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UHPLC-MS/MS based quantification of DOACs and application to patients undergoing cardiac catheterization treated with rivaroxaban
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Background
The direct acting oral anticoagulants (DOACs) have been developed and introduced as alternatives to vitamin K antagonists (VKAs) and are now widely used in clinical practice. DOACs do not require routine coagulation monitoring; however, inter-individual differences in pharmacokinetics can lead to considerable variability of plasma concentrations. Management of DOACs involves temporary discontinuation before invasive procedures. Several reports have demonstrated the safety of this approach; however, little is known about periprocedural DOAC plasma concentrations in real-life patients.

Methods
We previously reported an UHPLC-MS/MS method for the simultaneous quantification of DOACs with use of stable isotope labeled analogues (¹³C₂H₇-apixaban, ¹³C₆-dabigatran, ¹³C₆-rivaroxaban) as internal standards. Since apixaban and dabigatran were rarely used in our clinic during the time of enrollment (06/2015-11/2015), the study focused on patients treated with rivaroxaban. 56 patients undergoing cardiac catheterization were included in this study, and rivaroxaban concentrations were determined in plasma samples collected at the time of admission to hospital and at the beginning of catheterization. UHPLC-MS/MS rivaroxaban concentration results were compared to those obtained by a commercial coagulation assay (chromogenic anti-Xa).

Results
The developed UHPLC-MS/MS method covers a quantitation range of 1 to 500g/L for all DOACs, and the lower limit of quantification of rivaroxaban was 0.91g/L. The method therefore allows precise determination of rivaroxaban, even at low concentrations. The mean age of our patients was 67 years. Median (range) rivaroxaban plasma concentrations determined at the time of admission to hospital and at the start of catheterization were 9.0 ( ˂LOQ-300.6g/L) and 2.2g/L ( ˂LOQ-55.5g/L), respectively. Concentration results obtained by LC-MS/MS and the coagulation assay were in good agreement (r²=0.981); however, the coagulation assay failed to precisely determine low rivaroxaban concentrations.

Conclusions
In urgent cases, the UPLC-MS/MS method enables rapid determination of DOACs and report of results within one hour upon sample arrival. Observed median rivaroxaban concentrations were comparably low at the time of catheterization. Nevertheless, patient factors such as renal function can result in unexpectedly high periprocedural rivaroxaban concentrations. More studies are needed to establish valid and safe “post-
discontinuation” concentration ranges of DOACs which appear especially useful before procedures that carry a high risk of bleeding.