

## RESEARCH OUTPUTS / RÉSULTATS DE RECHERCHE

### Betrixaban

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Romain Siriez<sup>1</sup>, Jonathan Evrard<sup>1</sup>, Jean-Michel Dogné<sup>1</sup>, Lionel Pochet<sup>1</sup>, Damien Gheldof<sup>1</sup>, Bernard Chatelain<sup>2</sup>, Christelle Vancraeynest<sup>1</sup>, Philippe Devel<sup>1</sup>, Maïté Guldenpfennig<sup>2</sup>, Célia Devroye<sup>2</sup>, François Mullier<sup>2</sup>, Jonathan Douxfils<sup>1,3</sup>

<sup>1</sup> University of Namur, Department of Pharmacy, Namur Thrombosis and Hemostasis Center (NTHC), Namur Research Institute for Life Sciences (NARILIS), Namur, Belgium  
<sup>2</sup> Université catholique de Louvain, CHU UCL Namur, Hematology Laboratory, Namur Thrombosis and Hemostasis Center (NTHC), Namur Research Institute for Life Sciences (NARILIS), Yvoir, Belgium

## Introduction and aim

Betrixaban is a novel oral direct factor Xa inhibitor approved by the Food and Drug Administration for prophylaxis of venous thromboembolism (VTE) in adult patients hospitalized for an acute illness at risk for thromboembolic complications. As for other DOACs, assessment of the anticoagulant effect of betrixaban may be useful in some situations. Also, clinicians need to know how routine coagulation assays are influenced.

The aim of this study is to determine which coagulation assay(s) should be used to assess the impact of betrixaban on hemostasis and provide laboratory guidance for their interpretation.

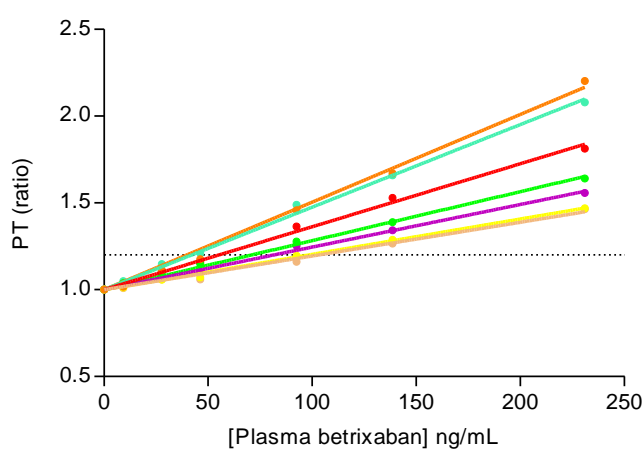
## Methods

Betrixaban was spiked at final concentrations ranging from 0 to 250 ng/mL in platelet-poor plasma. These concentrations cover the on-therapy range (from  $\pm 9$  ng/mL at  $C_{trough}$  to  $\pm 122$  ng/mL at  $C_{max}$  for 40 and 120 mg once daily dose, respectively). We tested the impact of betrixaban on prothrombin time (PT), activated partial thromboplastin time (aPTT), dilute Russel viper venom time (dRVVT), chromogenic anti-Xa assays, thrombin generation assay (TGA) and a large panel of hemostasis diagnostic tests using different reagents from several manufacturers.

## Results : Betrixaban influence routine and specific coagulation assays

A concentration-dependent prolongation of aPTT, PT and dRVVT is observed. The sensitivity mainly depends on the reagent. FXa chromogenic assays show high sensitivity and a linear correlation both depending on the reagent and/or the methodology. Several methodologies applicable for other direct factor Xa inhibitors have to be adapted. As for others direct FXa inhibitors, chromogenic anti-Xa assays are the most sensitive assays for the measurement of betrixaban in a routine setting. However, only two methodologies appear to be adapted to the low levels of betrixaban observed in pharmacokinetic studies. For others chromogenic assays, procedures need to be adapted to increase the sensitivity. Some parameters of the TGA (especially peak and mVRI) are very sensitive to the presence of betrixaban but the lack of standardization and its turnaround time reduce its implementation in routine.

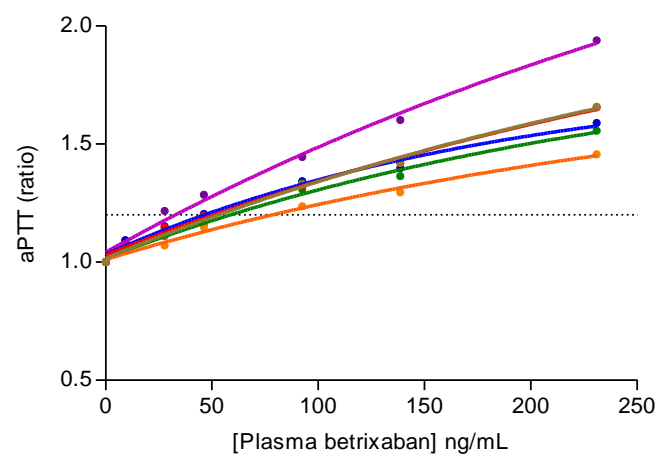
### Impact of betrixaban on PT



- STA<sup>®</sup>-Neoplastine<sup>®</sup> R ( $r^2=0.99$ ;  $2xCT=198$  ng/mL; CV= 0.6%)
- TriniCLOT<sup>®</sup> PT HTF ( $r^2=0.99$ ;  $2xCT=491$  ng/mL; CV= 0.9%)
- TriniCLOT<sup>®</sup> PT Excel ( $r^2=0.99$ ;  $2xCT=354$  ng/mL; CV= 1%)
- TriniCLOT<sup>®</sup> PT Excel S ( $r^2=0.99$ ;  $2xCT=210$  ng/mL; CV= 0.5%)
- RecombiPlasTin 2G<sup>®</sup> ( $r^2=0.99$ ;  $2xCT=407$  ng/mL; CV= 1.1%)
- STA<sup>®</sup>-Neoplastine<sup>®</sup> Cl+ ( $r^2=0.99$ ;  $2xCT=276$  ng/mL; CV= 0.7%)
- Dade<sup>®</sup> Innovin<sup>®</sup> ( $r^2=0.99$ ;  $2xCT=514$  ng/mL; CV= 1%)

Betrixaban showed a concentration dependent prolongation of the prothrombin time. The relation was linear and the  $2xCT$  depended on the reagent. The  $2xCT$  was ranging from 198ng/mL for STA<sup>®</sup>-Neoplastine R<sup>®</sup> to 514ng/mL for Dade<sup>®</sup> Innovin<sup>®</sup>.

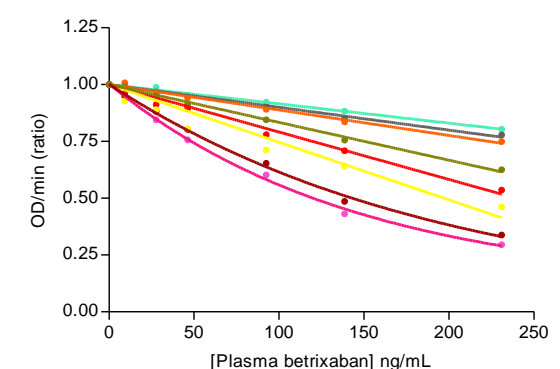
### Impact of betrixaban on aPTT



- SynthAfax<sup>®</sup> ( $r^2=0.99$ ;  $2xCT=257$  ng/mL; CV= 0.9%)
- STA<sup>®</sup>-PTT Automate ( $r^2=0.99$ ;  $2xCT=NC$ ; CV= 0.6%)
- STA<sup>®</sup>-Cephascreen<sup>®</sup> ( $r^2=0.99$ ;  $2xCT=NC$ ; CV= 0.4%)
- SynthASil<sup>®</sup> ( $r^2=1.00$ ;  $2xCT=NC$ ; CV= 1.2%)
- STA<sup>®</sup>-C.K. Prest<sup>®</sup> ( $r^2=0.99$ ;  $2xCT=479$  ng/mL; CV= 1%)
- Actin<sup>®</sup> FS ( $r^2=0.99$ ;  $2xCT=474$  ng/mL; CV= 0.9%)

Betrixaban showed a concentration dependent prolongation of the aPTT. The relation was curvilinear and the  $2xCT$  depended on the reagent. The  $2xCT$  was ranging from 257 ng/mL for SynthAfax<sup>®</sup> to 479 ng/mL for C.K. Prest<sup>®</sup>.

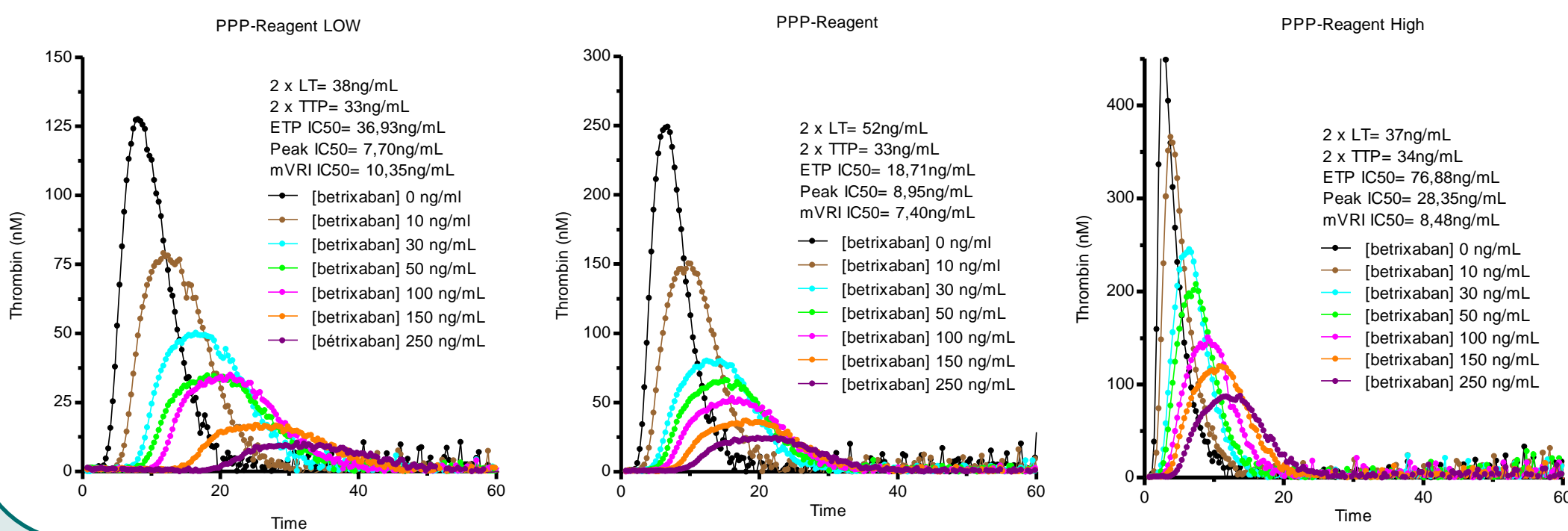
### Measurement of betrixaban pharmacodynamics with chromogenic anti-Xa assays



- Technochrom<sup>®</sup> Anti-Xa High ( $r^2=0.96$ ;  $1/2xOD/min=569$  ng/mL; CV= 1.3%)
- Technochrom<sup>®</sup> Anti-Xa ( $r^2=0.99$ ;  $1/2xOD/min=240$  ng/mL; CV= 0.9%)
- HemosIL<sup>®</sup> Liquid Heparin ( $r^2=0.97$ ;  $1/2xOD/min=197$  ng/mL; CV= 3.1%)
- Biophen<sup>®</sup> Heparin LRT<sup>®</sup> ( $r^2=0.99$ ;  $1/2xOD/min=499$  ng/mL; CV= 0.6%)
- Biophen<sup>®</sup> Direct Factor Xa Inhibitors<sup>®</sup> ( $r^2=0.98$ ;  $1/2xOD/min=447$  ng/mL; CV= 0.8%)
- STA<sup>®</sup>-Liquid Anti-Xa ( $r^2=0.99$ ;  $1/2xOD/min=300$  ng/mL; CV= 0.7%)
- Biophen<sup>®</sup> Heparin LRT<sup>®</sup> Low ( $r^2=1.00$ ;  $1/2xOD/min=120$  ng/mL; CV= 1.5%)
- Biophen<sup>®</sup> Direct Factor Xa Inhibitors<sup>®</sup> Low ( $r^2=0.99$ ;  $1/2xOD/min=143$  ng/mL; CV= 1.5%)

There was a concentration-dependent decrease of the OD/min. Tests with higher baseline OD/min had a wider range of quantitation compared to those starting at lower OD/min at baseline.

### Impact of betrixaban on calibrated automated thrombogram<sup>®</sup>



The most influenced CAT<sup>®</sup> parameters are the peak and the mean velocity rate index. There is an inter-reagent variability. Thanks to their low  $IC_{50}$  for the peak and the mVRI, the better resolution and their large range of application, PPP-Reagent and PPP-Reagent High seemed to be the best reagents to monitor patients on betrixaban. (ETP: Endogenous Thrombin Potential;  $IC_{50}$ : half-maximum inhibitory concentration; LT: Lag Time; mVRI: mean Velocity Rate Index; TTP: Time to Peak). mVRI was defined as follow: (Peak) / (Time to Peak - Lag Time).

Betrixaban also affect diagnostic tests : for factors of the intrinsic pathway (FVIII, FIX, FXI and FXII), the aPTT-based clotting method showed a mean decrease of  $\pm 5\%$  at 10 ng/mL of betrixaban, 26% at 50 ng/mL and 58% at 150 ng/mL. The impact was more pronounced for FXI and FVIII. For FV, FVII and FX, a mean decrease of 1% at 10 ng/mL of betrixaban, 9% at 50 ng/mL and 25% at 150 ng/mL was observed, while prothrombin measurement seemed to be less affected (maximal decrease of 6% at 150 ng/mL) (*Data not shown*).

## Conclusion

Adapted-chromogenic anti-Xa assays are the most appropriate assays to measure the pharmacodynamics of betrixaban in a routine setting. Betrixaban significantly affects several hemostasis diagnostic tests and this must be taken into consideration when requesting and interpreting such tests.

## Contact

Romain Siriez : [romain.siriez@unamur.be](mailto:romain.siriez@unamur.be)  
 Jonathan Douxfils : [jonathan.douxfils@unamur.be](mailto:jonathan.douxfils@unamur.be)  
 Tel. : (+32)81.72.43.25  
 Rue de Bruxelles, 61  
 5000 - Namur