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### *Citation for published version (APA):*

Patel, J. P., Chitongo, P. B., Dighe, P., Roberts, L., Vadher, B., Patel, R. K., & Arya, R. (2018). Prothrombin times in the presence of edoxaban - in-vivo experience from King's College hospital. *British Journal of Haematology*. Advance online publication.

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## Prothrombin times in the presence of edoxaban – *in-vivo* experience from King's College hospital

Dear Sir,

The British Committee for Standards in Haematology have stipulated that individual laboratories should be aware of the impact that the direct oral anticoagulants (DOACs) have on the common tests of haemostasis (Kitchen *et al*, 2014). When these standards were published, 3 DOACs were available for clinicians to prescribe in the UK; apixaban, rivaroxaban and dabigatran. Since then, edoxaban has become available following NICE approval for the acute treatment of venous thromboembolism (VTE) and secondary prevention of VTE and stroke prophylaxis in non-valvular AF (National Institute for Health and Care Excellence, 2015a; National Institute for Health and Care Excellence, 2015b).

In the past, we have shared our experience of the impact of rivaroxaban and apixaban on the prothrombin time (PT) reagent used at our Denmark Hill laboratory site (Patel *et al*, 2013, 2015), and how the sensitivity of this reagent has influenced the bleeding guidelines we have in place in our Trust. With the recent availability of edoxaban, we sought to understand edoxaban's impact on the prothrombin time reagents used locally. Although studies have evaluated this in the past, they have involved *in-vitro* spiking of samples (Cuker & Hussein-zadeh, 2015; Morishima & Kamisato, 2015). We share our experience from patients actually receiving edoxaban at King's College Hospital (Denmark Hill and Princess Royal Hospital sites).

Where clinically indicated (e.g. extremes of body weight, renal dysfunction, or presence of interacting drugs), we measured the activity of the edoxaban and the corresponding prothrombin time. Our Denmark Hill laboratory (Trust

central laboratory) used the STA-Neoplastine® CI Plus PT time assay for detection of the presence of edoxaban, and the STA-liquid anti-Xa assay® (Diagnostica Stago, France), with appropriate calibrators and controls for quantification of edoxaban concentration in the patient's plasma, analysed on STA-R evolution (Diagnostica Stago) analyser. Our Princess Royal Hospital laboratory utilises the RecombiPlasTin 2G® reagent (Werfen) for analysis of the prothrombin time, which is analysed on the ACLTop 500 analyser (Instrumentation Laboratory, Werfen). Anti-Xa samples from the PRUH were centrifuged and frozen within 4 h of sample collection and then were couriered to the Trust central laboratory site for processing.

Figure 1 illustrates the PT and corresponding edoxaban plasma concentrations for 25 patients. The therapeutic concentrations of edoxaban reported in the literature are ~220 ng/ml (peak) and ~30 ng/ml (trough) (Niebecker *et al*, 2015; Krekels *et al*, 2016) thus the concentrations described here, cover the breadth of concentrations expected to be seen in clinical practice.

Our results demonstrate that the PT response for patients prescribed edoxaban, is similar to what we have seen with rivaroxaban, even with the different reagent utilised at the PRUH and mirror the findings of published *in-vitro* work.

These findings our important, as in our Trust, the current guidelines (<http://www.kingsthorbosiscentre.org.uk/index.php/anticoagulation>) for the management of bleeding for those patients receiving rivaroxaban recommends a PT screening test, in order to determine whether the presence of rivaroxaban may be contributing to bleeding. Our findings

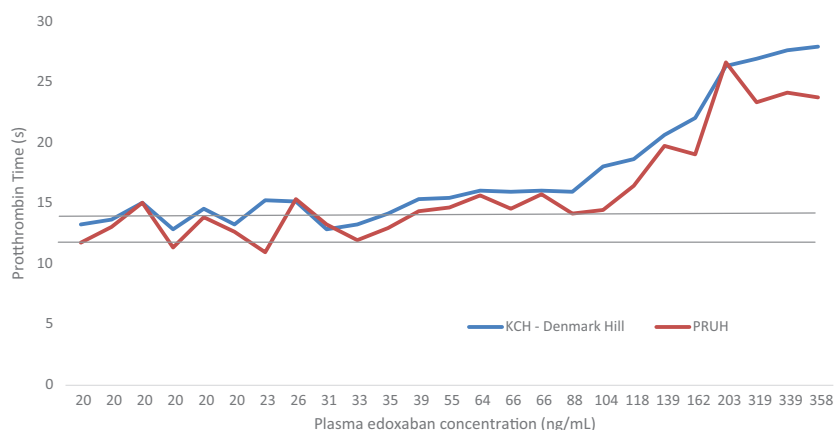


Fig 1. Prothrombin time *versus* edoxaban concentrations (grey parallel lines represent our laboratory range for PT). Note: Concentrations listed as 20 ng/ml, were reported as <20 ng/ml by the Trust central laboratory as the concentration was below the limit of quantification of the assay. [Colour figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

suggest using the same strategy for patients prescribed edoxaban would be appropriate.

Our results once again highlight the importance of the BCSH recommendation of individual laboratories knowing how sensitive their reagents of the routine tests of haemostasis are to DOACs. Furthermore, the results highlight the importance of educating and raising the awareness of this amongst general medical and surgical staff, so they may appropriately interpret the results.

## Conflicts of Interests

The authors have no relevant conflicts of interest to declare.

## Author contributions

JPP oversaw the collection of samples, PBC oversaw the analysis of the samples in the laboratory. PD, LNR, BV, RKP and RA referred patients for measuring the edoxaban

concentrations. The letter was drafted by JPP, and subsequently reviewed and finalised by all authors.

**Jignesh P. Patel**<sup>1,2</sup>   
**Paradzai B. Chitongo**<sup>1</sup>  
**Preetam Dighe**<sup>1</sup>  
**Lara N. Roberts**<sup>1</sup>   
**Bipin Vadher**<sup>1</sup>  
**Raj K. Patel**<sup>1</sup>  
**Roopen Arya**<sup>1</sup>

<sup>1</sup>King's Thrombosis Centre, Department of Haematological Medicine, King's College Hospital Foundation NHS Trust, and <sup>2</sup>Institute of Pharmaceutical Science, King's College London, London, UK.  
E-mail: jig.patel@kcl.ac.uk

**Keywords:** direct-Xa inhibitors, edoxaban, prothrombin time

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