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LETTER

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Direct oral anticoagulants in patients with nonvalvular atrial fibrillation and extreme body weight

1 | INTRODUCTION

Bodega et al.'s recent report on the efficacy and safety of direct oral anticoagulants (DOACs) in patients with nonvalvular atrial fibrillation and extreme body weight reinforces recent therapeutics advances in anticoagulation in these patient cohorts.[1] Their finding of lack of difference in recurrent thromboembolic events between two weight categories (extreme and normal) in patients with atrial fibrillation stabilized on a DOAC-based anticoagulation strategy is consistent with the most recent guideline updates in these patient cohorts (body mass index [BMI] >40 kg/m^2 or weight > 120 kg). Clinical decisions regarding the commencement of anticoagulation amongst certain patients' groups have continued to be subjects of ongoing therapeutic debate. One of these is the utility and safety of DOACS (for all indications) amongst patients' cohorts with BMI >40 kg/m^2 or weight > 120 kg. These are vulnerable therapeutic groups for which 'actionable' trial data (regarding both efficacy and safety) have been lacking (until recently). DOACs as a class have variable pharmacokinetics (PK) accounting for the well-reported differences in PK parameters amongst its various analogues.[2] Conversely, their pharmacodynamic (PD) outcome data thus far have shown insignificant differences between the various analogues.[3,4] Currently, available PD data with regard to DOACs and from which prescriptive guideline-directed recommendations for their use were made have principally accrued from clinical trials of which patients with outlying BMI ranges were either limited (in number) or excluded[3,4] Table 1. Their use in patients with BMI >40 kg/m^2, therefore, raises understandable concerns regarding both clinical effectiveness and safety.

2 | PHARMACOKINETICS AND PHARMACODYNAMICS OF DOACs IN OVERWEIGHT PATIENTS

To date, there has not been any validated scheme of therapeutic drug monitoring (TDM) amongst DOAC analogues. Much of these is due to a combination of non-availability of reliable data, but also inter- and intra-individual variability evident in approach to PK data interpretation in general. The limited PK/PD studies that have thus far been reported show a negligible impact of weight on various outcomes across most of the analogues. Even in cases where significant differences in *Cmax, Cmin, AUC* thresholds were reported (as was the case for both rivaroxaban and apixaban),[5,6] this has not had any meaningful impact on hard clinical outcomes (including recurrent events and major bleeding risks). There are, however, still outstanding residual concerns with regard to the limited dabigatran TDM data in morbidly obese patient cohorts, with drug levels reported below quoted 'normal ranges'. It is pertinent to note that the latter is not equivalent to 'therapeutic drug levels' (for which an abiding consensus is still lacking). Similarly, data for the effect of extremes of weight on edoxaban PK outcomes are still discordant and await evaluation by further well-designed PK studies.

3 | CLINICAL GUIDELINES TRANSITION

The 2016 decision by the international society of Thrombosis and Haemostasis (ISTH) advising against the use of DOACSs in patients weighting >120 kg or BMI >40 kg/m^2 (or where their use becomes inevitable to

TABLE 1 Proportion of overweight patient cohorts enrolled into selected recent randomized controlled clinical trials of direct oral anticoagulants (DOACs) across clinical risks

DOAC analogue	Clinical risk	Weight category	Proportion of overweight patients *N* (%)	Name of study
Rivaroxaban	Atrial fibrillation (AF)	BMI > 35	1898 (13.5)	ROCKET-AF
Dabigatran	AF	BMI > 36	1787 (10)	RE-LY
Rivaroxaban	Venous thromboembolism (VTE)	>100 kg	245/1731 (14.2)	EINSTEIN-DVT
Apixaban	VTE	BMI > 35	349/2691 (13)	AMPLIFY
Apixaban	AF	>40	1006 (5.5)	ARISTOTLE
Edoxaban	AF	>40	1149 (5.5)	ENGAGE AF-TIMI 48
Dabigatran	VTE	>35	306/2538 (12)	RECOVER-1
Edoxaban	VTE	>100 kg	611/4118 (14.8)	HOKUSAI-VTE

Note: It is noteworthy the proportion of overweight patients in these studies was comparatively small vis-à-vis their respective study populations.

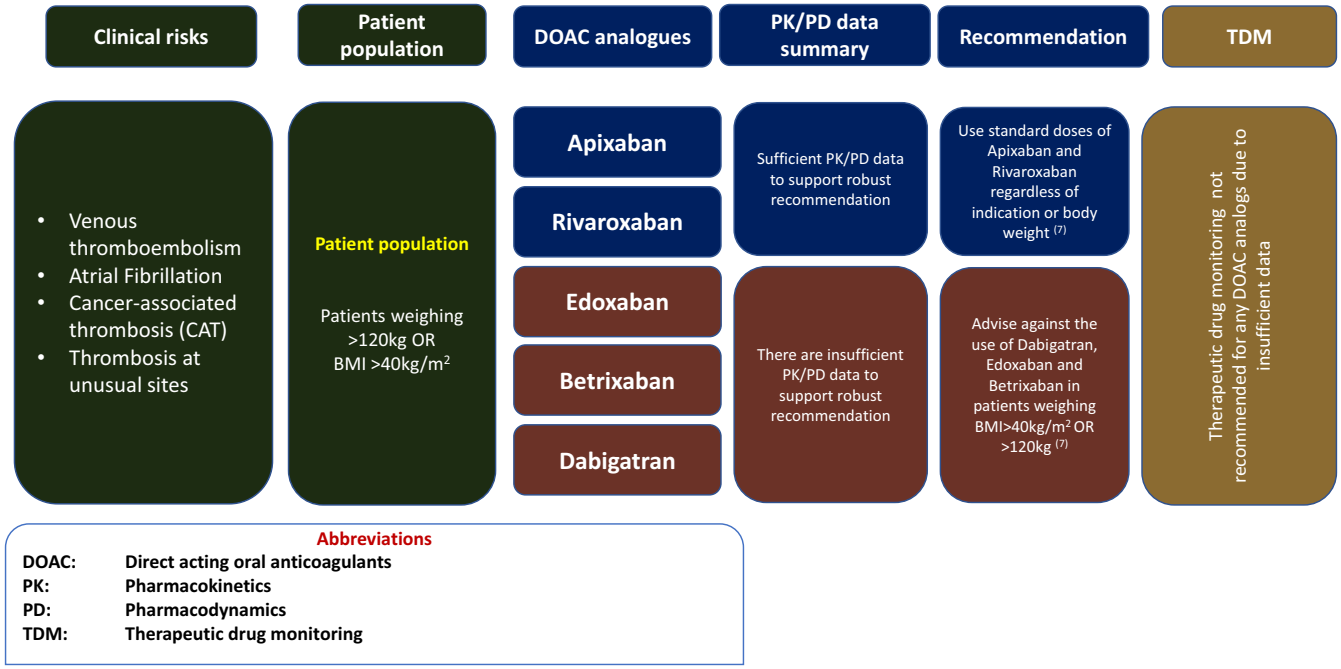

FIGURE 1 Schematic representation of where current evidence for the efficacy and safety of direct oral anticoagulants (DOACs) for all indications in morbidly obese patient cohorts fits into clinical practice

follow-up with appropriate TDM) was based on lack of adequate PK/PD data.[7] Since the publication of Elshafei et al.'s meta-analytical synthesis[8] and other PK/PD studies, the relationship between rivaroxaban and apixaban exposure and reduction in hard clinical endpoints as well as major bleeding risks in these unique cohorts has become much clearer. For the therapeutic utility of DOAC's as a strategy for anticoagulation in patients who are morbidly obese (>120 kg or BMI > 40 kg/m^2) with acute venous thromboembolism (VTE), we were the first to undertake a comprehensive systematic evaluation (by way of a meta-analysis) of currently published reports in these cohorts of patients to ascertain any adverse effect of weight on the efficacy and safety of DOACs.[8] The aim of this was to establish an abiding consensus on the treatment of this therapeutically challenging patient population. In our pooled analyses of ($N = 6585$) patients across five studies exploring the non-inferiority of DOAC analogues versus warfarin, we found rivaroxaban was non-inferior compared with the vitamin K antagonist (VKA) warfarin in reducing pre-specified primary efficacy outcomes of VTE recurrence (OR 1.07, 95% CI 0.93–1.23) as well as the primary safety outcome (major bleeding events) (OR 0.80, 95% CI 0.54–1.17) in patients weighing >120 kg or BMI > 40 kg/

m^2). Bodega et al.'s recent report[1] is consistent with the result of our pooled analyses and supports prevailing practice consensus around this; or be it in a setting of different clinical risks (atrial fibrillation) but with similar therapeutic challenges (BMI > 40 kg/m^2). Unlike Bodega et al.'s report which showed a 'trend' towards decreased bleeding risks at lower body weight categories, we found no weight-related dichotomy of the point estimates of bleeding risks with DOACs in our synthesis (Figure 1). Following a comprehensive review of these data (phase 3, phase 4, and observational studies) by ISTH, the 2016 guidance has since been updated in April 2021.[9] Consistent with this new update are individual recommendations for each DOAC analogue for patients with BMI >40 kg/m^2 or weighting >120 kg. Rivaroxaban and apixaban have now been recommended for use in their standard doses regardless of clinical indication or weight/BMI category. There is still residual uncertainty regarding the data with both dabigatran and edoxaban, and the 2016 recommendation for them therefore still subsists, that is, they are restricted for use in patient cohorts with BMI <40 kg/m^2 or weighting <120 kg. Additionally, there are insufficient PK/PD data linking DOAC drug levels with hard clinical endpoints to favourably advise TDM with peak and trough drug levels.

Despite the above updated guideline recommendations, going forward there remains an outstanding need to conclusively investigate the exact effect of extremes of body weight on efficacy and safety of DOACs for which residual uncertainty still exists (such as edoxaban and dabigatran) across all clinical risks and indications. A single study design (such as an RCT) is unlikely to robustly resolve this; it is likely to be a combination of data from either individual standalone RCTs and PK studies, or studies where PK blood sampling is integrated into an RCT design.

CONFLICT OF INTEREST

None of the authors have any relevant conflict of interest to report.

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REFERENCES

1. Bodega F, Russi A, Melillo F, et al. Direct oral anticoagulants in patients with nonvalvular atrial fibrillation and extreme body weight. *Eur J Clin Invest*. 2022;52(1):e13658.
2. Russo V, Cattaneo D, Giannetti L, et al. Pharmacokinetics of direct Oral anticoagulants in patients with atrial fibrillation and extreme obesity. *Clin Ther*. 2021;43(9):e255-e263.
3. Agnelli G, Buller HR, Cohen A, et al. Oral apixaban for the treatment of acute venous thromboembolism. *N Engl J Med*. 2013;369(9):799-808.
4. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med*. 2011;365:883-891.
5. Upreti VV, Wang J, Barrett YC, et al. Effect of extremes of body weight on the pharmacokinetics, pharmacodynamics, safety and tolerability of apixaban in healthy subjects. *Br J Clin Pharmacol*. 2013;76(6):908-916.
6. Wasan SM, Feland N, Grant R, Aston CE. Validation of apixaban anti-factor Xa assay and impact of body weight. *Thromb Res*. 2019;182:51-55.
7. Martin K, Beyer-Westendorf J, Davidson BL, Huisman MV, Sandset PM, Moll S. Use of the direct oral anticoagulants in obese patients: guidance from the SSC of the ISTH. *J Thromb Haemost*. 2016;14(6):1308-1313.
8. Elshafei MN, Mohamed MFH, El-Bardissy A, et al. Comparative effectiveness and safety of direct oral anticoagulants compared to warfarin in morbidly obese patients with acute venous thromboembolism: systematic review and a meta-analysis. *J Thromb Thrombolysis*. 2021;51(2):388-396.
9. Martin KA, Beyer-Westendorf J, Davidson BL, Huisman MV, Sandset PM, Moll S. Use of direct oral anticoagulants in patients with obesity for treatment and prevention of venous thromboembolism: updated communication from the ISTH SSC subcommittee on control of anticoagulation. *J Thromb Haemost*. 2021;19(8):1874-1882.