Body weight is negatively associated with direct oral anticoagulant trough concentrations in dabigatran and apixaban users

Direct oral anticoagulants (DOACs, i.e. dabigatran, apixaban, edoxaban and rivaroxaban) are prescribed in fixed-dose regimens to treat and prevent thrombosis.[1] The market authorization holders state that routine monitoring of plasma concentrations of DOACs is not required. However, clinical studies indicate that DOAC trough concentrations are associated with both bleeding and thrombosis.[2-5] A wide variability in DOAC trough concentrations between patients is observed and can be caused by patient factors such as age, sex, renal function, interacting drugs and body weight or body mass index (BMI) as described in the summary of product characteristics.

To date, guidelines advise to be cautious with prescribing DOACs to patients with extreme body weights.[6] Patients with obesity may have low DOAC trough levels and be at risk for thrombosis,[7-9] while underweight patients may be at risk for bleeding.[5,9] However, data about the association between body weight and DOAC trough concentrations are contradictory: some studies show that body weight is associated with DOAC trough concentrations[3,4,10] while other studies do not.[11] With a rising prevalence of obesity, evidence whether body weight and DOAC trough levels are associated is crucial for the treatment of these patients.[1,7] Therefore the aim of this study was to determine the association between body weight and trough concentrations of all registered DOACs.

We performed a cross-sectional study and included 148 in- and outpatients who used a DOAC for at least five days (99 male, 67%; 49 female, 33%) from the Haga Teaching Hospital, with a mean body weight of 88 kg (standard deviation 18). Patients were excluded if they received an off-label dosage, had an estimated glomerular filtration rate <50 ml/min or used interacting medications. Patient characteristics were similar in the four treatment groups (Table SI). All patients had to provide written informed consent before starting the study. Ethical approval was obtained by the local ethics committee and the study was conducted according to the Declaration of Helsinki (version October 2013). Blood samples were collected prior to the administration of the DOAC to determine DOAC trough concentrations, which were measured using a validated liquid chromatography–mass spectrometry/mass spectrometry assay. Quantification of trough concentrations expressed as anti-FXa activity (rivaroxaban, apixaban or edoxaban) or anti-FIIa (dabigatran) activity was performed by a validated chromogenic assay. DOAC trough concentrations and anti-FXa activity or anti-FIIa activity values were converted to standard doses using mean half-lives and assuming linear kinetics. The standard doses were dabigatran 150 mg twice daily, apixaban 5 mg twice daily, edoxaban 60 mg once daily and rivaroxaban 20 mg once daily. We used multivariable linear regression to estimate the association between body weight, BMI and DOAC trough concentrations with 95% confidence intervals (CIs) and adjusted for age and sex, and furthermore stratified by sex.

The univariable analysis showed a significant negative association between body weight and dabigatran concentrations (−0·73 ng/ml/kg, 95%CI −1·35 to −0·11) and body weight was negatively associated with apixaban concentrations (−0·45 ng/ml/kg, 95%CI −1·38 to 0·47), while results were around unity among edoxaban (−0·10 ng/ml/kg, 95% CI −0·25 to 0·04) and rivaroxaban (−0·02 ng/ml/kg, 95% CI −0·34 to 0·31) users (Fig 1 and Table SII). After adjustment for sex and age, the associations remained similar for dabigatran and were less pronounced or similar for the other three DOACs. Results were similar when considering anti-FXa activity or anti-FIIa activity as the outcome as compared with DOAC concentrations (Table SII).

Similar results were found for BMI on all outcomes (DOAC trough concentrations, anti-Fxa activity or anti-FIIa activity, see Table SII). After stratifying by sex, more pronounced regression coefficients (Fig 1) were found in female patients as compared with male patients. This last association was the strongest in female dabigatran patients.

The negative association between body weight and dabigatran trough concentrations suggests that increasing body weight results in lower dabigatran trough concentrations. Distribution of medications through the body is dependent on the lipophilicity of the drugs,[12] which is expressed as log *P*, where high log *P* values indicate high lipophilicity of drugs. DOACs have been reported as moderately lipophilic[13] with edoxaban as the least lipophilic (log *P* 0·90 to 1·61), followed by rivaroxaban (log *P* 1·74 to 1·90), apixaban (log *P* 1·83 to 2·22) and finally dabigatran with the highest lipophilicity (log *P* 4·59 to 5·17).[14] As a result dabigatran is most likely to distribute to adipose tissue, which correspond with our findings that dabigatran concentrations decreased most with increasing body weight, whereas this association was less pronounced for the other DOACs. An additional explanation for our results may be that the renal clearance of dabigatran is higher than for other DOACs[12] and renal function could increase due to a increase in body weight.[15] This may result in lower

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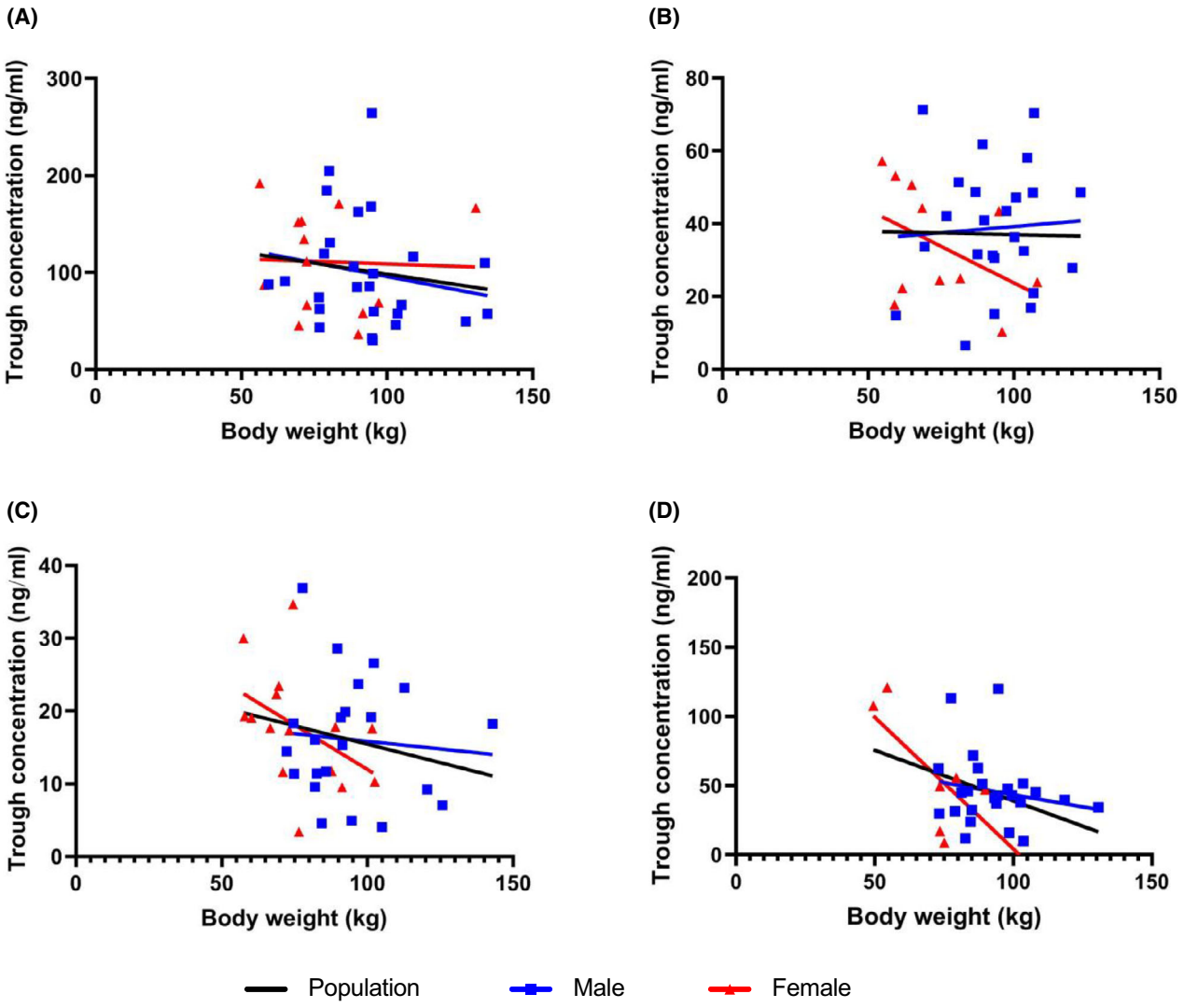

Fig 1. Association between body weight (kg) and direct oral anticoagulant (DOAC) trough concentration (ng/ml): (A) apixaban, (B) rivaroxaban, (C) edoxaban and (D) dabigatran.]

dabigatran trough concentrations, which was also reported by Graves *et al.*[7]

For the other three DOACs, there was no statistically significant negative association. Risk estimates were around unity for edoxaban and rivaroxaban, whereas we found a negative association of body weight and BMI with unadjusted apixaban concentrations. This finding is in line with results of Upreti *et al.*, who observed a negative association between body weight and plasma anti-factor Xa activity in apixaban users.[10]

An unexpected finding was a stronger association between body weight or BMI and DOAC trough concentrations in female patients as compared with male patients, with the exception of apixaban. These results indicate that pharmacokinetics of DOACs may vary between male and female patients, which indicatesd that the DOAC dosages may need different adjustments in female patients as compared with male patients with extreme body weights.

This study showed that body weight and BMI are negatively associated with dabigatran and apixaban trough concentrations and anti-FXa activity or anti-FIIa activity. The negative association between body weight or BMI and the dabigatran trough concentration was strongest in female patients, which indicates that dabigatran dosages may need adjustment in (female) patients with extreme body weights.

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Conflicts of interest

The authors report no conflicts of interest.

Author contributions

JMB, NvR, LBEB, ATAM, EBW and LEV: designed the research. JMB, NvR, ECMDB, NV, MR and ATAM collected the data. JMB, NvR, ECMD, FH and EBW analyzed the data. JMB and NvR wrote the manuscript. LBEB, FH, ATAM, EBW and LEV critically revised the paper for important intellectual content. JMB obtained funding for the research.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table SI. Patient characteristics.

Table SII. Association between body weight or body mass index (BMI) on direct oral anticoagulant (DOAC) trough concentrations and anti-FXa activity or anti-FIIa activity.

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