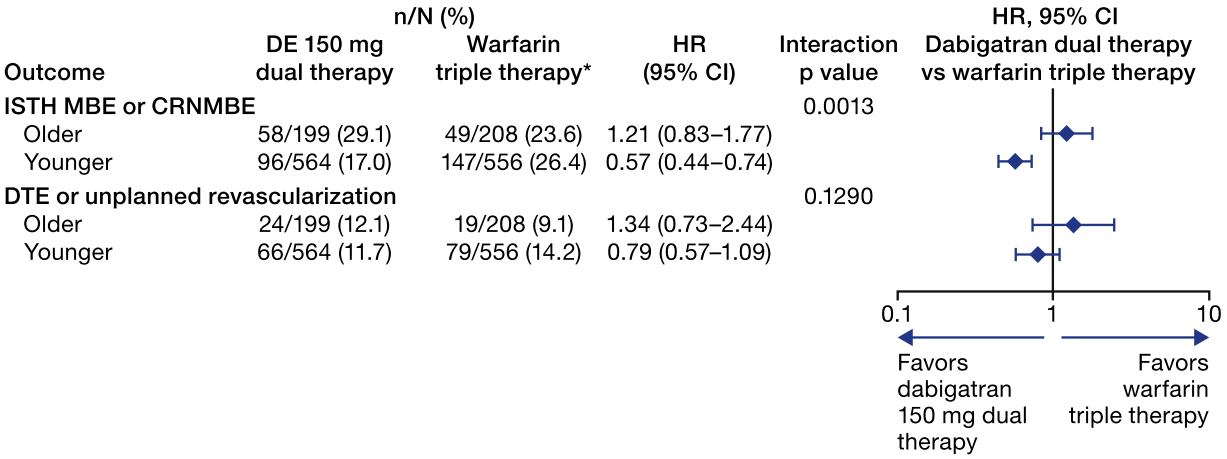


Figure 4. Outcomes in older and younger patients according to treatment: dabigatran 150 mg dual therapy.
Patients aged ≥ 80 years outside the United States and patients aged ≥ 70 years from Japan were assigned to either DE 110 mg or warfarin in a 1:1 ratio; all other patients are randomized to all 3 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.

formal statistical analysis. The moderate size of the RE-DUAL PCI patient cohort, and the fact that outcomes data were prospectively collected and adjudicated, alleviate this limitation to an extent, but for the low number of older patients treated with dabigatran 150 mg dual therapy, a reliable conclusion is difficult.

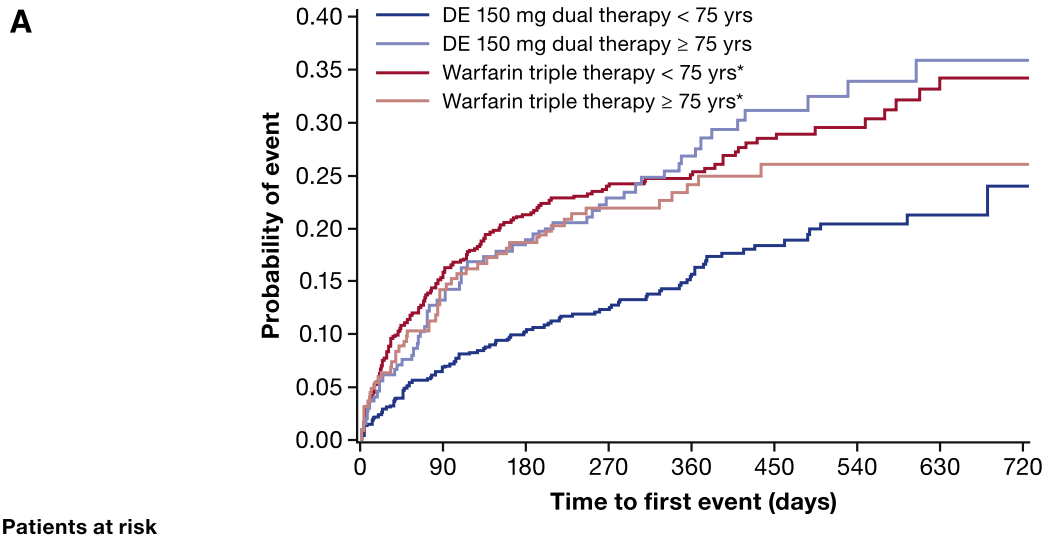
In conclusion, dabigatran 110 mg dual therapy provided a consistent reduction in bleeding risk compared with warfarin triple therapy in both older and younger patients. The risk for the thromboembolic end point appeared to be higher in older patients with dabigatran 110 mg dual therapy versus warfarin triple therapy but the risk was similar in younger patients. Dabigatran 150 mg dual therapy lowered bleeding risk compared with warfarin triple therapy in younger patients, whereas the benefit for risk of bleeding in older patients could not be observed. For the thromboembolic end point, the results suggest similar risks with dabigatran 150 mg dual therapy as for warfarin triple therapy in both 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.

Disclosures

Jurrien M. ten Berg reports advisory/consulting/speakers' fees from Accumetrics, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Eli Lilly, The Medicines Company, and Pfizer, and research grants from AstraZeneca and ZonMw.

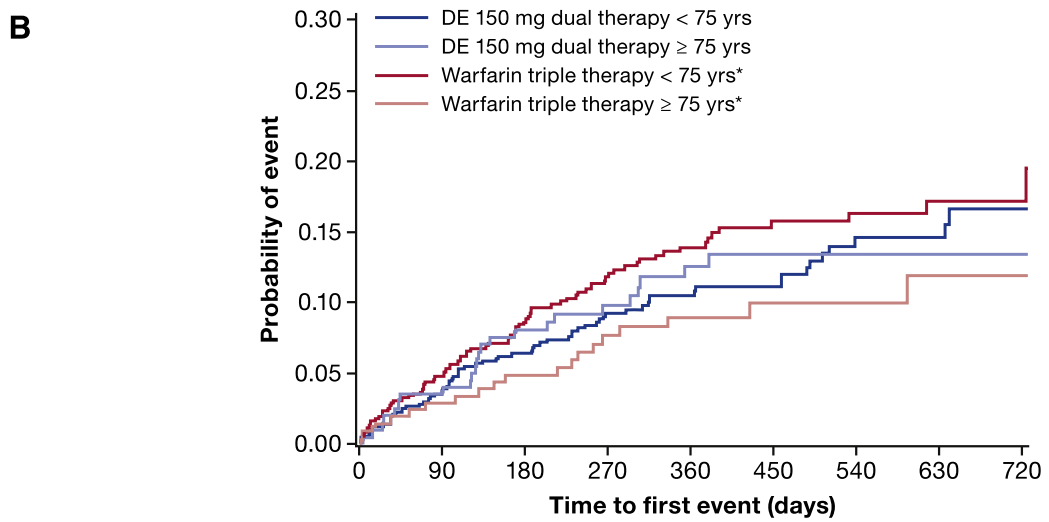
Philippe Gabriel Steg reports research grants from Amarin, Bayer, Sanofi, and Servier; speaking or consulting fees from Amarin, Amgen, AstraZeneca, Bayer/Janssen, Boehringer Ingelheim, Bristol-Myers-Squibb, Idorsia, Lilly, Merck, Novartis, Novo Nordisk, Pfizer, Regeneron, Sanofi, Servier.

Deepak L. Bhatt discloses the following relationships - Advisory Board: Cardax, Cereno Scientific, Elsevier Practice Update Cardiology, Medscape Cardiology, PhaseBio, Regado Biosciences; Board of Directors: Boston VA Research Institute, Society of Cardiovascular Patient Care, TobeSoft; Chair: American Heart Association Quality Oversight Committee; Data Monitoring Committees: Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute, for the PORTICO trial, funded by St. Jude Medical, now Abbott), Cleveland Clinic (including for the ExCEED trial, funded by Edwards), Duke Clinical Research Institute, Mayo Clinic, Mount Sinai School of Medicine (for the ENVISAGE trial, funded by Daiichi Sankyo), Population Health Research Institute; Honoraria: American College of Cardiology (Senior Associate Editor, Clinical Trials and News, ACC.org; Vice-Chair, ACC Accreditation Committee), Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute; RE-DUAL PCI clinical trial steering committee funded by Boehringer Ingelheim; AEGIS-II executive committee funded by CSL Behring), Belvoir Publications (Editor in Chief, Harvard Heart Letter), Duke Clinical Research Institute (clinical trial steering committees, including for the PRONOUNCE trial, funded by Ferring Pharmaceuticals), HMP Global (Editor in Chief, Journal of Invasive Cardiology), Journal of the American College of Cardiology (Guest Editor; Associate Editor), Medtelligence/ReachMD (CME steering committees), Population Health Research Institute (for the COMPASS operations committee, publications committee, steering committee, and USA national co-leader, funded by Bayer), Slack Publications (Chief Medical Editor, Cardiology Today's Intervention), Society of Cardiovascular Patient Care (Secretary/Treasurer), WebMD (CME steering committees); Other: Clinical Cardiology (Deputy Editor), NCDR-ACTION Registry Steering Committee (Chair), VA CART Research and Publications Committee (Chair); Research Funding: Abbott, Afimmune, Amarin, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Chiesi, CSL Behring, Eisai, Ethicon, Ferring Pharmaceuticals, Forest Laboratories, Fractyl, Idorsia, Ironwood, Ischemix, Lilly, Medtronic,



Patients at risk

DE 150 mg dual therapy < 75 yrs	564	523	485	390	301	207	137	85	49
DE 150 mg dual therapy ≥ 75 yrs	199	171	155	124	103	71	45	28	16
Warfarin triple therapy < 75 yrs*	556	455	399	320	252	157	103	61	31
Warfarin triple therapy ≥ 75 yrs*	208	175	163	126	97	65	49	27	16



Patients at risk

DE 150 mg dual therapy < 75 yrs	564	541	512	415	327	234	153	98	53
DE 150 mg dual therapy ≥ 75 yrs	199	192	176	143	120	87	56	33	19
Warfarin triple therapy < 75 yrs*	556	518	472	380	304	203	130	81	41
Warfarin triple therapy ≥ 75 yrs*	208	198	191	154	122	83	63	37	20

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.

PhaseBio, Pfizer, Regeneron, Roche, Sanofi Aventis, Synaptic, The Medicines Company; Royalties: Elsevier (Editor, Cardiovascular Intervention: A Companion to Braunwald's Heart Disease); Site Co-Investigator: Biotronik, Boston Scientific, CSI, St. Jude Medical (now Abbott), Svelte; Trustee: American College of Cardiology; Unfunded Research: FlowCo, Merck, Novo Nordisk, PLx Pharma, Takeda.

Stefan H. Hohnloser reports personal fees from Bayer HealthCare, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Medtronic, Pfizer, SJM, and ZOLL.

Anne de Veer reports consulting fees from Bayer and Boehringer Ingelheim.

Matias Nordaby is an employee of Boehringer Ingelheim International GmbH.

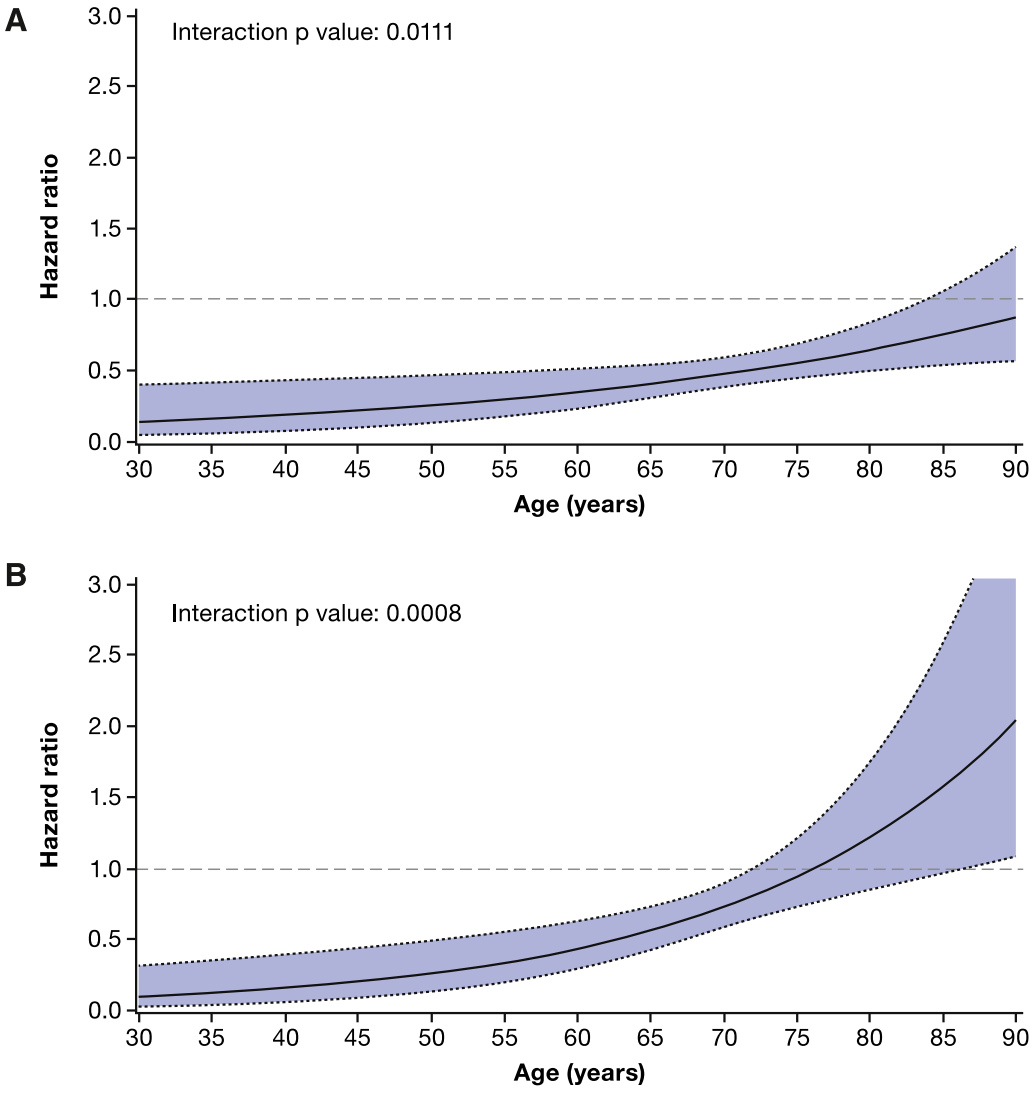


Figure 6. ISTH MBE and CRNMBE—interaction plot for varying values of age as a continuous variable: (*A*) dabigatran 110 mg dual therapy; (*B*) dabigatran 150 mg dual therapy.
HRs (solid lines) and Wald 95% CIs from Cox proportional hazard model including treatment, age, and interaction between treatment 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.

Corinna Miede is an employee of HMS Analytical Software GmbH.

Takeshi Kimura reports grants from Boehringer Ingelheim.

Gregory Y.H. Lip has served as a consultant for Bayer/Janssen, Bristol-Myers Squibb/Pfizer, Medtronic, Boehringer Ingelheim, Novartis, Verseon, and Daiichi Sankyo. He has been a speaker for Bayer, Bristol-Myers Squibb /Pfizer, Medtronic, Boehringer Ingelheim, and Daiichi Sankyo. No fees are directly received personally.

Jonas Oldgren reports fees to his institution from AstraZeneca, Bayer HealthCare, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Pfizer, Portola, Roche Diagnostics, and Sanofi.

Christopher P. Cannon reports research grants from Amgen, Boehringer-Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Janssen, Merck; consulting fees from Aegerion, Alnylam, Amarin, Amgen, Boehringer Ingelheim, Bristol-Myers Squib, Corvidia, Eisai, Innovent, Janssen, Kowa, Merck, Pfizer, Regeneron, Sanofi.

Author Contributions

JM ten Berg, PG Steg, DL Bhatt, SH Hohnloser, A de Veer, T Kimura, GYH Lip, J Oldgren, and CP Cannon: Conceptualization; Investigation; Methodology; Validation; Writing (review and editing).

M Nordaby: Conceptualization; Methodology; Project administration; Resources; Software; Supervision; Validation; Writing (review and editing).

C Miede: Conceptualization; Data curation; Formal analysis; Methodology; Project administration; Resources; Software; Supervision; Validation; Writing (review and editing).

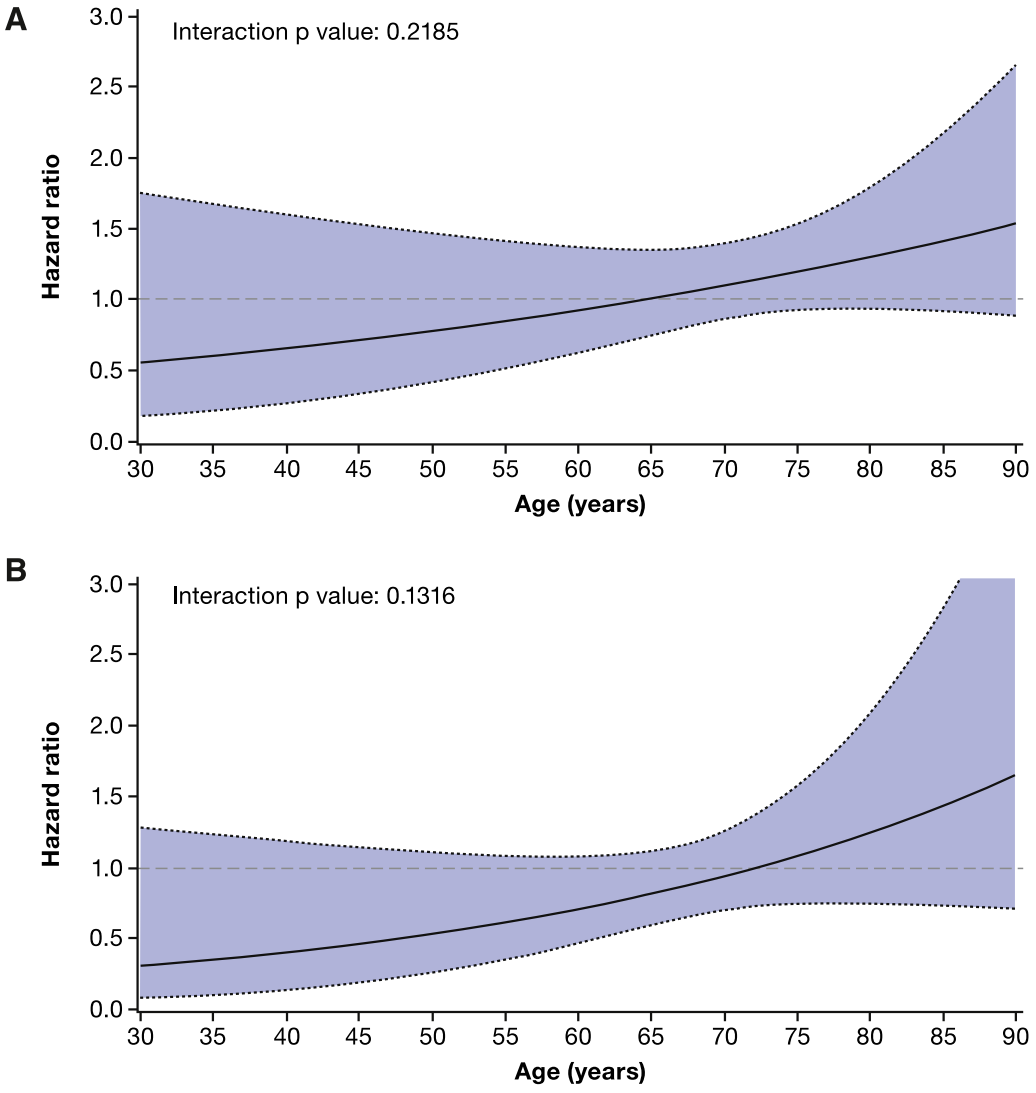


Figure 7. DTE and unplanned revascularization—interaction plot for varying values of age as a continuous variable: (*A*) dabigatran 110 mg dual therapy; (*B*) dabigatran 150 mg dual therapy.
HRs (solid lines) and Wald 95% CIs from Cox proportional hazard model including treatment, age, and interaction 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.

Acknowledgment

Editorial assistance limited to formatting and figure preparation was provided by Bill Wolvey at Parexel, with funding from Boehringer Ingelheim.

Availability of Data and Material

To ensure independent interpretation of clinical study results, Boehringer Ingelheim grants all external authors 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 (eg, study report, study protocol, and 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 Boehringer Ingelheim Policy on Transparency and Publication of Clinical Study Data: https://trials.boehringer-ingelheim.com/transparency_policy.html

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/trial_results/clinical_submission_documents.html

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://clinicalstudydatarequest.com to request access to study data.

Submission of Declaration

This article has not been published previously and is not under consideration for publication elsewhere.

Its publication is approved by all the authors.

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