DIRECT ORAL ANTICOAGULANTS IN EXTREMELY OBESIVE 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/m², 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/m²) or mild to moderately obese (30-40 kg/m²) 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

[Article updated on January 4, 2019, after first online publication on December 24, 2018: Author listing was updated to include the correct academic degrees for Dr. Daniel J. Crona.]
Table 1: Pharmacologic parameters of DOACs and publications relevant to obesity

|        | logPb | 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 obesityc (references) | Clinical studies relevant to extreme obesity (references) |
|--------|-------|---------------------------|---------------------|-----------------------------------------------|---------------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
| Apixaban | 2.71  | 21                        | 87                  | 7                                             | 7, 10                                                   | 28-30                                           | 10.27                                           |
| Dabigatran | 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.

aData are referring to the active drug component dabigatran, not the pro-drug dabigatran etexilate.

blogP 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.

cThe 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

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/m² 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 \( (T_{\text{max}}) \) for each DOAC.\(^{16,21-23} \) Therefore, perhaps a more reliable parameter for drug concentration assessments would be trough drug concentrations \( (C_{\text{min}}) \), 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 \( \geq 100 \text{ kg or } \text{BMI} \geq 35 \text{ kg/m}^2 \). 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 4,918 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 \( \geq 40 \text{ kg/m}^2 \).\(^{26} \) Another retrospective, single-center study of 128 extremely obese patients \( (\text{BMI} \geq 40 \text{ kg/m}^2 \text{ or weight } > 120 \text{ kg}) \), 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 \( C_{\text{max}}, \text{ AUC and increased clearance for apixaban} \), 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 \text{ kg/m}^2 \text{ 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 \text{ kg/m}^2 \text{ or } > 120 \text{ 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

Dr. Moll has been a consultant for Janssen. Dr. Crona and Martin do not have any disclosures.

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