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-2 trial: Impact of dabigatran and phenprocoumon on clopidogrel mediated 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 10 months **first patient in:** April 2011 **last patient out:** March 2013	**Phase:** IV

Objectives: Evaluation whether dabigatran alters the clopidogrel mediated ADP induced platelet aggregation in patients with atrial fibrillation who also have an indication for dual antiplatelet therapy (DAT).

Methodology:

DABI-ADP-2 was a single centre randomized open label trial. Patients with atrial fibrillation and dual antiplatelet therapy were enrolled at the Deutsches Herzzentrum Munich between April 2011 and February 2013. In total, 46 patients were enrolled and randomized to receive dabigatran (n=22) or phenprocoumon (n=24). At randomization patients received dabigatran 110 mg or 150mg twice daily or phenprocoumon with a target INR of 2.0-2.5. Laboratory tests to measure platelet aggregation have been performed at randomization and at follow-up. Furthermore coagulation parameters, such as aPTT, INR and thrombin coagulation time as well as Dabigatran plasma levels were quantified 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. Primary and secondary endpoints could be analyzed in 20 patients receiving dabigatran and 20 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: 40 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 with an INR value ≤ 1.7 and DAT and had provided written informed consent.

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

Patients in the dabigatran group received 110mg or 150mg dabigatran twice daily taken orally.

Duration of treatment: 2 weeks

Reference therapy, dose and mode of administration, batch number

Patients in the phenprocoumon group received phenprocoumon orally with a target INR of 2.0-2.5.

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 this study was the clopidogrel mediated ADP-induced platelet aggregation in patients treated with dabigatran versus patients with phenprocoumon treatment at 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 was based on the assumption that administration of dabigatran as compared to phenprocoumon results in a 25 % absolute decrease of maximal ADP. Choosing a power of 80% and a two-sided α value of 0.05 a sample size of at least 29 per group was required. To compensate for losses at follow-up, the study was designed to enroll a total of 70 patients (35 per group).
A total of 46 patients were enrolled from April 2011 to February 2013 in the DABI ADP-2 trial. The follow up period in DABI ADP-2 is 2 weeks and last patient out was in March 2013. Since then no additional patient could be recruited in DABI-ADP-2. Therefore we decided to perform an analysis of available data. This analysis demonstrated the necessity of inclusion of over 1000 patients to reach significance. In view of the very slow recruitment rate, the steering committee considered the achievement of this goal infeasible and decided to terminate the study for futility reasons in May 2014. A comparison of categorical variables, expressed as counts (percentages), was performed using the Fisher exact or the χ^2 test, as appropriate. Continuous variables were expressed as means (±SD) and compared with the unpaired, 2-sided Student t test if normally distributed; otherwise, they were expressed as medians [25th-75th percentile] and statistically analyzed by means of the Wilcoxon test (2-sided?).
A P value < 0.05 was considered to indicate statistical significance. All statistical analyses were performed with the software R (version 2.15.0; The R Foundation for Statistical Computing).

Summery – Conclusions:
Efficacy and Safety Results:

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

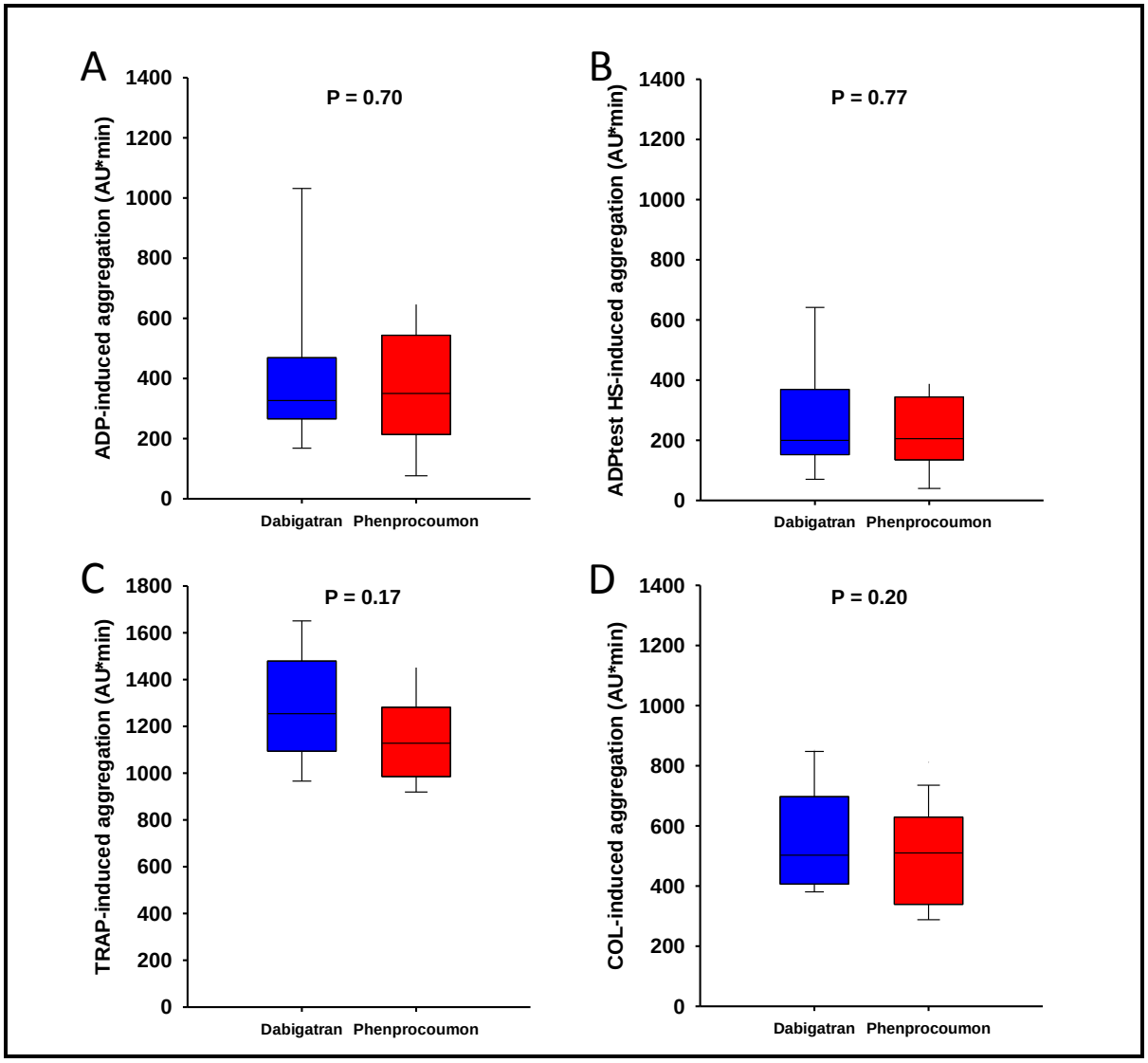

Figure 1: Box plot analyses of multiple electrode platelet aggregometry (MEA) measurements for **A:** ADP, **B:** ADPtest HS, **C:** TRAP and **D:** COL-induced platelet aggregation in patients with either dabigatran (n=20, blue) vs. phenprocoumon (n=20, red)
Boxes indicate 25th and 75th percentiles and whiskers denote 10th and 90th percentiles.

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	Dabigatran (n=20)	Phenprocoumon (n=20)	P value
ADP (AU x min)	326 [268 - 462]	350 [214-535]	0.70
ADPtest HS (AU x min)	200 [154 – 344]	205 [139 – 335]	0.77
TRAP (AU x min)	1254 [1106 - 1468]	1128 [1001 - 1275]	0.17
COL (AU x min)	503 [428 - 658]	510 [365 - 616]	0.20
aPTT	51 ± 12	48 ± 9	0.41
INR	1.3 ± 0,2	3.2 ± 1.4	< 0.001
TZ	115 ± 23	18 ± 3	< 0.001

Table 1: Primary and secondary endpoint
Data is median [25th,75th percentile] and mean ± standard deviation

For the entire study population, ADP-induced platelet aggregation (median [IQR]) assessed with MEA after 2 weeks was 340 [249-495] AU x min. There was no significant difference regarding the primary endpoint between patients treated with dabigatran as compared to patients with phenprocoumon treatment (326 [268-462] AU x min vs. 350 [214-535] AU x min, P=0.70). There was also no significant difference regarding the secondary endpoints ADPtest HS, TRAP and COL (table 1). The plasma concentration of free dabigatran was 103 ± 92 ng/mlin the group of patients receiving dabigatran.
In the phenprocoumon group there was one patient who suffered from stent thrombosis on day 13 due to clopidogrel discontinuation. In this patient ADP induced platelet aggregation was 1417 AU x min when he presented with STEMI to our emergency department. After clopidogrel loading and PCI of the culprit vessel he could be discharged and ADP values on follow up under treatment with aspirin, clopidogrel and phenprocoumon were 307 AU x min. There were 3 cases of type 1 BARC bleeding, 1 in the dabigatran group and 2 in the phenprocoumon group. No patient suffered from death, stroke, TIMI minor or TIMI major bleeding during the follow up period of 2 weeks (table 2).

Conclusion:
In this randomized trial in patients with atrial fibrillation and DAT we could not find an impact on clopidogrel mediated ADP induced platelet aggregation in patients treated with dabigatran as compared to phenprocoumon.

Datum des Berichts:

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December 9th 2014

APPENDIX

EARLY TERMINATION:

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