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Short study name: Treatment with APO-Dabigatran Absorption (TADA) Study

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Brief Summary (75 words): APO-dabigatran, a generic formulation, was approved in Canada based on bioequivalence data in the fasted state but its bioavailability in settings of reduced gastric acidity was not examined. In this cross-over study, we found that when APO-dabigatran is administered with a proton pump inhibitor, the exposure to dabigatran is reduced by about 30%; and that about a third of participants had a > 50% reduction in exposure.

Abstract (250 words)

Background: Dabigatran is effective and safe for stroke prevention in patients with atrial fibrillation and for venous thromboembolism prevention and treatment. In Canada, APO-dabigatran, a generic formulation, has been approved based on a bioequivalence study but its bioavailability in settings of reduced gastric acidity has not been examined.

Methods: The Treatment with APO-Dabigatran Absorption study was an open-label crossover study in 46 healthy male volunteers comparing the absorption of APO-dabigatran (150 mg) with and without rabeprazole. The primary outcome was the 24-hour total dabigatran exposure as measured by area under the curve (AUC) and peak concentration (C_{max}).

Results: Compared with no rabeprazole pre-treatment, the total dabigatran AUC (gmean $AUC_{0\text{-}tz}$: 567.2 vs. 804 ngh/mL and gmean $AUC_{0\text{-}\infty}$: 609.7 vs. 804) and C_{max} (gmean: 64.1 vs. 104.4 ng/mL) were significantly reduced with rabeprazole. The percent geometric mean ratios for $AUC_{0\text{-}tz}$, $AUC_{0\text{-}\infty}$ and C_{max} (with rabeprazole vs. without) were 70.5% (95% CI: 51.9 to 95.7%), 71.8% (95% CI: 53.1 to 96.9%) and 61.4% (95% CI: 44.1 to 85.5%), respectively. With rabeprazole, the proportions of participants with >50% reduction in $AUC_{0\text{-}tz}$, $AUC_{0\text{-}\infty}$, and C_{max} were 32.6%, 30.4% and 39.1%, respectively

Conclusions: When APO-dabigatran is administered with rabeprazole, the exposure to dabigatran is reduced by about 30%, which is similar to that observed with Pradaxa® when it was co-administered with a proton pump inhibitor. However, the finding that a third of participants had > 50% reduction in exposure, is concerning and highlights the need for caution in patients with or at risk of reduced gastric acidity.

Introduction

The results of multiple randomized controlled trials indicate that dabigatran etexilate, a direct oral anticoagulant (DOAC), is effective and safe for stroke prevention in patients with atrial fibrillation and for the prevention and treatment of venous thromboembolism.[1, 2] These findings led to the rapid approval of dabigatran etexilate and its widespread use in over 100 countries worldwide.

The patent for dabigatran etexilate expired in Canada in 2018 and soon thereafter Health Canada approved a generic formulation marketed by Apotex (APO-Dabigatran) based on the demonstration of bioequivalence to the originator.[3, 4] The original formulation is a capsule containing dabigatran-coated tartaric acid pellets.[5, 6] An acidic environment is essential for the dissolution of dabigatran etexilate and the absorption of dabigatran, which is a small, highly polar molecule that is otherwise poorly absorbed. This specialized dabigatran etexilate formulation ensures a consistent absorption of dabigatran despite a bioavailability of 6-7%, including in patients taking proton pump inhibitors.[7, 8] Unlike the originator, APO-dabigatran is formulated as a capsule containing fumaric acid. APO-dabigatran was approved after it was shown to be bioequivalent to dabigatran etexilate when tested in healthy volunteers but was not tested in the elderly or in other patients at risk of low gastric acidity.[3] This might be important because a reduction in bioavailability could substantially affect efficacy.

In this crossover study, we explore the possible effect of gastric acid suppression in healthy volunteers taking APO-dabigatran with and without a proton pump inhibitor. We measured blood concentration of dabigatran in participants treated with a single dose of APO-dabigatran and repeated blood concentration during the crossover period, following a second dose of APO-

dabigatran given after 5 days of rabeprazole, a potent proton pump inhibitor. We chose to use a proton pump inhibitor to suppress gastric acid secretion, thereby simulating a reduced gut acid environment in older patients and in those treated with gastric acid suppressants.

Methods

The Treatment with APO-Dabigatran Absorption (TADA) study was an open-label crossover study comparing the absorption of dabigatran (150 mg) in the presence and absence of concomitant rabeprazole treatment (20mg once daily for 5-7 days). The study (ClinicalTrials.gov identifier: NCT04157881) was approved by the Hamilton Integrated Ethics Board and was conducted in compliance with the protocol, the International Conference on Harmonization – Good Clinical Practice (ICH-GCP(R2)) and all applicable regulatory requirements. All participants provided written informed consent.

Participants

We recruited healthy male volunteers aged between 20 and 40 with a body mass index (BMI) of 18-30 mg/m^2. We excluded subjects with a history of heart, lung, liver, kidney, gastrointestinal, genitourinary, musculoskeletal or endocrine disease or other systemic illness, as well as those taking regular medications or herbal supplements/remedies. We also excluded subjects with routine laboratory values outside of reference range, smoking or excessive alcohol consumption, pulse rate >90 beats per minute, blood pressure >140 mmHg systolic or >90 mmHg diastolic, patients who were not expected to comply with the protocol requirements or not expected to complete the trial as scheduled, and those enrolled in another investigational device or drug trial within the last 30 days.

Study procedures

Following a fast of at least 8 hours, participants took dabigatran 150 mg with 200 mL of water and underwent serial measurement of blood concentration of dabigatran over 24 hours. They

subsequently underwent a 5 to 7-day washout period during which they took rabeprazole 20mg once daily. To ensure maximal proton pump inhibition, participants were instructed to take rabeprazole each morning and prior to APO-dabigatran administration. On the final day of rabeprazole ingestion (at least day 5), participants took a further dose of dabigatran 150 mg with 200 mL of water after which they again underwent serial measurements of blood concentration of dabigatran over 24 hours.

Blood sampling and analysis

We collected blood prior to the dose of dabigatran (baseline) and then 30, 60, 90min, 2-, 3-, 4-, 6-, 8- and 24-hours post-dabigatran. At each timepoint, we collected blood into 1 x 6 mL EDTA and 1 x 4.5 mL citrate tube as well as into 2 x 2.7 mL citrate tubes. After centrifugation at 2500 g for 10 min at 4-8°C, we separated plasma for measurement of activated partial thromboplastin time (aPTT), dilute thrombin time (dTT), and dabigatran concentration by calibrated dTT (Hemoclot), and stored additional aliquots of EDTA plasma at -80°C for further testing. In addition, measurement of total dabigatran concentration in plasma samples was performed by Nuvisan GmbH, Neu Ulm, Germany using a validated high-performance liquid chromatography tandem mass spectrometry (LC-MS/MS).

The primary outcome was the 24-hour total dabigatran exposure as measured by area under the curve (AUC) and peak concentration (Cmax). The secondary outcomes were proportion of participants with > 50% reduction in 24-hour total dabigatran exposure; AUC and the Cmax by Hemoclot dabigatran assay; and maximum dTT and aPTT

Statistical analysis

We assumed that a 50% reduction in Cmax or AUC would be clinically relevant based on a) the observation that contraindicated co-medications which are potent p-glycoprotein inducers generally result in > 50% reduction in Cmax or AUC, b) lesser reductions (<50%) have not been shown to be clinically relevant with dabigatran (e.g., pantoprazole co-administration did not alter the efficacy of Pradaxa®).[1, 7, 9] Therefore, a sample size of 46 subjects was determined to ensure that a two-sided test with alpha = 0.05 has 90% power to detect a 50% reduction in Cmax or AUC.

We analysed pharmacokinetic and coagulation variables using a non-compartmental analysis. We calculated ratios (test versus reference treatment) for PK endpoints in all participants who provided pharmacokinetic measurement for both test and reference study treatments. We determined point estimates, geometric means (gMean) and gMean ratios of natural log-transformed data, together with their two-sided 95% confidence intervals (CIs) by repeated measures analysis of variance (ANOVA). We also calculated the intra-individual percent changes in total dabigatran AUC and Cmax across the two periods, which are graphically presented in Waterfall plots. The proportions of participants (and 95% CI) with a > 50% reduction in AUC and Cmax were estimated. To examine the agreement between test and reference methods (dabigatran concentration by Hemoclot™ and LC-MS/MS, respectively), we calculated the mean difference and 95% limit of agreement using the Bland-Altman method.

Safety

We documented all adverse events (AEs) including the frequency, severity and causal relationships from the time of first study drug administration to three days after last study drug treatment.

Results

Participant Demographics: From January 2020 to August 2021, a total of 46 healthy male volunteers successfully completed the two treatment periods in this cross-over study (Figure 1). Baseline characteristics are presented in Table 1. The mean age of participants was 24.4 years, mean BMI was 23.7 and mean creatinine was 81.2 µmol/L.

Pharmacokinetic analyses of APO-dabigatran in the absence and presence of rabeprazole: Figure 2 compares the plasma concentration-time profile of total dabigatran (as measured by LC-MS/MS) with and without rabeprazole pre-treatment during the 24-hour sampling period. Compared with no rabeprazole pre-treatment, the total dabigatran AUC (gmean $AUC_{0\text{-}tz}$: 567.2 vs. 804 ngh/mL and gmean $AUC_{0\text{-}\infty}$: 609.7 vs. 804) and C_{max} (gmean: 64.1 vs. 104.4 ng/mL) were significantly reduced with rabeprazole pre-treatment (Table 2). The geometric mean ratios for $AUC_{0\text{-}tz}$, $AUC_{0\text{-}\infty}$ and C_{max} (calculated as the pharmacokinetic value with rabeprazole divided by the corresponding value without rabeprazole times 100) were 70.5% (95% CI: 51.9 to 95.7%), 71.8% (95% CI: 53.1 to 96.9%) and 61.4% (95% CI: 44.1 to 85.5%), respectively. Conversely, the t_{max} (gmean: 2.4 vs. 1.9 hours; ratio 125.8%; 95% CI: 111.4 to 142.1%) and $t_{1/2}$ (gmean: 5.0 vs. 4.3 hours; ratio: 115.2%; 95% CI: 106.9 to 124.3%) were significantly prolonged.

Similar pharmacokinetic differences were found when dabigatran concentration was measured by the Hemoclot™ assay (Table 1). Compared with no rabeprazole, the dabigatran AUC (gmean $AUC_{0\text{-}tz}$: 511.5 vs. 741.3 ngh/mL and gmean $AUC_{0\text{-}\infty}$: 611.8 vs. 828.2) and C_{max} (gmean: 54.3 vs. 93.4 ng/mL) were significantly reduced in the presence of rabeprazole (Table 2). The geometric mean ratios for $AUC_{0\text{-}tz}$, $AUC_{0\text{-}\infty}$ and C_{max} were 69.0 % (95% CI: 53.6 to 88.9%), 73.9% (95%

CI: 59.2 to 92.1%) and 58.1% (95% CI: 41.8 to 80.8%), respectively. Conversely, the t_{max} (gmean: 2.4 vs. 2.0 hours; ratio 120.6%; 95% CI: 106.9 to 135.9%) and $t_{1/2}$ (gmean: 5.8 vs. 4.5 hours; ratio: 129.3%; 95% CI: 106.8 to 156.6%) were significantly prolonged.

Pharmacodynamic analyses of APO-dabigatran in the absence and presence of rabeprazole: Changes in clotting times are presented in Table 3. Compared with no rabeprazole, both peak dilute thrombin time (dTT gmean: 37.5 vs. 40.6 sec; ratio: 92.3%; 95% CI: 87.2 to 97.6%) and the activated partial thromboplastin time (aPTT gmean: 43.5 vs. 49.4 sec; ratio 88.1%; 95% CI: 82.5 to 94.0%) were shorter when APO-dabigatran was administered with rabeprazole pre-treatment. The dTT t_{max} (gmean: 2.5 vs. 2.2 hours; ratio 117.6%; 95% CI: 102.1 to 135.4%) and dTT $t_{1/2}$ (gmean: 53.2 vs. 48.4 hours; ratio: 110.8%; 95% CI: 82.2 to 149.4%) were prolonged by rabeprazole pre-treatment. Similarly, the aPTT t_{max} (gmean: 2.4 vs. 1.9 hours; ratio 126.8%; 95% CI: 110.6 to 145.4%) and aPTT $t_{1/2}$ (gmean: 59.2 vs. 41.0 hours; ratio: 146.0%; 95% CI: 110.9 to 192.1%) were prolonged by rabeprazole pre-treatment.

Intra-individual changes in dabigatran exposure after raboprazole: Figures 3A and 3B show the percent changes in $AUC_{0\text{-}tz}$ and Cmax, respectively, for each participant after rabeprazole pretreatment. With rabeprazole pre-treatment, the proportions of participants with >50% reduction in $AUC_{0\text{-}tz,}$ and C_{max} were 32.6% (95% CI: 20.8 to 47.1%), and 39.1% (95% CI: 26.4 to 53.8%), respectively.

Correlation between dabigatran concentration by LC-MS/MS and Hemoclot™: Figure 4 shows that dabigatran concentration as measured by the Hemoclot™ assay correlated strongly with total

dabigatran concentration as measured by LC-MS/MS (correlation coefficient, r = 0.970; 95% CI: 0.965 to 0.973). The mean difference between the two methods was 7.5 ng/ml (95% limits of agreement: -23.8 to 38.7).

Correlations between total dabigatran by LC-MS/MS and clotting times: The dTT showed a strong positive correlation (r=0.902; 95% CI: 0.889 to 0.913) with total dabigatran concentration (Figure 5) as did the aPTT (r= 0.859; 95% CI: 0.841 to 0.875)

Safety: Treatment with APO-dabigatran tablet alone or with rabeprazole pre-treatment were well tolerated. There were no deaths and no serious adverse events. There were no adverse events reported in the 8 participants who discontinued the study. Of the 46 participants who completed the study, mild adverse events were reported in 3 participants. One participant reported mild nausea determined not to be related to study procedure or drugs that resolved without intervention. Two participants had mild vasovagal reaction following venipuncture, which resolved without intervention.

Discussion

APO-dabigatran has been approved in Canada based on studies demonstrating bioequivalence but its bioavailability has not been previously evaluated in the setting of reduced gastric acidity, a prevalent condition in older patients. Because the solubility of dabigatran etexilate is pH dependent, the bioavailability of generic formulations may be compromised in settings of reduced acidity unless the acidifier (fumaric acid for APO-dabigatran) maintains an acidic microenvironment that optimizes the dissolution of APO-dabigatran. To investigate the bioavailability of APO-dabigatran in the setting of reduced gastric acidity, we performed a cross-over study whereby healthy volunteers received APO-dabigatran with or without pre-treatment with rabeprazole. The results of our study indicate that with rabeprazole pre-treatment the bioavailability of APO-dabigatran is reduced by about 30-40% and that the time to maximum concentration and half-life of the APO-dabigatran are prolonged by 15-25%. Importantly, about one third of participants taking APO-dabigatran had > 50% reduction in drug exposure after rabeprazole pre-treatment.

The reduction in AUC with APO-dabigatran after PPI pre-treatment of about 30% is consistent with that observed in secondary analyses of clinical trials and pharmacokinetic studies of Pradaxa® when it was co-administered with pantoprazole or other proton pump inhibitors (PPIs).[7, 8, 10, 11], Reassuringly, for Pradaxa®, in two clinical outcome trials, RE-LY and RE-DUAL PCI, concomitant PPI treatment did not appear to reduce its efficacy®.[1, 9] Although the average reduction in bioavailability with APO-dabigatran after rabeprazole was similar in magnitude to that reported for Pradaxa® the finding that about one third of participants had a > 50% reduction in AUC after rabeprazole pre-treatment is concerning because such a reduction in bioavailability

might lower the efficacy. In the absence of clinical outcome studies with APO-dabigatran, our findings highlight the need for caution in patients with or at risk of reduced gastric acidity and support the need for additional studies such as ours or in the fed states when trying to establish bioequivalence of complex pharmaceuticals.[3]

Our results are likely to be valid because of careful timing and completeness of drug concentration sampling, the consistency in our findings when dabigatran concentration was measured by LC-MS/MS and the Hemoclot™ assay; the consistency in both pharmacokinetic and pharmacodynamic findings; and the use of 5 days of rabeprazole to effectively reduce gastric pH.[12]. Potential limitations of our study are the absence of intragastric pH sampling to confirm reduced gastric acidity with PPI treatment, and the enrolment of healthy male volunteers in whom the pharmacokinetic profile of APO-dabigatran may differ from older patients. Nonetheless, our study provides important data on the effect of low gastric pH on the bioavailability of APO-dabigatran.

Conclusion

Our data indicate that when APO-dabigatran is administered with rabeprazole, the exposure to dabigatran is reduced by about 30%, which is similar to that observed with Pradaxa® when it was co-administered with a proton pump inhibitor. However, the finding that a third of participants had a > 50% reduction in exposure, is concerning and highlight the need for caution in patients with or at risk of reduced gastric acidity.

Table 1: Baseline characteristics (n=46)

Characteristic	Mean (SD)*
Age, years	24.4 (4.3)
Height, cm	180.2 (6.9)
Weight, kg	77.0 (10.8)
BMI, kg/m2	23.7 (2.7)
Smoking, % current	21 (45.7)
Systolic BP, mm Hg (v0)	125.2 (7.2)
Diastolic BP, mm Hg (v0)	74.3 (8.1)
Heart rate, bpm (v0)	68.5 (12.0)
Creatinine, µmol/L	81.2 (13.2)
Haemoglobin, g/L	151.3 (10.3)
Platelet count, $x10^9$/L	237.8 (48.9)
Prothrombin time, s (INR)	1.1 (0.1)
Activated partial thromboplastin time, s	32.1 (2.6)
Thrombin clotting time, s (dTT)	26.5 (1.9)
Fibrinogen, g/L	2.8 (0.6)

cm, centimetre; kg, kilogram; BMI, body mass index; BP, blood pressure; mm Hg, milimeters of mercury; bpm, beats per minute; µmol/L, micromole per litre; g/L, gram per litre; s, second
*Mean and standard deviation unless indicated otherwise

Table 2: Pharmacokinetic parameters of APO-dabigatran in the absence and presence of rabeprazole

	APO-Dabigatran		**APO-Dabigatran + Rabeprazole**		**gMean ratio* (%)**	**95% CI**	
	gMean	**gCV (%)**	**gMean**	**gCV (%)**		**Lower**	**Upper**
Total dabigatran by LC-MS/MS							
$AUC_{0\text{-}tz}$ [ng h/mL]	804.5	11.2	567.2	13.6	70.5	51.9	95.7
$AUC_{0\text{-}\infty}$ [ng h/mL]	849.4	11.1	609.7	13.2	71.8	53.1	96.9
C_{Max} [ng/mL]	104.4	17.3	64.1	23.0	61.4	44.1	85.5
t_{Max} [h]	1.9	52.5	2.4	41.5	125.8	111.4	142.1
$t_{1/2}$ [h]	4.3	14.3	5.0	15.4	115.2	106.9	124.3
Dabigatran concentration by Hemoclot assay†							
$AUC_{0\text{-}tz}$ [ng h/mL]	741.3	9.3	511.5	11.5	69.0	53.6	88.9
$AUC_{0\text{-}\infty}$ [ng h/mL]	828.2	8.3	611.8	9.7	73.9	59.2	92.1
C_{Max} [ng/mL]	93.4	16.3	54.3	23.4	58.1	41.8	80.8
t_{Max} [h]	2.0	49.5	2.4	40.4	120.6	106.9	135.9
$t_{1/2}$ [h]	4.5	28.5	5.8	33.9	129.3	106.8	156.6

LC-MS/MS, high-performance liquid chromatography tandem mass spectrometry; gCV, geometric coefficient of variation; gMean, geometric mean; AUC, Area under the Curve; C_{max}, maximum plasma concentration; t_{max}, time from dose to maximal concentration; tz, time from dose to last timepoint with measurable drug concentration; $t_{1/2}$, terminal half life; aPTT, Activated partial thromboplastin time; dTT, Dilute thrombin time

* Calculated as APO-Dabigatran with rabeprazole treatment gMean divided by APO-Dabigatran alone gMean times 100

† Dabigatran concentration are calculated from a calculated concentration curve from dilute thrombin time.

Table 3: Pharmacodynamic properties of coagulation testing of APO-dabigatran

	APO-Dabigatran		**APO-Dabigatran + Rabeprazole**		**gMean ratio* (%)**	**95% CI**	
	gMean	**gCV (%)**	**gMean**	**gCV (%)**		**Lower**	**Upper**
Dilute Thrombin time							
C_{Max} [sec]	40.6	3.8	37.5	4.3	92.3	87.2	97.6
t_{Max} [h]	2.2	53.4	2.5	41.9	117.6	102.1	135.4
$t_{1/2}$ [h]	48.4	20.3	53.2	17.8	110.8	82.2	149.4
Activated partial thromboplastin time							
C_{Max} [sec]	49.4	5.3	43.5	4.9	88.1	82.5	94.0
t_{Max} [h]	1.9	56.6	2.4	47.5	126.8	110.6	145.4
$t_{1/2}$ [h]	41.0	16.3	59.2	20.5	146.0	110.9	192.1

gCV, geometric coefficient of variation; gMean, geometric mean; AUC, Area under the Curve; C_{max}, maximum plasma concentration; t_{max}, time from dose to maximal concentration; $t_{1/2}$, terminal half life; aPTT, Activated partial thromboplastin time; dTT, Dilute thrombin time

* Calculated as APO-Dabigatran with rabeprazole treatment gMean divided by APO-Dabigatran alone gMean times 100

Figure 1: Study flow

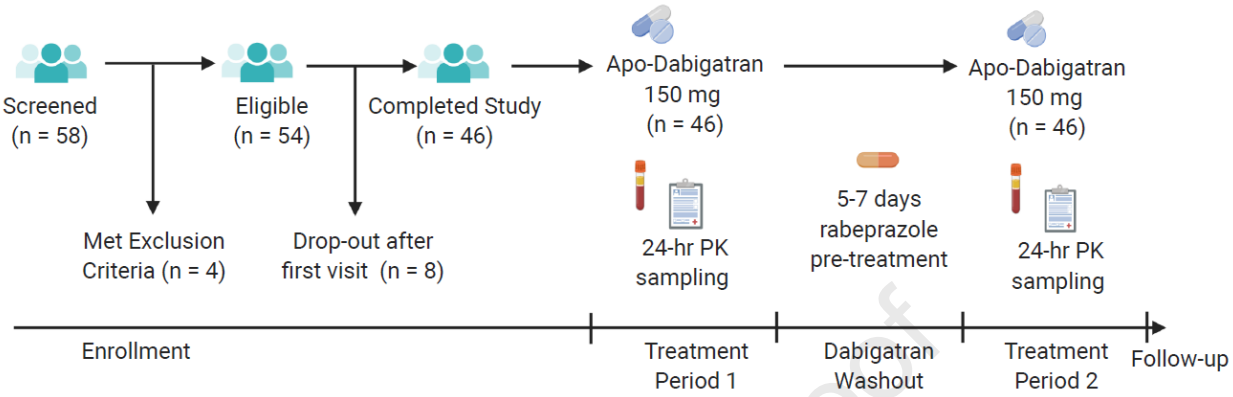
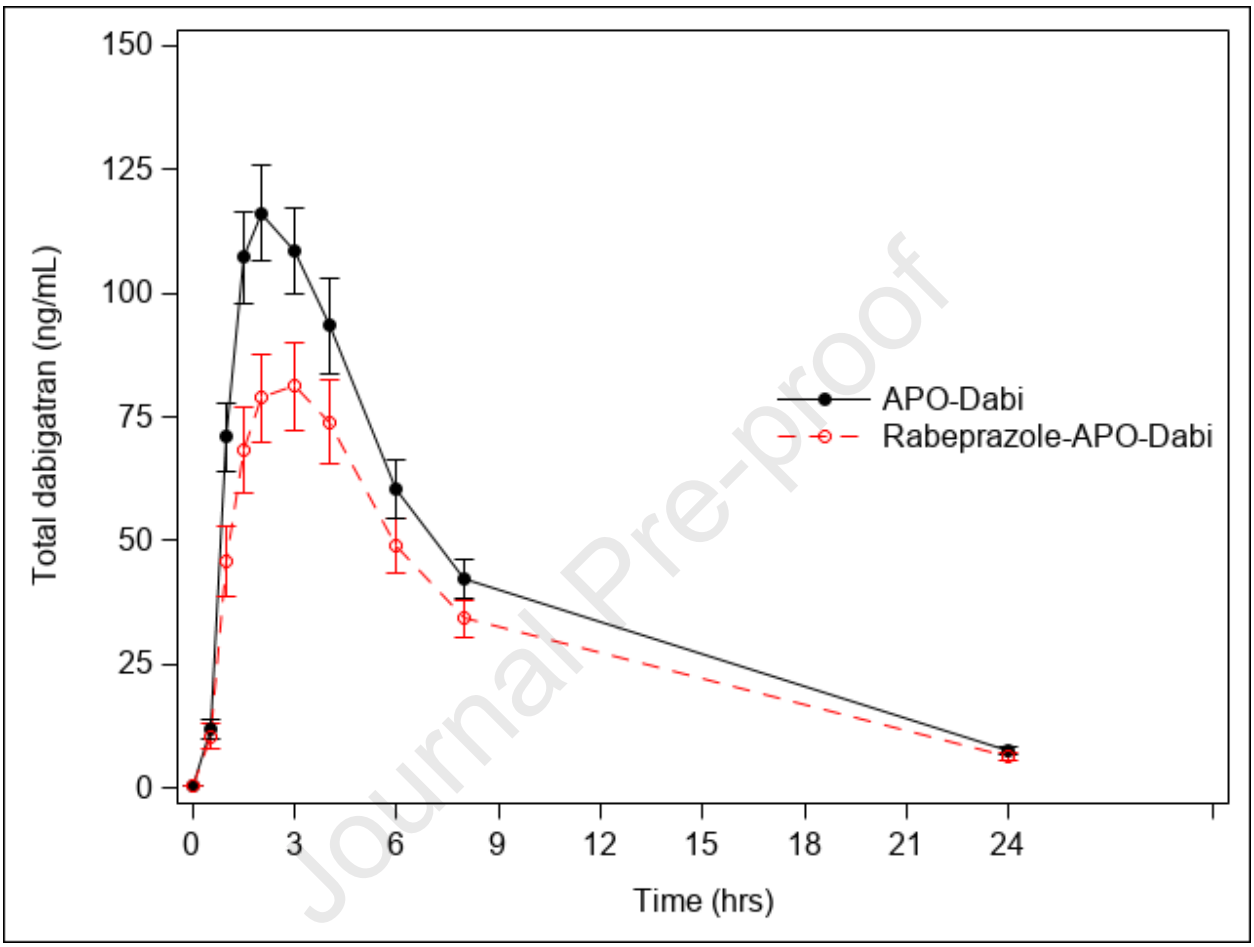


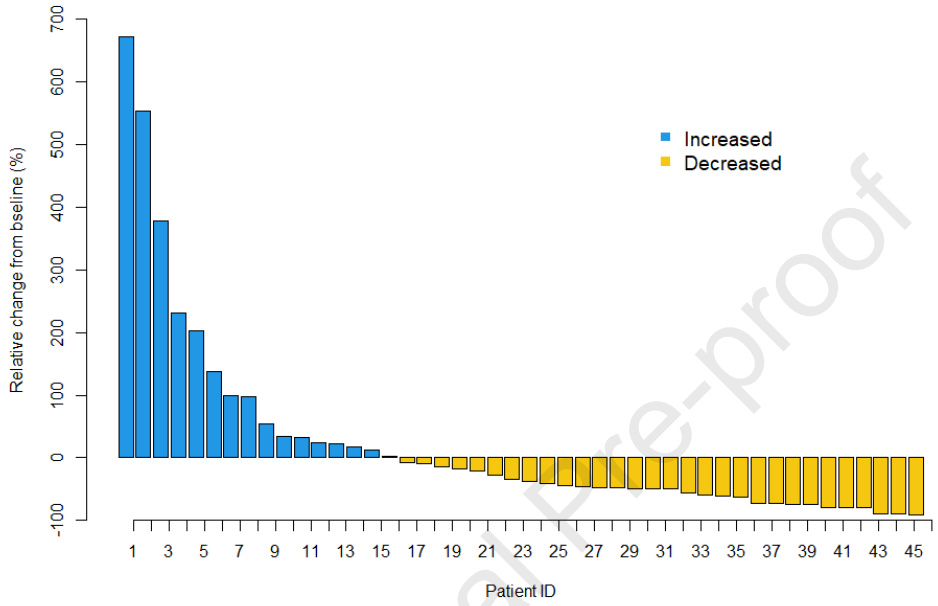
Figure 2. Dabigatran plasma concentration as measured by LC-MS/MS in the presence and absence of rabeprazole. Data presented as mean ± SE, n =46.



Data presented as mean ± SE, n =46.

Figures 3. Waterfall plots detailing percent changes in dabigatran AUC_{0-tz} (A) and C_{max} (B) for each participant after rabeprazole pretreatment.

A



B

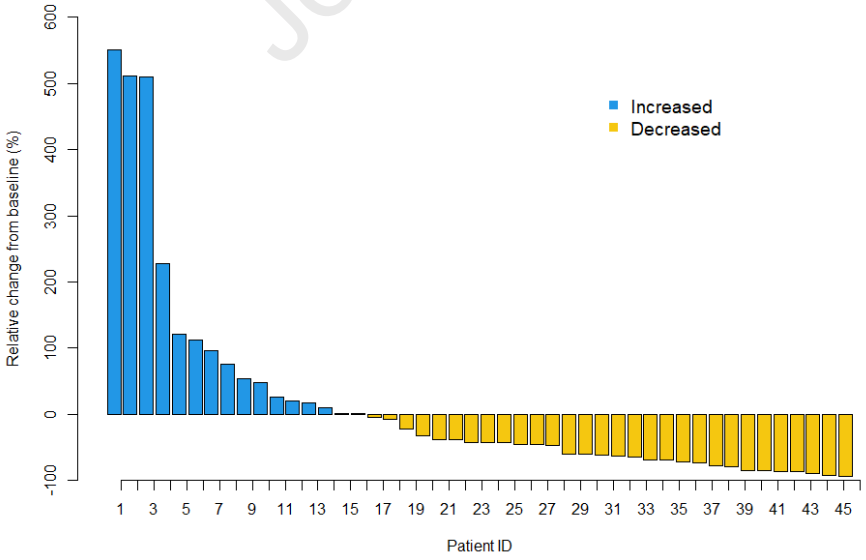


Figure 4. Correlation between the measurement of dabigatran plasma concentration using LC-MS/MS and diluted thrombin time. Both are given in ng/mL concentrations. All individual data are shown.

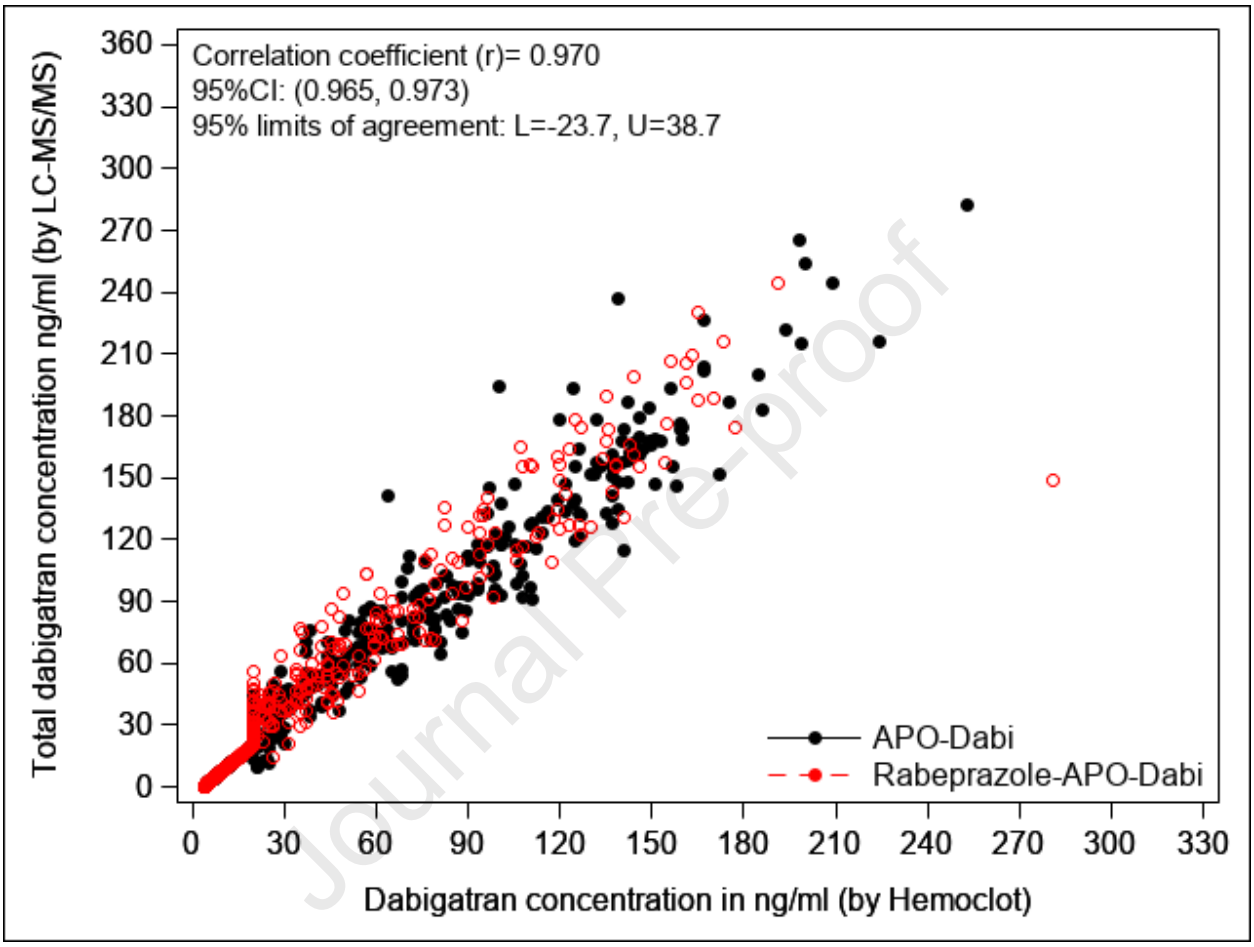
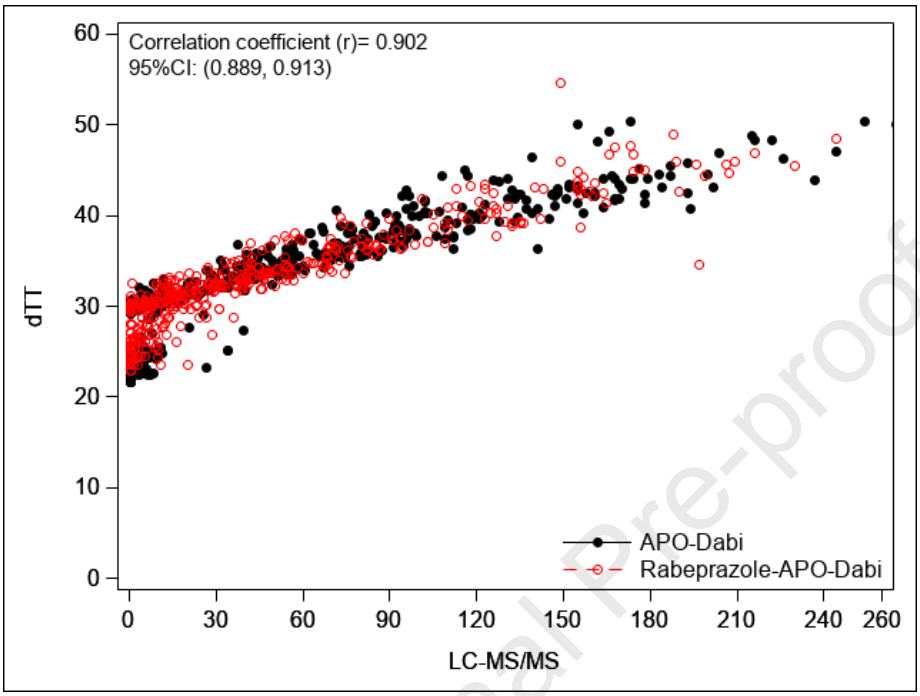
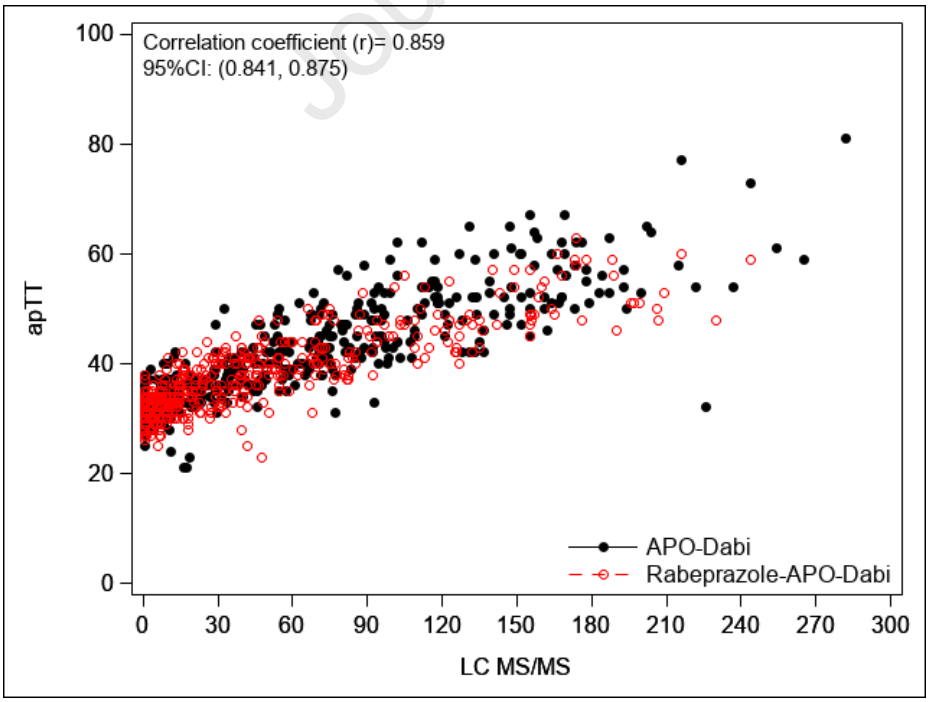


Figure 5. Correlation between measurement of dabigatran plasma concentration using LC-MS/MS and dTT (A) or aPTT (B). All individual data are shown.

A



B



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