

Finally, the observed relationship between adolescent BMI and poor health outcomes, including poorer general health, cardiovascular disease, asthma, kidney disease, and obstructive sleep apnea, in adulthood further underscores the need for early intervention. Pediatricians caring for adolescents should guide and support patients and their families to implement and maintain positive health behaviors. These findings provide additional support for cardiovascular disease prevention and intervention efforts for adolescents, such as physical activity classes and healthy meal options at schools.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the [Author Center](#).

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## Do We Need to Define Therapeutic Ranges for Edoxaban Plasma Concentration?



We read with interest the paper by Steffel et al. (1) reporting a pre-specified analysis of the ENGAGE AF TIMI-48 (Global Study to Assess the Safety and Effectiveness of Edoxaban [DU-176b] vs Standard Practice of Dosing With Warfarin in Patients With Atrial Fibrillation-Thrombolysis In Myocardial Infarction-48) trial to compare patients on lower-versus higher-dose edoxaban regimens, with or without dose reduction, if indicated. Edoxaban plasma levels were also reported, with maximum and minimum plasma concentrations ranging from 49.5 to 288 ng/mL and from 5.47 to 46.2 ng/mL, respectively.

We recently described the preliminary results of edoxaban administration via percutaneous endoscopic gastrostomy in fragile patients (2), and we are currently conducting an observational, prospective, study on the topic (NCT04271293). In line with the pharmacokinetic effects described by Steffel et al. (1), we observed a wide range of plasma edoxaban concentrations at steady state, and these findings are coherent with other evidence (3) reporting peak edoxaban levels ranging from 125 to 317 ng/mL after oral administration.

One of the advantages of direct oral anticoagulants is that they do not need continuous blood samplings to monitor drug concentration. Nevertheless, this could be useful in specific settings, such as in fragile patients, to assess whether the drug has reached a sufficient concentration to determine the anticoagulant effect but not is above levels that may determine increased bleeding risks.

To date, in the setting of direct oral anticoagulants, neither a lower limit to define efficacy nor an upper limit to define a safety of anticoagulant activity has been established for plasma concentrations. Therefore, considering plasma edoxaban levels reported within extremely variable ranges in literature, and aiming at a more tailored balance between ischemic and bleeding risks, the question arises whether a more precise and standardized definition of a therapeutic range for drug plasma concentration is necessary, maybe also using new assays, such as the thrombin generation assay.

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## REPLY: Do We Need to Define Therapeutic Ranges for Edoxaban Plasma Concentration?



We thank Dr. Cappannoli and colleagues for their interest in our paper and for raising this important point (1). Direct oral anticoagulants (DOACs) were developed and tested in randomized clinical trials (RCTs) to be used at a fixed dose without the need for repetitive plasma level measurements. The results of the 4 pivotal RCTs comparing DOACs versus vitamin K antagonists (VKAs) showed that as a class DOACs are even more efficacious than VKAs and are at least as safe (if not safer) than VKAs (2). At the same time, plasma levels were collected during preclinical and clinical testing demonstrating a wide range of both trough and peak plasma levels across all 4 DOACs (3).

Despite the correlation of plasma levels with some clinical outcomes, however, these observed ranges are far from equivalent to “therapeutic ranges” of DOACs. Indeed, measured plasma levels were not used for clinical decision making during the pivotal

trials including, most importantly, individual adjustments of DOAC doses. In order to establish an evidence-based definition of therapeutic DOAC plasma level ranges, adequately powered, dedicated RCTs investigating precisely such an approach would be required. In the very few situations during which this may be considered (e.g., extremes of renal function or weight, multiple strong drug-drug interactions), this needs to be done with great caution and after informed consent of the patient regarding the lack of supporting outcome data.

The large interindividual and intraindividual variations as well as technical challenges (e.g., incorporating the exact timing since last dose) add to the complexity of such strategies, limiting their use primarily to large centers with ample experience both in the technical assessment of plasma levels and in their interpretation. Although the current European Heart Rhythm Association Practical Guide on the use of DOACs—in which the topic of DOAC plasma level measurements including their practical implications is discussed in great detail—supports the measurement of plasma levels in these situations to guide clinical decision making, the evidence to support this approach is scarce (3).

Alternatively, measures to assess the pharmacodynamic effect of DOACs may represent an attractive target, but also these have not been prospectively validated. Adequately powered trials to investigate this topic are indispensable to move such strategies out of their current niche and into mainstream clinical practice to further improve the efficacy and safety profile of DOACs and individualize therapy.

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