COMMENTARY

Direct oral anticoagulants in extremely obese patients: OK to use?

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1 | PREVALENCE OF EXTREME OBESITY

Extreme obesity—also referred to as severe, grade III, or morbid obesity—is defined as a body mass index (BMI) > 40 kg/m^2, and occurs in 7.7% of the adult US population.[1] This translates to nearly 20 million extremely obese adults living in the US.[2] Considering the prevalence of atrial fibrillation (AF), there may be at least 615 000 extremely obese adults with atrial fibrillation in the US.[3] As 67%-88% of AF patients are on anticoagulation,[4] this suggests that at least 500 000 extremely obese individuals in the US with AF have an indication for, or are being treated with, anticoagulation. Similar calculations can be performed for venous thromboembolism (VTE): the Centers for Disease Control (CDC) estimate that as many as 900 000 people in the US could be affected by VTE,[5] most of whom will require anticoagulation for some period of time. Hence, there may be at least 70 000 extremely obese patients in the US with VTE who require treatment with anticoagulation. Taking both AF and VTE together, there are more than half a million extremely obese individuals in the US for whom a decision may be needed regarding whether to use a direct oral anticoagulant (DOAC) or warfarin for anticoagulation. Clearly, the topic is of significant relevance—for an individual patient, for prescribers, as well as for the population at large.

2 | DOAC PHARMACOKINETIC AND PHARMACODYNAMIC CONSIDERATIONS IN OBESITY

Quality pharmacokinetic and pharmacodynamic (PK/PD) studies evaluating the impact of obesity, and particularly of extreme obesity, on a drug's absorption, distribution, metabolism, and excretion (ADME) are typically needed to draw solid conclusions about expected drug exposure and drug clearance. Only scarce such studies exist for DOAC use in subjects with extreme obesity (Table 1), making it impossible to conclude with confidence whether the use of DOACs at standard doses leads to appropriate drug exposure and clearance.[6-10] While it is tempting to look at individual ADME drug parameters (Table 1) to draw conclusions about a drug's PK/PD in extremely obese patients, the mechanisms that influence PK/PD are complex and individual ADME parameters do not always align with either PD measurements or clinical efficacy and safety. Further, it is of limited usefulness to use PK/PD data derived from non-obese (BMI < 30 kg/m^2) or mild to moderately obese (30-40 kg/m^2) patients and apply them to those patients with extreme obesity, as PK/PD in extreme obesity may be very different compared to PK/PD in mild or moderate obesity. Similarly, PK/PD results from single and prophylactic dose studies, as well as those from healthy volunteer studies, cannot necessarily be generalized to steady-state, therapeutically dosed patient populations.

3 | FDA PRESCRIBING INFORMATION FOR DOACS

Per FDA-approved prescribing information (package inserts), none of the four DOACs approved for therapeutic dosing in AF and VTE needs to be dose-adjusted for high body weight or BMI and, therefore, they can be used at standard doses even in the patient with extreme body weight. The package inserts for

TABLE 1 Pharmacologic parameters of DOACs and publications relevant to obesity

	logP[b]	Volume of distribution (L)	Protein binding (%)	PK/PD studies relevant to obesity (references)	PK/PD studies relevant to extreme obesity (references)	Clinical studies relevant to obesity[c] (references)	Clinical studies relevant to extreme obesity (references)
Apixaban	2.71	21	87	7	7,9,10	28-30	10,27
Dabigatran[a]	−2.4	60-70	35	19	10	19,29-32	10,27
Edoxaban	1.72	107	55	33	—	29	—
Rivaroxaban	2.18	50	94	25,26,34	6,8,10	24,29,32	8,10,27,35

DOAC, direct oral anticoagulant; logP, logarithm of partition coefficient; PK/PD, pharmacokinetic/pharmacodynamic.

[a]Data are referring to the active drug component dabigatran, not the pro-drug dabigatran etexilate.

[b]logP is a parameter indicating a compound's hydrophilicity (logP < 0) and lipophilicity (logP > 0). Values for apixaban, dabigatran and rivaroxaban are from https://pubchem.ncbi.nlm.nih.gov/compound. Edoxaban values are from "New Drug Application" (NDA) submitted to FDA.

[c]The phase III studies that demonstrated the efficacy and safety of DOACs as compared to warfarin included a moderate number of obese patients, and most included a subgroup analysis of efficacy by weight. Severely obese patients were not specifically identified in those studies. Summary of weight categories in the phase III studies is provided in 2016 ISTH publication.[17]

dabigatran (version 3/2018) and edoxaban (version 11/2017) do not provide any PK data.[11,12] The apixaban label (section 12.3; version 6/2018) includes a PK section, in which Figure 3 reports a lower peak plasma concentration (C_{max}) and area under the curve (AUC) in patients with a body weight of ≥120 kg (n = 19) compared to those with a body weight of 65-85 kg (n = 18), tested after a single dose of 10 mg apixaban in healthy adult subjects (study CV185059 in the apixaban NDA from 2012)[13,14]; this is consistent with previously published PK data.[7] For rivaroxaban, the PK section (version 8/2018) reports a C_{max} and AUC for patients weighing >120 kg (n = 12) similar to those of patients with a weight of 70-80 kg (n = 12) based on a single dose of rivaroxaban in healthy volunteers (study 011568 in the rivaroxaban NDA from 2011).[15,16] Based on ADME and physiochemical properties for the DOACs, complemented by published clinical data, extreme obesity would not be predicted to significantly affect PK and PD of apixaban and rivaroxaban; however, available clinical data is scarce. For dabigatran and edoxaban, clinical efficacy and clinical pharmacology data are even much less clear from the limited peer-reviewed literature and from the US FDA label.

4 | ISTH SSC 2016 GUIDANCE DOCUMENT

In 2016, the International Society on Thrombosis and Haemostasis (ISTH) published a guidance document, "Use of the direct oral anticoagulants in obese patients."[17] It highlighted that, while subgroup analyses of obese patients from the large phase III DOAC vs warfarin trials suggest that DOACs are efficacious and safe in obese patients, this conclusion must be tempered by the paucity of available data on patients at extremes of weight. The limitations of available data included numbers of patients and their clinical outcomes at extreme weights in these trials, as well as available PK data. Therefore, the guidance suggested that DOACs not be used in patients with a BMI > 40 kg/m^2 or a weight >120 kg, but that if a DOAC is used in these patients, a peak and trough level should be obtained to ensure the levels fall within the expected range.[18]

5 | RECENT PIRAN ET AL PUBLICATION

A study by Piran et al in *Research and Practice in Thrombosis and Haemostasis* was performed to add to the relative paucity of available data on the efficacy and safety of DOACs in patients with BMI > 40 kg/m^2 or weight >120 kg.[10] A peak DOAC drug concentration was determined 2-3 hours after oral administration in 38 extremely obese patients on anticoagulation, mostly for AF and VTE. The primary outcome was the "proportion of patients with peak plasma DOAC concentrations that fall below the median trough of published population median trough levels." The study found that only two patients (5%; 95% CI: 0.5%-18%) had such low concentrations (both treated with dabigatran).

While the manuscript acknowledges that no consensus exists on the best method to define adequate drug plasma concentrations, the authors' primary outcome construct is odd and not backed by available data. The statement that only 5% of patients had low concentrations according to their defined outcome, while scientifically accurate, is misleading, as it may imply that the other 36 patients (95%) had adequate drug concentrations. However, no solid interpretation of adequacy of drug concentrations is possible because: (a) the validity of having a peak concentration lower than the population median trough is unclear, and (b) correlation between plasma drug concentrations and clinical efficacy and safety of DOACs (ie, a validated exposure–response relationship) has not yet been well established. While such correlations have been described for dabigatran and edoxaban trough concentrations, they have not been published for apixaban and rivaroxaban, nor described for peak plasma levels for any of the DOACs.[19,20]

The key finding of the Piran et al study is that 21% (95% CI: 11%-37%) of patients had a peak DOAC concentration below the expected range (ie, below the fifth percentile for apixaban and rivaroxaban and below the tenth percentile for dabigatran), which could be interpreted as indicating suboptimal drug exposure. However, assessments of peak DOAC concentrations have significant limitations, because (a) as previously mentioned, there

is no validated exposure-response relationship between drug concentrations and clinical outcomes, and (b) there is relatively wide variation in the time to reach maximal drug levels (T_{max}) for each DOAC).[16,21-23] Therefore, perhaps a more reliable parameter for drug concentration assessments would be trough drug concentrations (C_{min}), which were not measured in this study. The study reported that none of the patients who had available clinical data (N = 22/38) had recurrent VTE or stroke, though information surrounding follow-up was limited. Given the limitations of its findings, this study does not increase our comfort to use DOACs in extremely obese patients.

6 | ADDITIONAL PUBLICATIONS

Since the 2016 ISTH guidance document was published,[17] several additional publications have explored whether DOACs are effective and safe in patients with extreme obesity. First, a sub-analysis of the EINSTEIN DVT and PE trials investigating rivaroxaban showed no association between body weight or BMI and risk of recurrent VTE, major or clinically relevant bleeding.[24] However, the extremely obese patients were not specifically analyzed, but rather grouped into ≥100 kg or BMI ≥ 35 kg/m^2. This limits the strength of conclusions about the safety and efficacy of rivaroxaban in the extremely obese patients.[24] Second, a population PK analysis of rivaroxaban, which included 22 843 PK sampling observations from 4918 patients in seven clinical trials, showed that the influence of weight on rivaroxaban PK was minor.[25] However, many of the PK data were from prophylactic dosing studies and the number of extremely obese patients in the studies was likely very low, given the study designs, reported mean body weights and standard deviations.[25] Additionally, a population PK analysis of 101 patients receiving prophylactic or treatment doses of rivaroxaban also found that weight alone had little effect on rivaroxaban PK, but the study included only six patients with a BMI ≥ 40 kg/m^2.[26] Another retrospective, single-center study of 128 extremely obese patients (BMI > 40 kg/m^2 or weight >120 kg), half of whom were on a DOAC and the other half on warfarin, found that apixaban and rivaroxaban appeared similarly effective and safe as warfarin, whereas dabigatran had a numerically higher rate of stroke or TIA.[27] Finally, several abstracts have been presented at scientific meetings in the last 2 years that have evaluated either plasma DOAC concentrations or clinical outcomes in patients with extreme obesity. The publication of these data in the peer-reviewed literature will provide further information to better understand whether a DOAC or warfarin is a better choice in patients with extreme obesity.

7 | SUMMARY

In spite of some additional data published since the publication of the 2016 ISTH guidance document, data about the efficacy of DOACs in patients with extreme obesity are still limited and

treatment decisions on whether to use a DOAC or warfarin cannot be made with confidence. It is unclear whether moderately altered PK parameters (such as lower C_{max}, AUC and increased clearance for apixaban), or the below-expected peak values seen in the current Piran et al study, translate into decreased clinical efficacy or an increase in safety concerns.

Given the currently available data, we feel comfortable using DOACs in patients with a BMI up to 40 kg/m^2 or a body weight up to 120 kg. However, above these parameters, we have reservations using DOACs because it remains unclear whether adequate drug concentrations are achieved to be clinically effective (particularly when using apixaban). In these extremely obese patients, our preference is to either use warfarin or, if a DOAC is chosen, to obtain a trough drug concentration after five or more doses (when the DOAC has reached a steady-state concentration), to determine whether concentrations are roughly within the range published for other patient or healthy volunteer populations.[18]

Ultimately, there is still an absence of robust clinical data to support definitive prescribing recommendations of DOACs in patients with BMI > 40 kg/m^2 or >120 kg total body weight. Therefore, we advocate for prospective studies to characterize DOAC PK and PD in extremely obese patients to better guide management decisions.

RELATIONSHIP DISCLOSURE

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