Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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Additional information on this study and the drug concerned may be provided upon request based on **Boehringer Ingelheim's Policy on Transparency and Publication of Clinical Study Data**.

Name of Company: Boehringer Ingelheim		**Synopsis**	Boehringer Ingelheim
BI Proprietary Name: Pradaxa®		**EudraCT No.:** 2013-003201-26	
BI Investigational Product: Dabigatran etexilate		**Page:** 1 of 17	
Report Date: 13 Nov 2017	**Trial No. / Doc. No.:** 1160.186 / c13531195-01	**Dates of Trial:** 06 Aug 2014 – 05 Jun 2017	**Date of Revision:** Not applicable

Title of Trial:	A prospective **R**andomised, open label, blinded endpoint (PROBE) study to **E**valuate **DUAL** antithrombotic therapy with dabigatran etexilate (110 mg and 150 mg b.i.d.) plus clopidogrel or ticagrelor vs. triple therapy strategy with warfarin (INR 2.0 – 3.0) plus clopidogrel or ticagrelor and aspirin in patients with non valvular atrial fibrillation (NVAF) that have undergone a percutaneous coronary intervention (**PCI**) with stenting **(RE-DUAL PCI)**
Coordinating Investigator:	Dr [redacted] USA
Trial Sites:	Multinational trial in 41 countries in 6 geographical regions (North America, Central Europe, Western Europe, Latin America, Asia, and others [Australia, New Zealand, and Israel])
Publications:	Cannon CP, Gropper S, Bhatt DL, et al. Clin Cardiol 2016: 39(10):555-564 Cannon CP, Bhatt DL, Oldgren J, et al. N Engl J Med, published on 27 Aug 2017, doi: 10.1056/NEJMoa1708454
Clinical Phase:	IIIb
Objectives:	The main objective of the trial was to compare a dual antithrombotic regimen of 110 mg dabigatran etexilate (DE 110) twice daily plus clopidogrel or ticagrelor (110 mg DE-DAT) and 150 mg dabigatran etexilate (DE 150) twice daily plus clopidogrel or ticagrelor (150 mg DE-DAT) with a triple antithrombotic therapy (TAT) of warfarin plus clopidogrel or ticagrelor plus aspirin (warfarin-TAT) in patients with non-valvular atrial fibrillation (NVAF) that underwent a percutaneous coronary intervention (PCI) with stenting.
Methodology:	Randomised, active-controlled, open-label, blinded endpoint, prospective trial comparing fixed-dose DE (110 mg or 150 mg twice daily) with warfarin (target international normalised ratio [INR] 2.0 to 3.0; 2.0 to 2.6 for Japanese patients aged ≥70 years). The trial employed a time-to-event analysis and all patients were to remain on trial treatment until the last entered patient completed at least 6 months of treatment. The patients were stratified by age (<70 or ≥70 in Japan and <80 or ≥80 years old everywhere else) and region (Europe/rest of world, USA, and Japan).

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No. of Patients:	
Planned:	Entered: 2502 (initial approximation which was planned to be adjusted in accordance with the event-driven character of the trial)
Actual:	Enrolled: 2845 Entered: 2725 110 mg DE-DAT (110 mg dabigatran etexilate plus clopidogrel or ticagrelor): Entered: 981 Treated: 972 Analysed (for primary endpoint): 981 150 mg DE-DAT (150 mg dabigatran etexilate plus clopidogrel or ticagrelor): Entered: 763 Treated: 758 Analysed (for primary endpoint): 763 Warfarin-TAT (warfarin plus clopidogrel or ticagrelor plus aspirin): Entered: 981 Treated: 948 Analysed (for primary endpoint): 981
Diagnosis:	Patients with NVAF that underwent a successful PCI with stenting (elective or due to an acute coronary syndrome [ACS])
Main Criteria for Inclusion:	Male or female patients aged ≥18 years (≥20 years for Japan) with NVAF presenting with either ACS that had been successfully treated by PCI and stenting (either bare metal stent or drug eluting stent) or stable coronary artery disease with at least one lesion eligible for PCI that had been successfully treated by elective PCI and stenting (either bare metal stent or drug eluting stent). The patients were included if they had been receiving oral anticoagulant treatment (with warfarin, another vitamin K antagonist, or other novel oral anticoagulant) or had been treatment-naïve prior to PCI.
BI Investigational Product:	Dabigatran etexilate
Dose:	1 capsule of 110 mg twice daily or 1 capsule of 150 mg twice daily
Mode of Admin.:	Oral
Batch Nos.:	110 mg: 10222126-007D, 10222126-012D, 10222126-026D, 10222126-024D, 10222126-037D, CT3283/3 150 mg: 10222126-008D, 10222126-013D, 10222126-027D, 10222126-025D, 10222126-038D, CT3283/4 110 mg for Japan: 10222126-020D, CT3283/1 150 mg for Japan: 10222126-021D, CT3283/2

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Comparator Product:	Warfarin
Dose:	1 tablet of 1 mg, 3 mg, or 5 mg once daily (as needed to maintain a target INR of 2.0 to 3.0; 2.0 to 2.6 for Japanese patients aged ≥70 years)
Mode of Admin.:	Oral
Batch Nos.:	1 mg: 10222126-004D, 10222126-009D, 10222126-031D, 10222126-028D, 10222126-039D, E119327-0003L006 3 mg: 10222126-005D, 10222126-010D, 10222126-032D, 10222126-029D, 10222126-040D, E119327-0004L002 5 mg: 10222126-006D, 10222126-011D, 10222126-033D, 10222126-030D, 10222126-041D, E119327-0005L001 1 mg for Japan: 10222126-022D, E119327-0003L005 3 mg for Japan: 10222126-023D, E119327-0004L001
Duration of Treatment:	The planned minimum duration of trial treatment was 6 months.
Criteria for Evaluation:	

Efficacy:	The secondary efficacy endpoints (all time-to-first-event and based on adjudicated data) were:
	• A composite endpoint of death, thrombotic events (i.e. all deaths, myocardial infarction, stroke, and systemic embolism), or unplanned revascularisation by PCI/coronary artery bypass graft (CABG)
	• A composite endpoint of death or thrombotic events (i.e. all deaths, myocardial infarction, stroke, and systemic embolism)
	• Individual outcome events:
	  o All deaths (cardiovascular death, non-cardiovascular death, undetermined cause)
	  o Myocardial infarction
	  o Stroke
	  o Systemic embolism
	  o Stent thrombosis
	• Composite endpoint of death, myocardial infarction, or stroke
	• Unplanned revascularisation by PCI/CABG

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Criteria for Evaluation (cont.):
Safety:
	The primary endpoint for this trial was time to first major (MBE) or clinically relevant non-major bleeding event (CRNMBE) based on the definition of the International Society of Thrombosis and Haemostasis (ISTH) and was analysed based on adjudicated data.
	The following other safety endpoints complement the analysis of the primary endpoint:
	• ISTH MBE
	• ISTH CRNMBE
	• Life-threatening bleeds
	• Intracranial haemorrhage
	• Fatal bleeds
	• Clinically relevant bleeding measured using the following definitions
	  o Bleeding Academic Research Consortium (BARC) ≥3
	  o Thrombolysis in myocardial infarction (TIMI) group (i.e. major plus minor bleeding events)
	• Total bleeds

Statistical Methods:	Time-to-event endpoints were analysed based on a Cox proportional hazards regression model. The model for the 110 mg DE-DAT versus warfarin comparison was stratified by age group (elderly versus non-elderly) and treatment arm (110 mg DE-DAT versus warfarin-TAT and the combination of 110 mg and 150 mg DE-DAT versus warfarin-TAT). Non-elderly was defined as <70 years (Japan) and <80 years (rest of world); elderly was defined as ≥70 years (Japan) and ≥80 years (rest of world). The model for 150 mg DE-DAT was an unstratified Cox proportional hazards regression model which compared 150 mg DE-DAT versus warfarin-TAT, excluding elderly patients outside the USA in the warfarin-TAT group. As sensitivity analysis, an unstratified analysis of only the non-elderly patients was conducted. Models were fitted for each comparison separately, i.e. 110 mg DE-DAT versus warfarin-TAT and 150 mg DE-DAT versus warfarin-TAT. To control the type I error rate at a 1-sided 0.025 level, a 6-step hierarchical procedure for multiple testing was used to test the safety hypotheses, comparing the individual or pooled DE-DAT groups versus warfarin-TAT. Additional testing for safety and efficacy endpoints was also included in this hierarchical procedure.

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Statistical Methods (cont.):

The hierarchical procedure started with the non-inferiority testing of the primary endpoint, first for 110 mg DE-DAT and then for 150 mg DE-DAT. If established, non-inferiority of the pooled DE-DAT groups (all DE) was to be tested for the secondary endpoint 'death, thrombotic events, or unplanned revascularisation by PCI/CABG'. If established, superiority of 110 mg DE-DAT was tested for the primary endpoint, followed by non-inferiority testing of all DE for the secondary endpoint 'death or thrombotic events'. If established, superiority of 150 mg DE-DAT was to be tested for the primary endpoint. All non-inferiority tests were based on a margin of 1.38. The primary analysis was performed on the full analysis set of randomised patients, following the intention-to-treat principle. No interim analysis was planned or conducted.

The other safety endpoints were analysed using the same methods as the primary safety endpoint. However, multiplicity adjustments and model assumption checking were not performed; sensitivity analyses were only run to a limited extent.

SUMMARY - CONCLUSIONS:

Trial Subjects and Compliance with Trial Protocol:

Of the 2845 screened patients, 2725 patients (100.0%) were randomised and 2678 patients (98.3%) were treated with trial medication. A total of 120 patients were screening failures. The following text summarises the disposition, compliance, and patient characteristics based on the full analysis set containing all randomised patients.

Of the 2678 patients (98.3%) treated with randomised trial medication, a total of 287 patients (10.5%) prematurely discontinued the trial. The proportion of patients who prematurely discontinued the trial was higher on warfarin-TAT (13.5%) than on DE-DAT (110 mg DE-DAT: 9.7%, 150 mg DE-DAT: 7.9%). The most frequent reasons for premature trial discontinuation were AEs (6.1%), with similar frequencies in all treatment groups, and withdrawn consent (3.1%), with more patients on warfarin-TAT who withdrew consent compared with patients on DE-DAT. Of the 287 patients who prematurely discontinued the trial, 6 patients were lost to follow-up without vital status at the end of the trial and 62 patients withdrew their consent and had no vital status information available at the end of the trial.

Of the patients who completed the trial, the majority of patients completed it on trial medication (75.1%). About a quarter of all randomised patients prematurely discontinued the intake of trial medication, with a higher

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Trial Subjects and Compliance with Trial Protocol (cont.):

proportion in the warfarin-TAT (29.5%) than in the DE-DAT groups (110 mg DE-DAT: 22.5%, 150 mg DE-DAT: 20.7%). The most frequent reasons for premature discontinuation of trial medication were AEs (other than worsening of trial disease or other pre-existing disease), followed by the refusal to continue with trial medication. Important protocol violations were reported more frequently in the warfarin-TAT group (66.0%, excluding elderly patients outside the USA: 65.5%) than on DE-DAT (110 mg DE-DAT: 48.9%, 150 mg DE- DAT: 47.1%); this difference was primarily driven by the important protocol violation 'time in therapeutic range' which only applied to patients on warfarin.

Demographics and baseline characteristics were well balanced across the 3 treatment groups except for differences regarding age and age-related parameters which were to be expected due to the applied randomisation strategy. Overall, 76.0% of patients were men. The majority of patients were White (86.0%). The overall mean age was 70.8 years (SD: 8.66). The mean age in the 150 mg DE-DAT (68.6 years, SD: 7.65) and the corresponding warfarin-TAT group (68.8 years, SD: 7.66) groups was about 3 years lower than in the 110 mg DE-DAT (71.5 years, SD: 8.87) and complete warfarin-TAT group (71.7 years, SD: 8.90). This difference reflects the randomisation strategy: the vast majority of patients randomised to 150 mg DE-DAT were non-elderly as elderly patients outside the USA were not randomised to 150 mg DE-DAT mg DE-DAT.

The most frequent indication for PCI was acute coronary syndrome (50.5%), followed by stable angina/positive stress test in 43.4% of patients. The vast majority of patients received a drug-eluting stent (82.6%). Overall, 86.7% of patients took clopidogrel and few patients received ticagrelor (12.0%) at baseline.

Exposure results were consistent with the trial design and similar across the treatment groups. In line with the planned minimum treatment duration of 6 months, most treated patients were exposed to trial medication for 6 to <12 months (31.0%) or for 12 to <18 months (27.9%) with a mean treatment duration of 12.2 months.

In the DE-DAT groups, 91.3% of the treated patients achieved treatment compliance of 80 to 120%. In the warfarin-TAT group, the overall mean % of time that patients were in the guideline-defined target INR range (2.0 to 3.0) was 58.97% (SD 23.09).

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Efficacy Results:

Secondary endpoints

According to the prespecified hierarchical testing strategy, the data demonstrated that dual antithrombotic therapy with dabigatran etexilate (combined 110 mg DE-DAT and 150 mg DE-DAT) was non-inferior to triple therapy with warfarin (warfarin-TAT) with respect to the composite endpoint of 'death, thrombotic events (myocardial infarction, stroke, systemic embolism), or unplanned revascularisation by PCI/CABG'. The frequency of patients with events in the combined dual therapy groups with dabigatran etexilate was with 13.7% similar to the frequency of patients with events observed for warfarin-TAT (13.4%), see Table 1. For the comparisons based on individual DE-DAT groups, the HR versus warfarin-TAT was 1.13 (95% CI 0.90, 1.43) for 110 mg DE-DAT and 0.89 (95% CI 0.67, 1.19) for 150 mg DE-DAT, with all 95% CIs of the HR versus warfarin-TAT containing 1.

For all secondary endpoints, the results of the main analyses were confirmed by sensitivity and subgroup analyses, with some heterogeneity among few subgroups.

Table 1 Cox regression for time to first death, thrombotic event, or unplanned revascularisation by PCI/CABG (ITT period) - FAS

	All DE	110 mg DE-DAT	Warfarin-TAT	150 mg DE-DAT	Warfarin-TAT[1]
Randomised patients, N	1744	981	981	763	764
Patients with an event, N (%)	239 (13.7)	149 (15.2)	131 (13.4)	90 (11.8)	98 (12.8)
HR vs. warfarin	1.04	1.13		0.89	
95% CI	(0.84, 1.29)	(0.90, 1.43)		(0.67, 1.19)	
Non-inferiority p-value[2]	0.0047				
Superiority p-value[3]	0.7381	0.3002		0.4432	

[1] Excluding elderly patients outside the USA
[2] Non-inferiority margin = 1.38; non-inferiority was formally only tested for all DE vs. warfarin-TAT.
[3] Superiority was not formally tested; p-value provided for descriptive purposes only.

For the secondary composite endpoint 'death or thrombotic events (myocardial infarction, stroke, systemic embolism)', non-inferiority of the combined groups of 110 mg DE-DAT and 150 mg DE-DAT versus warfarin-TAT was not formally shown based on the predefined 1-sided alpha level of 2.5%. The frequency of patients with events in the combined dual therapy

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Efficacy Results (cont.):

groups with dabigatran etexilate (9.6%) was slightly higher than on triple therapy with warfarin (8.5%), see Table 2. The HR versus warfarin-TAT was 1.30 (95% CI 0.98, 1.73) for 110 mg DE-DAT and 0.97 (95% CI 0.68, 1.39) for 150 mg DE-DAT, with all 95% CIs of the HR versus warfarin-TAT containing 1.

Table 2 Cox regression for time to first death or thrombotic event (ITT period) - FAS

	All DE	110 mg DE-DAT	Warfarin-TAT	150 mg DE-DAT	Warfarin-TAT[1]
Randomised patients, N	1744	981	981	763	764
Patients with an event, N (%)	168 (9.6)	108 (11.0)	83 (8.5)	60 (7.9)	60 (7.9)
HR vs. warfarin	1.17	1.30		0.97	
95% CI	(0.90, 1.53)	(0.98, 1.73)		(0.68, 1.39)	
Non-inferiority p-value[2]	0.1128				
Superiority p-value[3]	0.2450	0.0720		0.8750	

[1] Excluding elderly patients outside the USA
[2] Non-inferiority margin = 1.38; non-inferiority was formally only tested for all DE vs. warfarin-TAT.
[3] Superiority was not formally tested; p-value provided for descriptive purposes only.

The outcome event death from any cause included CV death, non-CV death, and undetermined cause of death. The majority of all deaths were due to CV deaths. The number of patients with non-CV deaths and undetermined deaths was low. For both treatment comparisons, similar proportions of patients died from any cause in this trial (Table 3). For all categories of death, no statistically significant treatment difference to warfarin-TAT was noted for the DE-DAT groups. All 95% CIs of the HR versus warfarin-TAT contained 1.

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Efficacy Results (cont.):

Table 3 Cox regression for time to death (ITT period) - FAS

	110 mg DE-DAT	Warfarin-TAT	150 mg DE-DAT	Warfarin-TAT[1]
Randomised patients, N	981	981	763	764
All-cause death				
Patients with an event, N (%)	55 (5.6)	48 (4.9)	30 (3.9)	35 (4.6)
HR vs. warfarin (95% CI)	1.12 (0.76, 1.65)		0.83 (0.51, 1.34)	
p-value[2]	0.5579		0.4414	
CV death				
Patients with an event, N (%)	37 (3.8)	31 (3.2)	21 (2.8)	24 (3.1)
HR vs. warfarin (95% CI)	1.17 (0.72, 1.88)		0.84 (0.47, 1.51)	
p-value[2]	0.5252		0.5670	
Non-CV death				
Patients with an event, N (%)	14 (1.4)	13 (1.3)	4 (0.5)	8 (1.0)
HR vs. warfarin (95% CI)	1.06 (0.50, 2.25)		0.49 (0.15, 1.61)	
p-value[2]	0.8853		0.2380	
Undetermined death				
Patients with an event, N (%)	4 (0.4)	4 (0.4)	5 (0.7)	3 (0.4)
HR vs. warfarin (95% CI)	0.99 (0.25, 3.95)		1.59 (0.38, 6.64)	
p-value[2]	0.9862		0.5277	

[1] Excluding elderly patients outside the USA
[2] Wald 2-sided p-value from (stratified) Cox proportional hazards model; provided for descriptive purposes only.

The Cox regression analyses for time to individual thromboembolic outcome event are summarised in Table 4, showing in general comparable proportions of patients with an event for both treatment comparisons. Treatment with 150 mg DE-DAT showed a tendency towards lower or similar frequencies of thromboembolic events when compared with the corresponding warfarin-TAT; treatment with 110 mg DE-DAT showed a tendency towards similar or higher frequencies of thromboembolic events when compared with warfarin-TAT. For the secondary endpoints stroke, systemic embolism, and definite stent thrombosis, the absolute number of patients with events was low.

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Efficacy Results (cont.):

Table 4 Cox regression for time to individual thromboembolic outcome event (ITT period) - FAS

	110 mg DE-DAT	Warfarin-TAT	150 mg DE-DAT	Warfarin-TAT[1]
Randomised patients, N	981	981	763	764
Myocardial infarction				
Patients with an event, N (%)	44 (4.5)	29 (3.0)	26 (3.4)	22 (2.9)
HR vs. warfarin (95% CI)	1.51 (0.94, 2.41)		1.16 (0.66, 2.04)	
p-value[2]	0.0861		0.6144	
Stroke				
Patients with an event, N (%)	17 (1.7)	13 (1.3)	9 (1.2)	8 (1.0)
HR vs. warfarin (95% CI)	1.30 (0.63, 2.67)		1.09 (0.42, 2.83)	
p-value[2]	0.4803		0.8537	
Systemic embolism				
Patients with an event, N (%)	3 (0.3)	3 (0.3)	1 (0.1)	3 (0.4)
HR vs. warfarin (95% CI)	0.94 (0.19, 4.66)		0.30 (0.03, 2.93)	
p-value[2]	0.9388		0.3030	
Definite stent thrombosis				
Patients with an event, N (%)	15 (1.5)	8 (0.8)	7 (0.9)	7 (0.9)
HR vs. warfarin (95% CI)	1.86 (0.79, 4.40)		0.99 (0.35, 2.81)	
p-value[2]	0.1546		0.9789	

[1] Excluding elderly patients outside the USA
[2] Wald 2-sided p-value from (stratified) Cox proportional hazards model; provided for descriptive purposes only.

For the composite endpoint of death, myocardial infarction, or stroke, treatment with 110 mg DE-DAT resulted in a higher frequency of patients with events compared with warfarin-TAT, resulting in a HR versus warfarin-TAT of 1.34 (95% CI 1.00, 1.79), see Table 5. Similar frequencies of patients with events were observed for the comparison of 150 mg DE-DAT versus warfarin-TAT (HR 1.03, 95% CI 0.71, 1.47). For unplanned revascularisation by PCI/CABG, similar frequencies of patients with event were observed for both treatment comparisons, resulting in HRs versus warfarin-TAT of 1.09 (95% CI 0.79, 1.51) for 110 mg DE-DAT and in 0.96 (0.65, 1.41) for 150 mg DE-DAT (Table 5). All 95% CIs of the HR versus warfarin-TAT contained 1.

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Efficacy Results (cont.):

Table 5 Cox regression for time to composite thromboembolic event (ITT period) - FAS

	110 mg DE-DAT	Warfarin-TAT	150 mg DE-DAT	Warfarin-TAT[1]
Randomised patients, N	981	981	763	764
Death, myocardial infarction, or stroke				
Patients with an event, N (%)	107 (10.9)	80 (8.2)	60 (7.9)	57 (7.5)
HR vs. warfarin (95% CI)	1.34 (1.00, 1.79)		1.03 (0.71, 1.47)	
p-value[2]	0.0484		0.8903	
Unplanned revascularisation by PCI/CABG				
Patients with an event, N (%)	76 (7.7)	69 (7.0)	51 (6.7)	52 (6.8)
HR vs. warfarin (95% CI)	1.09 (0.79, 1.51)		0.96 (0.65, 1.41)	
p-value[2]	0.6080		0.8348	

[1] Excluding elderly patients outside the USA
[2] Wald 2-sided p-value from (stratified) Cox proportional hazards model; provided for descriptive purposes only.

Safety Results:

Primary endpoint (time to first ISTH MBE or CRNMBE)

The primary endpoint of this trial was time to first adjudicated ISTH MBE or CRNMBE. The treatment with 110 mg DE-DAT was found to be superior to warfarin-TAT (HR 0.52; 95% CI 0.42, 0.63), while 150 mg DE-DAT was found to be non-inferior to warfarin-TAT (HR 0.72; 95% CI 0.58, 0.88). The treatment with 150 mg DE-DAT treatment was nominally superior to warfarin-TAT (p=0.0020), but this hypothesis was not formally tested. See Table 6 for details. Sensitivity analyses confirmed the findings of the primary analysis. Results of primary endpoint were confirmed by subgroup analyses, with some heterogeneity among few subgroups.

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Safety Results (cont.):

Table 6 Cox regression for time to first ISTH MBE or CRNMBE (ITT period) - FAS

	110 mg DE-DAT	Warfarin-TAT	150 mg DE-DAT	Warfarin-TAT[1]
Randomised patients, N	981	981	763	764
Patients with an event, N (%)	151 (15.4)	264 (26.9)	154 (20.2)	196 (25.7)
HR vs. warfarin (95% CI)	0.52 (0.42, 0.63)		0.72 (0.58, 0.88)	
Superiority p-value	<0.0001		0.0020[2]	
Non-inferiority p-value[3]	<0.0001		<0.0001	

[1] Excluding elderly patients outside the USA
[2] Superiority was not formally tested; p-value provided for descriptive purposes only.
[3] Non-inferiority margin = 1.38

The descriptive analysis of other safety endpoints was in line with the analyses of the primary endpoint. For most types of bleeding events, a nominally statistically significant decrease in bleeding events was observed for both treatment comparisons, favouring treatment with DE-DAT (Tables 7 and 8).

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Safety Results (cont.): Table 7 Cox regression for time to first ISTH MBE, life-threatening bleed, intracranial haemorrhage, and fatal bleed (ITT period) - FAS

	110 mg DE-DAT	Warfarin-TAT	150 mg DE-DAT	Warfarin-TAT[1]
Randomised patients, N	981	981	763	764
ISTH MBE				
Patients with an event, N (%)	49 (5.0)	90 (9.2)	43 (5.6)	64 (8.4)
HR vs. warfarin (95% CI)	0.52 (0.37, 0.74)		0.64 (0.43, 0.94)	
p-value[2]	0.0003		0.0220	
Life-threatening bleeding event				
Patients with an event, N (%)	19 (1.9)	38 (3.9)	16 (2.1)	30 (3.9)
HR vs. warfarin (95% CI)	0.49 (0.28, 0.85)		0.51 (0.28, 0.93)	
p-value[2]	0.0107		0.0286	
Intracranial haemorrhage				
Patients with an event, N (%)	3 (0.3)	10 (1.0)	1 (0.1)	8 (1.0)
HR vs. warfarin (95% CI)	0.30 (0.08, 1.07)		0.12 (0.02, 0.98)	
p-value[2]	0.0639		0.0474	
Fatal bleeding event				
Patients with an event, N (%)	4 (0.4)	5 (0.5)	3 (0.4)	4 (0.5)
HR vs. warfarin (95% CI)	0.79 (0.21, 2.93)		0.73 (0.16, 3.26)	
p-value[2]	0.7202		0.6802	

[1] Excluding elderly patients outside the USA
[2] Wald 2-sided p-value from (stratified) Cox proportional hazards model; provided for descriptive purposes only.

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Safety Results (cont.):

Table 8 Cox regression for time to first ISTH CRNMBE, clinically relevant bleed, and any bleed (ITT period) - FAS

	110 mg DE-DAT	Warfarin-TAT	150 mg DE-DAT	Warfarin-TAT[1]
Randomised patients, N	981	981	763	764
ISTH CRNMBE				
Patients with an event, N (%)	115 (11.7)	193 (19.7)	126 (16.5)	148 (19.4)
HR vs. warfarin (95% CI)	0.55 (0.44, 0.69)		0.79 (0.63, 1.01)	
p-value[2]	<0.0001		0.0581	
Clinically relevant bleeding event (BARC ≥3)				
Patients with an event, N (%)	37 (3.8)	75 (7.6)	34 (4.5)	53 (6.9)
HR vs. warfarin (95% CI)	0.48 (0.32, 0.71)		0.61 (0.40, 0.94)	
p-value[2]	0.0002		0.0240	
Clinically relevant bleeding event (TIMI major and minor)				
Patients with an event, N (%)	29 (3.0)	69 (7.0)	27 (3.5)	48 (6.3)
HR vs. warfarin (95% CI)	0.41 (0.26, 0.63)		0.53 (0.33, 0.85)	
p-value[2]	<0.0001		0.0090	
Total bleeding events				
Patients with an event, N (%)	266 (27.1)	421 (42.9)	254 (33.3)	316 (41.4)
HR vs. warfarin (95% CI)	0.54 (0.46, 0.63)		0.72 (0.61, 0.84)	
p-value[2]	<0.0001		<0.0001	

[1] Excluding elderly patients outside the USA
[2] Wald 2-sided p-value from (stratified) Cox proportional hazards model; provided for descriptive purposes only.

Adverse events

Overall, the frequencies of treatment-emergent AEs were very similar in all treatment groups in this open-label trial (110 mg DE-DAT: 76.9%, 150 mg DE-DAT: 76.9%, warfarin-TAT: 77.1%). Overall, the most frequently reported AEs on the preferred term (PT) level were epistaxis (110 mg DE-DAT: 5.5%, 150 mg DE-DAT: 7.9%, warfarin-TAT: 15.8%), dyspnoea (110 mg DE-DAT: 7.3%, 150 mg DE-DAT: 9.0%, warfarin-TAT: 7.9%), worsening of atrial fibrillation (110 mg DE-DAT: 7.4%, 150 mg DE-DAT: 7.1%, warfarin-TAT: 5.2%), cardiac failure (110 mg DE-DAT: 4.9%, 150 mg DE-DAT: 4.0%, warfarin-TAT: 4.9%), and haematoma (110 mg DE-DAT: 3.0%, 150 mg DE-DAT: 3.3%, warfarin-TAT: 7.1%). The majority of the

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Safety Results (cont.):

most frequently reported AEs were reported with similar frequencies in all groups. Dyspepsia was reported at a higher frequency on DE-DAT than on warfarin-TAT (110 mg DE-DAT: 3.0%, 150 mg DE-DAT: 3.3%, warfarin-TAT: 0.9%). Epistaxis and haematoma were reported with lower frequencies on DE-DAT than on warfarin-TAT. Increased international normalised ratio (INR) was only reported during warfarin-TAT treatment (3.7%), but this parameter was not measured in patients on DE-DAT.

For patients who discontinued the trial drug due to AEs, there was only a slight variation between the treatment groups (110 mg DE-DAT: 11.6%, 150 mg DE-DAT: 11.1%, warfarin-TAT: 8.9%). On the PT level, none of the AEs leading to treatment discontinuation was observed for ≥1% of patients.

The frequency of drug-related AEs as judged by the investigator was higher on warfarin-TAT compared with DE-DAT: 23.7% in the 110 mg DE-DAT group, 26.1% in the 150 mg DE-DAT group, and 35.3% in the warfarin-TAT group. Overall, the most frequently reported drug-related AEs on the PT level were epistaxis (110 mg DE-DAT: 4.3%, 150 mg DE-DAT: 5.3%, warfarin-TAT: 12.1%), haematoma (110 mg DE-DAT: 2.0%, 150 mg DE-DAT: 2.5%, warfarin-TAT: 4.5%), contusion (110 mg DE-DAT: 1.5%, 150 mg DE-DAT: 1.5%, warfarin-TAT: 3.0%), haematuria (110 mg DE-DAT: 1.7%, 150 mg DE-DAT: 2.0%, warfarin-TAT: 2.3%), and gingival bleeding (110 mg DE-DAT: 0.9%, 150 mg DE-DAT: 1.8%, warfarin-TAT: 3.2%). Drug-related dyspepsia was only reported in patients treated with DE-DAT (110 mg DE-DAT: 1.6%, 150 mg DE-DAT: 1.3%). Epistaxis, haematoma, contusion, and gingival bleeding were reported with lower frequencies on DE-DAT than on warfarin-TAT. Increased INR was only reported during warfarin-TAT treatment (3.1%), but this parameter was not measured in patients on DE-DAT.

AEs of severe intensity were reported for 19.2% of patients on 110 mg DE-DAT, 16.2% of patients on 150 mg DE-DAT, and 18.9% of patients on warfarin-TAT. Overall, the most frequently reported severe AEs on the PT level were vascular stent thrombosis (110 mg DE-DAT: 2.3%, 150 mg DE-DAT: 1.5%, warfarin-TAT: 2.0%) and cardiac disorders such as cardiac failure (110 mg DE-DAT: 1.2%, 150 mg DE-DAT: 1.8%, warfarin-TAT: 1.3%), acute myocardial infarction (110 mg DE-DAT: 1.3%, 150 mg DE-DAT: 1.3%, warfarin-TAT: 1.1%), myocardial infarction (110 mg DE-DAT: 1.2%, 150 mg DE-DAT: 0.5%, warfarin-TAT: 0.4%), and unstable angina (110 mg DE-DAT: 1.2%, 150 mg DE-DAT: 0.5%, warfarin-TAT: 0.1%).

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Safety Results (cont.):

Serious AEs (SAEs) were reported with similar frequencies in all treatment groups (110 mg DE-DAT: 42.7%, 150 mg DE-DAT: 39.6%, warfarin-TAT: 41.8%). Overall, the most frequent SAEs on the PT level were cardiac disorders, namely cardiac failure (110 mg DE-DAT: 4.9%, 150 mg DE-DAT: 4.0%, warfarin-TAT: 4.9%), worsening of atrial fibrillation (110 mg DE-DAT: 4.5%, 150 mg DE-DAT: 4.7%, warfarin-TAT: 3.6%), and angina pectoris (110 mg DE-DAT: 2.1%, 150 mg DE-DAT: 2.4%, warfarin-TAT: 1.9%). The frequency of patients with those events was similar in all treatment groups.

The frequencies of fatal AEs were similar in all treatment groups: 3.9% of patients died in the 110 mg DE-DAT group, 3.2% of patients died in the 150 mg DE-DAT group, and 4.3% of patients died in the warfarin-TAT group. On the PT level, all fatal AEs were reported for less than 1% of patients in every treatment group. Overall, the most frequently reported fatal AEs were defined as ‘death’ (110 mg DE-DAT: 0.8%, 150 mg DE-DAT: 0.8%, warfarin-TAT: 0.5%) and ‘sudden death’ (110 mg DE-DAT: 0.2%, 150 mg DE-DAT: 0.1%, warfarin-TAT: 0.7%). Frequencies for fatal AEs were generally similar between the DE-DAT and warfarin-TAT treatment groups.

AEs of special interest (AESIs), i.e. drug-induced liver injury, were specified in the first version of the CTP. However, the need for monitoring of AESIs was removed via Global Amendment 1 as there were no signs of dabigatran-related hepatotoxicity during the clinical development and post-marketing period. Before Global Amendment 1, a total of 4 patients were reported with AESIs in this trial: 3 patients (0.4%) on 150 mg DE-DAT, and 1 patient (0.1%) on warfarin-TAT.

Other significant AEs (based on the ICH E3 guideline) were reported for 5.5% of patients on 110 mg DE-DAT, 7.7% of patients on 150 mg DE-DAT, and 4.5% of patients on warfarin-TAT. On the PT level, no other significant AEs were reported for at least 1% of patients. The frequencies for individual PTs were similar in all treatment groups.

Clinical laboratory and vital signs

Regarding safety laboratory values, the analyses of mean changes from baseline to last value on treatment and of transitions relative to the reference ranges did not reveal any meaningful differences between the treatment groups. Also for possibly clinically significant abnormalities, no noteworthy differences between the treatment groups were noted.

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Safety Results (cont.):	For vital signs, no meaningful differences between treatment groups were observed. One patient on 150 mg DE-DAT had ALT and AST >3x ULN (AST: 160.00 U/L, reference range: 11.00 to 36.00 U/L; ALT: 299.00 U/L; reference range: 6.00 to 43.00 U/L) accompanied by elevations of bilirubin ≥2x ULN (85 µmol/L; reference range: 3 to 21 µmol/L) at the end of treatment visit. This case was not deemed as a drug-induced liver injury since the patient had already been reported at baseline with an altered liver panel (AST: 157 U/L, reference range: 11.00 to 36.00 U/L; ALT: 61 U/L, reference range: 6.00 to 43.00 U/L) as well as elevated bilirubin (32 µmol/L; reference range: 3 to 21 µmol/L), which showed normalisation during treatment with DE-DAT.
Conclusions:	In patients with atrial fibrillation who had undergone PCI, dual antithrombotic therapy including dabigatran etexilate and a P2Y12 inhibitor resulted in a risk of ISTH MBEs/CRNMBEs that was significantly lower than the risk with triple antithrombotic therapy including warfarin, a P2Y12 inhibitor, and aspirin. In addition, treatment with dual antithrombotic therapy with dabigatran etexilate (including both dose groups) was non-inferior to triple antithrombotic therapy with warfarin with respect to the frequency of major thromboembolic events, i.e. death, thrombotic events, or unplanned revascularisation by PCI/CABG. The safety profile of dabigatran etexilate in this trial population was consistent with the known profile of the drug. Dual antithrombotic therapy with dabigatran etexilate led to a clinically relevant decrease in bleeding risk and comparable frequency of major thromboembolic events, which offers clinicians 2 additional options for the treatment of patients with varying risks of major thromboembolic events and bleeding.