2 Synopsis

(according to ICH Topic E3 Structur and Content of Clinical Study reports – Annex I)

Name of Sponsor:
Deutsches Herzzentrum München
Lazarettstr.36
80636 München
Germany

Name of Finished. Product:
Pradaxa® (Boehringer Ingelheim International GmbH D-55216 Ingelheim am Rhein Deutschland)

Name of Active Ingredient:
Dabigatranetexilat

Title of Study:
Dabi-ADP-1: Impact of dabigatran and phenprocoumon on ADP induced platelet aggregation in patients with atrial fibrillation

Investigators:
Deutsches Herzzentrum, Munich, Germany:
N. Sarafoff, J. Mehilli, A. Kastrati;

Study centre(s):
Deutsches Herzzentrum, Munich, Germany

Publication (reference):

Studied period (years) one year 4 months **first patient in:** March 2011 **last patient out:** June 2012	**Phase:** IV

Objectives: The study was conducted to assess whether dabigatran is superior to phenprocoumon in reduction of ADP induced platelet aggregation.

Methodology:

In this single centre, open label, non-blinded trial, we included 70 patients with atrial fibrillation and an indication for oral anticoagulation. 35 patients were enrolled in the dabigatran and 35 patients were enrolled in the phenprocoumon group. At randomization patients received dabigatran 150mg twice daily or phenprocoumon with a target INR of 2.0-3.0. Laboratory tests to measure platelet aggregation and coagulation have been performed at randomization and at follow-up. Dabigatran plasma levels were assessed at follow up.The primary study end point was the ADP-induced platelet aggregation, secondary endpoints were ADPtest HS-, TRAP- and COL-induced platelet aggregations. The primary and secondary endpoints could be analyzed in 30 patients receiving dabigatran and 32 patients receiving phenprocoumon. After two weeks, patients obtaining dabigatran were switched to phenprocoumon, patients taking phenprocoumon continued with phenprocoumon therapy.

Number of patients (plannes and analyzed):

Planned: 70 patients

Analyzed: 62 patients

Diagnosis and main criteria for inclusion:

We enrolled patients if they were 18 years of age, had atrial fibrillation with an indication for oral anticoagulation, an INR value ≤ 1.3 and had provided written informed consent.

Test product, close and mode of administration, batch number:

Patients in the dabigatran group received 150mg dabigatran twice daily taken orally.

Duration of treatment: 2 weeks

Reference therapy, dose and mode of administration, batch number

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Patients in the phenprocoumon group received phenprocoumon orally with a target INR of 2.0-3.0.

1. Reference substance: phenprocoumon
2. Reference substance:

Unblinding:
In this randomized, open-label, non-blinded trial, sealed envelopes containing a computer generated sequence were used to assign patients to study groups according to a 1x1 factorial design at randomization.

Criteria for evaluation:

Efficacy:

The primary endpoint of the study was the ADP-induced platelet aggregation, measured by MEA in patients treated with dabigatran versus patients taking phenprocoumon after 14 days.

Secondary endpoints were ADPtest HS-. TRAP-and COL-induced platelet aggregation after 14 days.

Safety:

We also evaluated the occurrence of adverse events such as death, stroke, myocardial infarction and TIMI major or TIMI minor bleeding during study period.

Statistical methods:
Sample size calculation is based on the assumption that administration of dabigatran compared to phenprocoumon results in a 25% absolute decrease of maximal ADP. Choosing a power of 80% and the two-sided α value of 0.005, a sample size of at least 29 patients per group is required. To compensate losses to follow-up, an enrollment of a total of 70 patients is required.
Categorial variables, expressed as counts (percentages), were compared with the use of a chi-square test and Fischer exact test when expected values were less than 5. Continuous variables were expressed as means (±SD) and compared with the unpaired, 2-sided Student´s t test if normally distributed or expressed as medians [25^{th}-75^{th} percentile] and statistically analyzed by means of the Wilcoxon test.
All statistical analysis were performed with the software R (version 2.15.0, The R Foundation for Statistical Computing). A two-sided p-value of less than 0.05 was considered to indicate statistical significance.

Summery – Conclusions:
Efficacy and Safety Results:

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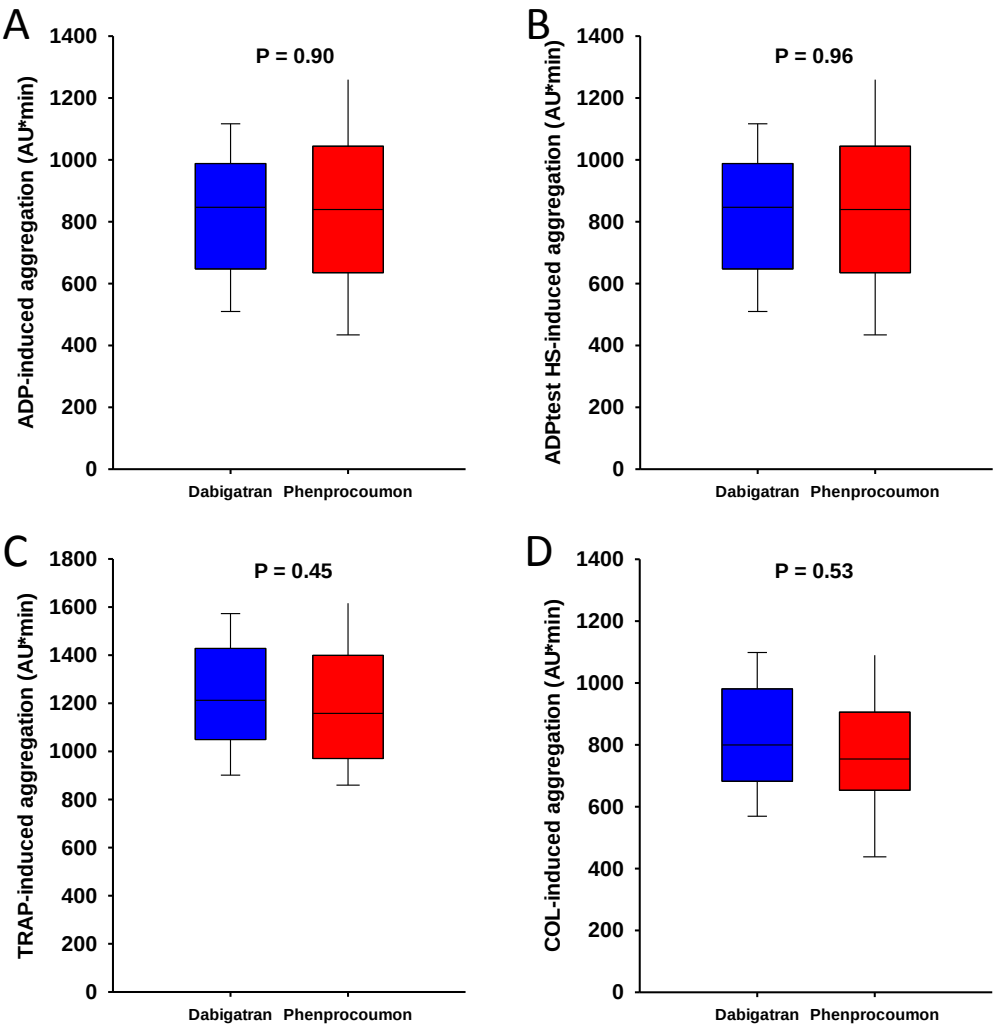
Figure 1: Platelet aggregation in patients with dabigatran and phenprocoumon therapy



Box plot analyses of multiple electrode platelet aggregometry (MEA) measurements for **A:** ADP, **B:** ADPtest HS, **C:** TRAP and **D:** COL-induced platelet aggregation in patients with either dabigatran (n=30, blue) vs. phenprocoumon (n=32, red)
Boxes indicate 25th and 75th percentiles and whiskers denote 10th and 90th percentiles.

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Table 1: Primary and secondary endpoints.

	Dabigatran (n= 30)	Marcumar (n=32)	P value
ADP units	846 [650 - 983]	839 [666 - 1039]	0.90
ADPHS units	642 [494 - 757]	621 [479 - 845]	0.96
COL	800 [682 - 979]	754 [655 - 901]	0.53
TRAP	1213 [1052 - 1425]	1158 [976 - 1396]	0.45
INR	1.2 ± 0.2	2.6 ± 0.9	<0.001
PTT	52 ± 12	45 ± 9	0.009
TZ	117 ± 19	21 ± 18	<0.001

Data is median [25^{th}-75^{th} percentile] and mean ± standard deviation

For the primary endpoint, ADP-induced platelet aggregation (median [IQR]) assessed with MEA was 846 [650-983] AU*min in the dabigatran group and 839 [665-1038] in the phenprocoumon group (Table 1). There was no statistical significant difference between the two study groups (Figure 1).
Regarding the secondary endpoints, ADPtest HS, COLtest and TRAPtest, also no statistical significant difference could be observed (Table 1).
The plasma levels of free dabigatran were 154 ± 113ng/ml in the group of patients receiving dabigatran.
During study period, no adverse event such as death, stroke, myocardial infarction and TIMI major or TIMI minor bleeding occurred in the entire study population.

Conclusion:
In our randomized study in patients with atrial fibrillation and an indication for oral anticoagulation, we could show that the direct thrombin inhibitor dabigatran has no impact on the ADP-induced platelet aggregation, ADPtest HS-, TRAP- and COL-induced platelet aggregations as compared to phenprocoumon.

Datum des Berichts:
December 10th 2014

APPENDIX:

SUBSTANTIAL AMENDMENTS:
There were no substantial amendments.

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SUSPENSIONS: There were no interruptions or suspensions oft the study EARLY TERMINATION: There was no early termination oft he study.