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DOACs use in extreme body-weighted patients: results from the prospective START-register

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Abstract

Background Direct oral anticoagulants (DOACs) are widely used for the treatment of venous thromboembolism (VTE) and for stroke prevention in atrial fibrillation (AF). However, evidence in obese and underweight patients is limited. We assessed the safety and effectiveness of DOACs and vitamin K antagonists (VKAs) in patients ≥ 120 kg or ≤ 50 kg enrolled in an observational prospective cohort study, the START-Register.

Methods Adult patients started on anticoagulant therapy were followed up for a median of 1.5 years (IQR 0.6–2.8). Primary efficacy outcome was the occurrence of VTE recurrence, stroke and systemic embolism. Primary safety outcome was major bleeding (MB).

Results 10,080 AF and VTE patients were enrolled between March 2011 and June 2021, 295 patients weighted ≤ 50 kg and 82 patients ≥ 120 kg. Obese patients were significantly younger than underweight patients. Rates of thrombotic events were low and similar between DOACs and VKAs in underweight patients (1 event on DOACs therapy [0.9% 95% CI 0.11–5.39] and 2 on VKAs [1.1% 95% CI 0.01–47.68]) and in overweight patients (0 events on DOACs, 1 on VKAs [1.6%, 95% CI 0.11–5.79]. Two MB events occurred on DOACs (1.9%, 95% CI 0.38–6.00) and 3 on VKAs (1.6%, 95% CI 0.04–22.06) in the underweight group; 1 MB on DOACs (5.3% 95% CI 0.33–16.68) and 2 on VKAs (3.3%, 95% CI 0.02–130.77) in the overweight group.

Conclusions DOACs seem to be effective and safe also for the treatment of patients with extreme body weights, both underweight and overweight. Further prospective studies are needed to support these findings.

Keywords DOACs · Direct oral anticoagulant · Anticoagulation · Weight · Venous thromboembolism · Atrial fibrillation

Introduction

Direct oral anticoagulants (DOACs)–the thrombin inhibitor dabigatran, and the activated factor X (FXa) inhibitors apixaban, edoxaban, and rivaroxaban–are widely used for the treatment and secondary prevention of venous thromboembolism (VTE) and for ischemic stroke prevention in patients with non-valvular atrial fibrillation (AF) [1, 2]. DOACs are administered at fixed doses and do not require laboratory monitoring, resulting in a more convenient patient management. This strategy was found to be as effective and safe, if not safer, than treatment with vitamin K antagonists (VKAs) [3–12].

There is currently limited evidence in the literature to support the use of DOACs in obese and underweight patients. Studies that have specifically assessed the safety and effectiveness of DOACs in patients with extreme body weights had observational retrospective designs [13, 14]. A meta-analysis of the pivotal RCTs comparing DOACs with VKAs for the treatment of VTE addressed this issue and found no difference in VTE recurrence in patients with obesity treated with DOACs compared to VKAs, while DOACs significantly reduced the risk of major bleeding compared

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to VKAs [15]. In another meta-analysis, underweighted AF and VTE patients had a paradoxical increase of the risk of thromboembolism compared with non-low body weight patients, while AF overweight patients had fewer thromboembolic outcomes compared with AF patients with a non-high body weight [16].

In 2016, a guidance document from the International Society of Thrombosis and Haemostasis (ISTH), updated in 2021, suggested not to use DOACs in patients with a BMI > 40 kg/m2 or body weight > 120 kg because of limited clinical data and because available pharmacokinetic (PK)/pharmacodynamic (PD) evidence indicated decreased drug exposure, peak concentration, and shorter elimination half-lives with increasing body weight. No guidance was provided for patients with body weight < 50 kg [1, 2].

Aim of this prospective, cohort study is to assess the safety and effectiveness of DOACs and VKAs in patients weighting ≥ 120 kg and in patients ≤ 50 kg.

Materials and methods

As detailed elsewhere [17] the START-Register (NCT02219984) is an inception, prospective, observational, multicenter, dynamic, independent study that enrolls adult patients who start anticoagulant therapy, whatever the indication of treatment and drug/dosage used. Authorisation to set up the registry was obtained from the Ethical Committee of the University Hospital 'S. Orsola-Malpighi', Bologna, Italy, in October 2011 ($n = 142/2010/0/0$ss). The same institution is charged with deploying and upkeeping the registry central database. The aim of the START-Register is to collect data on the effectiveness and safety of anticoagulant treatments, on the determinants of adverse events in patients who are anticoagulated, and on their quality of life and compliance to treatment. Patients are included only after providing signed informed consent and the study was conducted according the ethical principles for medical research as set out in the Declaration of Helsinki. All participating centers have professional personnel qualified by education, training and experience to perform the required tasks. All collected clinical material is property of the Arianna Anticoagulazione Foundation. All data were gathered using an electronic clinical report form (e-CRF) developed for the START-Register. Each participating center had access to the e-CRF by a specific account and password. All centers were invited to include patients consecutively in order to avoid as much as possible a selection bias. The e-CRF included all demographic patient data in anonymous form; only the enrolling center was able to connect the anonymous information with the name of each patient. The accuracy and completeness of data entry in the central database was monitored by dedicated study personnel, at the Arianna Foundation, who also solicits participating centers to contact, for the purpose of the study, patients lost to follow-up through a telephone call or their general practitioner. Information on the type, dosage, and duration of anticoagulant treatment was collected at study entry and during follow-up. Information on study outcomes occurring during follow-up was collected. At each participating center, patients were regularly followed with at least 1 in person visit at 6 and 12 months. A final visit, in person or by telephone contact was requested at the end of follow-up.

All therapeutic decisions were entirely left to the discretion of the treating physicians.

Here, we present the results of the cohort of the extreme weight patients (≤ 50 kg or ≥ 120 kg) who started anticoagulation for the treatment and secondary prevention of VTE and for ischemic stroke prevention in non-valvular AF. Cutoffs of 50 kg and 120 kg were established to define under and overweight patients respectively according to median weight of the Italian population. For the purpose of the present analysis, data were collected from March 2011 to June 2021; patients follow-up was registered until October 2021.

Primary endpoints of this study were the composite of VTE recurrence, stroke, systemic embolism (thrombotic events) for effectiveness and major bleeding events for safety. Information on and all-cause mortality and clinically relevant non-major bleeding was also collected. VTE recurrence was defined as objective diagnosis of symptomatic VTE by means of compression and/or color-doppler ultrasound, CT scan and laboratory tests. Stroke was defined as the occurrence of focal neurological symptoms lasting at least 24 h and supported by congruent ischemic lesions at CT or MRI scan. Systemic embolism was defined as symptomatic acute loss of blood flow to a peripheral artery, supported by objective evidence of embolism. Major bleeding (MB) and clinically relevant non-major bleeding (CRNMB) were defined according to the ISTH definitions [18, 19]. Thrombotic and bleeding events were adjudicated by the local investigators.

Statistical analysis

All variables were summarized with the usual descriptive statistics: categorical variables as absolute and relative frequency; age was described with mean and standard deviation, BMI as median and interquartile range (IQR). Chi-square test p value was applied for categorical variable; F test from ANOVA model for continuous variable. Kruskall–Wallis test was applied for median follow-up. Unadjusted incidence rate (IR) was calculated for efficacy and safety outcomes; 95% confidence interval (95% CI) estimates were based on the Poisson distribution.

A univariate and multivariable (adjusted for low dose) competing risk analysis was applied to explore the effect of

treatment on primary efficacy outcome and on bleedings, Fine and Grey model was applied and sub-distribution hazard ratios (sHR) together with 95% CIs were calculated.

All analysis was performed using SAS v9.4.

Results

Among the 12,819 patients on DOAC or AVK therapy enrolled in the START-Register during the interval time March 2011–June 2021 after the occurrence of VTE or for stroke prevention in AF, 56 subjects were excluded from the analysis due to lack of weight data and, among the remainder, 2782 were excluded due to lack of follow-up until October 2021. Therefore, the analysis was performed on 10,080 subjects.

Patients were stratified by weight into three groups: 295 patients ≤ 50 kg, 9703 patients 50–119 kg and 82 patients ≥ 120 kg, hereinafter referred to as under, normal and overweight respectively. The decision to prescribe VKAs or DOACs was entirely left to attending clinicians.

The baseline characteristics of the population are summarized in Table 1. Briefly, obese patients were significantly younger than normal weight and underweight patients and there were significantly more women in the underweight group than in the other two groups.

The mean Body Mass Index (BMI) was 42.2 kg/m^2 (IQR 39.4–45.2) in obese patients, defining these patients as morbidly obese.

DOACs were prescribed to 110 (37.3%) underweight patients (56.4% of them received a reduced dose), and to 20 (24.4%) morbidly obese patients, 2 of them received a reduced dose (10.0%). VKAs were prescribed to 185 (62.7%) underweight patients and to 62 (75.6%) overweight patients. Patients on VKAs showed a median time in therapeutic range (TTR) of 64% (IQR 50–77) in the low weight group, 66% (IQR 54–76) in normal weight and 70% (IQR 52–76) in the high weight group, respectively.

Median duration of follow-up was 1.5 years (interquantile range 0.6–2.8).

Study outcomes

Efficacy outcomes

Overall, a thrombotic event occurred in 3 underweight patients (1.0%), in 141 normal weight patients (1.4%), and in 1 overweight patient (1.2%).

In the underweight group, the primary efficacy outcome occurred in 1 patient on DOACs therapy (0.9%, IR 0.76, 95% CI 0.11–5.39) and in 2 patients on VKAs (1.1%, IR 0.61, 95% CI 0.01–47.68), while in the overweight group, the only event occurred on VKAs therapy (1.6%, IR 0.82, 95% CI 0.11–5.79). [Table 2]. In the normal weight group, the thrombotic outcome occurred in 89 patients on DOACs (2.2%, IR 1.46, 95% CI 1.18–1.79) and in 52 patients on AVKs (0.9%, IR 0.44, 95% CI 0.26–0.77).

The cumulative occurrence of thrombotic events did not show significant difference between DOACs and VKAs in the underweight group (sHR 1.42, 95% CI 0.14–14.07, $p = 0.77$), these data were confirmed also after adjusting for DOACs low-dose (sHR 4.90, 95% CI 0.50–48.32, $p = 0.17$).

Safety outcomes

During follow-up, MB or CRNMB occurred in a total of 569 patients.

There were 5 MB in the underweight group (1.7%), 234 in the normal weight group (2.4%), and 3 in the overweight group (3.7%).

Table 1 Baseline characteristics

	All			
	≤ 50 kg	51–119 kg	≥ 120 kg	*P* value
N	295	9703	82	
Age at enrollment, mean (SD)	76.0 (15.2)	71.0 (14.6)	58.9 (11.8)	< 0.0001
Male, *n* (%)	30 (10.2)	5205 (53.6)	64 (78.1)	< 0.0001
BMI, median (IQR)	18.7 (17.3–19.9)	26.9 (23.9–29.3)	42.2 (39.4–45.2)	< 0.0001
Median follow-up (years)	1.16	1.47	1.57	0.001
History of cancer, *n* (%)	56 (21.0)	1388 (15.5)	5 (6.6)	0.01
Active cancer, *n* (%)	10 (3.8)	388 (4.4)	1 (1.3)	0.40
Previous stroke or TIA, *n* (%)	50 (18.7)	1194 (13.3)	5 (6.8)	0.01
CKD, *n* (%)	36 (13.6)	931 (10.5)	3 (4.1)	0.05
Hypertension, *n* (%)	191 (70.7)	6477 (70.6)	64 (84.2)	0.03
Anticoagulation for FA, *n* (%)	200 (67.8)	5903 (61.1)	46 (56.1)	0.04

Chi-square test *p* value for categorical variable, *F* test from ANOVA model from continuous

Kruskall-Wallis test was applied for median follow-up

Table 2 Outcomes

Weight (Kg)	DOAC			VKA		
	≤ 50	51–119	≥ 120	≤ 50	51–119	≥ 120
	N (%) IR × 100PY (95% CI)	N (%) IR × 100PY (95% CI)	N (%) IR × 100PY (95% CI)	N (%) IR × 100PY (95% CI)	N (%) IR × 100PY (95% CI)	N (%) IR × 100PY (95% CI)
Thrombotic events	1 (0.9) 0.76 (0.11–5.39)	89 (2.2) 1.46 (1.18–1.79)	0 (0.0)	2 (1.1) 0.61 (0.01–47.68)	52 (0.9) 0.44 (0.26–0.77)	1 (1.6) 0.82 (0.11–5.79)
MB + CRNMB	3 (2.7) 2.25 (0.72–6.98)	183 (4.5) 3.02 (2.61–3.50)	2 (10.0) 4.70 (1.18–18.79)	11 (6.0) 3.38 (0.30–37.56)	368 (6.5) 3.25 (2.35–4.49)	2 (3.2) 1.67 (0.06–47.41)
MB	2 (1.9) 1.50 (0.38–6.00)	96 (2.4) 1.59 (1.30–1.94)	1 (5.3) 2.35 (0.33–16.68)	3 (1.6) 0.92 (0.04–22.06)	138 (2.4) 1.21 (0.77–1.92)	2 (3.3) 1.67 (0.02–130.77)
CRNMB	1 (0.9) 0.75 (0.11–5.33)	87 (2.1) 1.44 (1.17–1.77)	1 (5.3) 2.35 (0.33–16.68)	8 (4.3) 2.46 (0.04–139.53)	230 (4.1) 2.04 (1.29–3.22)	0 (0.0)
Death	7 (6.4) 5.24 (2.50–10.99)	201 (4.9) 3.21 (2.79–3.69)	0 (0.0)	28 (15.1) 8.33 (1.73–39.98)	501 (8.9) 4.25 (3.14–5.75)	4 (6.5) 3.26 (1.22–8.69)

In the underweight group, 2 events occurred in the DOAC group (1.9%, IR 1.50, 95% CI 0.38–6.00) and 3 in the VKA group (1.6%, IR 0.92, 95% CI 0.04–22.06). In overweight group, there was 1 MB in patients receiving DOACs therapy (5.3%, IR 2.35, 95% CI 0.33–16.68) and 2 in patients on VKAs (3.3%, IR 1.67, 95% CI 0.02–130.77). In the normal weight group, there were 96 MB in patients on DOACs (2.4%, IR 1.59, 95% CI 1.30–1.94) and 138 in those on VKAs (2.4%, IR 1.21, 95% CI 0.77–1.92).

CRNMB occurred in 9 underweight patients (3.1%), in 313 normal weighted (3.2%) and in 1 obese patient (1.2%).

CRNMB in underweight patients occurred in 1 patient on DOACs (0.9%, IR 0.75, 95% CI 0.11–5.33) and in 8 patients on VKAs (4.3%, IR 2.46, 95% CI 0.04–139.53). In overweight patients, the only event occurred in the DOAC group (5.3%, IR 2.33, 95% CI 0.33–16.68). In normal weight patients, 87 CRNMB occurred in the DOAC group (2.1%, IR 1.44, 95% CI 1.17–1.77) and 230 in the VKA group (4.1%, IR 2.04, 95% CI 1.29–3.22).

No significant difference in overall bleeding rates was detected between DOACs and VKAs in the underweight group (sHR 0.90, 95% CI 0.24–3.37, $p = 0.88$) or in the overweight group (sHR 3.17, 95% CI 0.46–21.92, $p = 0.24$).

Mortality outcomes

During follow-up, 35 underweight patients (11.9%), 702 normal weighted (7.2%) and 4 obese patients (4.9%) died.

In the underweight group, death occurred in 7 patients on DOACs (6.7%, IR 5.24, 95% CI 2.50–10.99) and in 28 patients on VKAs (15.1%, IR 8.33, 95% CI 1.73–39.98). Four overweight patients on VKAs died (6.5%, IR 3.26, 95% CI 1.22–8.69), none in the DOACs group. In the normal weight group, 201 patients on DOACs (4.6%, IR 3.21, 95% CI 2.79–3.69) and 501 patients on VKAs (8.9%, IR 4.25, 95% CI 3.14–5.75) died ($p = 0.0094$).

Discussion

In this observational, prospective cohort study we have compared the incidence rates of thrombotic and bleeding events in patients with extreme body weights treated with DOACs and VKAs. Overall, rates of thrombotic events were similar across body weight groups and between DOACs and VKAs in the subgroups of underweight and overweight patients. There was a trend toward more major bleeding events in overweight than in underweight patients, with no statistically significant difference between treatment groups.

Overall, the low number of events documented in our study seems to support the possibility to use the DOACs in patient populations with extreme body weights. In particular, the effectiveness and safety of the DOACs appears at least comparable to that of VKAs in patients with a body weight of equal to or lower than 50 kg. In the overweight population enrolled in our study, with a mean BMI of 42.2 kg/m^2, the number of events was reassuringly very low, but the small number of patients in this subgroup does not allow any firm conclusion.

Our results are in keeping with the results of Aloi and colleagues, who compared VTE recurrence rates between patients receiving DOAC therapy who weighed > 120 kg

and those who weighed < 120 kg in the Veterans Integrated Service Network (VISN) 8 database [20]. Also in this retrospective study the number of events was low and not statistically different between the two groups.

In another retrospective cohort study on VTE patients, Cardinal et al. showed that the risk of recurrent VTE is not associated with BMI, whereas MB occurred more frequently in underweight than in normal or overweight patients treated with DOACs [21]. These results also support our findings for the obese population, but show an inverse trend in terms of safety. The lower incidence of bleeding events in the underweight population enrolled in our study may be, at least in part, explained by the high proportion of patients receiving low-dose DOACs in our study.

Cohen and colleagues compared the risk of recurrent VTE, MB, and CRNMB among VTE patients with obesity and morbid obesity treated with apixaban or warfarin and found a lower risk of CRNMB with the DOAC compared to warfarin across non-obese, obese/non-morbid, and morbidly obese patients. [22] The incidence of the other outcome events was comparable between the treatment groups, again supporting the use of DOACs in obese patients.

Finally, in a real-world Korean retrospective study, patients with non-valvular AF and low weight included in the Korean National Health Insurance Service (NHIS) database, So-Ryoung Lee and colleagues included 21,679 patients with a body weight < 60 kg and showed a better effectiveness and safety of DOACs versus warfarin [23]. This result remained consistent in patients with extremely low body weight (< 50 kg). The main limitation of this study was the poor TTR control in Asian patients treated with warfarin [23]. In our study, the underweight population showed a lower median TTR than other groups, but it was still 64% (IQR 50–77), demonstrating a good level of anticoagulation also in this population.

The participating centers, expert in managing anticoagulation, prescribed VKAs to majority of extreme body weights patients, following 2016 and 2021 ISTH recommendation [1, 2], showing a good TTR control both in under and overweighted patients.

Finally, a lower mortality rate was found among DOACs treated patients of any weight category. This difference may be related, at least in part, to the selection criteria adopted by physicians in choosing anticoagulant treatment. For example, the higher prevalence of severe renal failure in VKAs patients may be one factor to explain the higher mortality rate recorded in this population in spite of the weight category. Data are not shown as they are beyond the scope of this study.

Differences in outcome rates of thrombotic events and bleeding events were observed between DOACs and VKAs in normal weight patients. This finding, which is out of the scope of the present study, has been already reported and discussed in a previous paper by this group [24].

This study presents a number of limitations. First, the observational design requires extreme caution in interpreting direct comparisons between drugs due to the high risks of bias of these studies. Second, the small sample size of under and overweighted patients does not allow to reach firm conclusions on the effectiveness and safety of anticoagulant drugs in these populations.

Finally, in this study there was no central adjudication of outcome events. Moreover, we decided to focus our analysis on patients body weight, therefore no clinical outcomes data on patients BMI are available. Strength of the study is the multicentric design with a prospective collection of the patient data, together with accuracy and completeness of follow-up for patients enrolled.

In conclusion, DOACs seem to be effective and safe also for the treatment of patients with extreme body weights, both underweight and overweight. Further prospective studies are needed to support these findings.

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Data availability Data cannot be shared openly, to protect study participant privacy.

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