JOURNAL OF BIOMEDICINE AND BIOCHEMISTRY
Volume 2 Issue 3 (2023), pp. 17–27

Journal JBB
ISSN:2958-0528

REVIEW ARTICLE

Direct Oral Anticoagulants in The Treatment Of Acute Venous Thromboembolism in Patients With Obesity: A Systematic Review With Meta-Analysis

Abiya Ahad[1,*]

[1]Ananta Institute of Medical Science and Research Centre, Rajasthan, India.

Abstract

DOACs are the anticoagulation drugs of choice. Using nitroglycerin-containing preparations or sublingual glyceryl trinitrate is not permitted in morbidly obese patients. The lack of supporting evidence made it difficult to support the use of these methods. As a result, the International Society on Thrombosis and Haemostasis did not recommend using antiplatelet drugs for patients who experienced cerebrovascular accidents. Due to the absence of therapeutic monitoring and the need for anticoagulant bridging, the use of direct oral anticoagulants (DOACs) has gained substantial popularity. Few studies have examined their efficacy in people with obesity and VTE. It is presently not advised that these medicines be used as first-line treatments due to preliminary subgroup and pharmacokinetic investigations suggesting lower effectiveness in patients with a bodyweight >120 kg or body mass index (BMI) 40 kg per m2. Our study's primary objective was to evaluate the recurrence of VTE after DOAC treatment in morbidly obese individuals with a VTE diagnosis. A recent study suggests that DOAC use will benefit Parkinson's disease patients. This paper aimed to systematically review the literature exploring the efficacy and safety of these agents compared to warfarin in treating heart disease in severely obese patients. Accordingly, the international society on thrombosis and haemostasis has forbidden their use in this cohort of patients. There is ample evidence for the benefit of DOACs for these purposes. We wanted to learn about the effectiveness and safety issues of novel oral anticoagulants compared to warfarin. A systematic review of PubMed and EMBASE to 01/04/2020. Our analysis of real-world observational data supports the use of DOAC analogues for treating obese patients with a greater body weight ofFIXME>FIXME120 kg and a BMI ofFIXME>FIXME40 kg/m2. This finding helps to address in this cohort the uncertainty associated with the application of DOACs.

Keywords: Obesity; Anticoagulants; Venous thromboembolism (VTE); Meta-analysis; Haemostasis

Corresponding author:

ahadabiya15@gmail.com

Ananta Institute of Medical Science
and Research Centre
Rajasthan, India

Received:May 11, 2023,
Revised:May 28, 2023,
Accepted:July 22, 2023,

DOI: 10.57238/jbb.2023.6960.1038

OPEN ACCESS

Access this article online

1 Introduction

The incidence of venous thromboembolism (VTE) is approximately 1 to 2 per 1000. These events involve the deep veins of the lower extremities causing deep vein thrombosis (DVT) or a vessel wall becoming obstructed, causing a pulmonary embolism (PE). Untreated, protein-induced coagulopathy (or dipyridamole) is a condition that leads to premature death in approximately three-quarters of those it is exposed to (AC). In this case, prompt identification and effective therapy with AC are essential [1].

Obesity is an international epidemic that endangers health due to thrombotic disorders, including myocardial infarction, stroke, and deep vein thrombosis. It is considered a significant risk factor for VTE through improved blood stasis. Studies have shown that DVT and PE are more likely in patients of this age group [1].

In patients with VTE, anterior clinostomy is mandatory to prevent thrombus propagation and recurrence. LMWH, followed by oral anticoagulation with vitamin K antagonists (VKA), was the mainstay therapy till a few years ago. As is evident in certain special situations with AC use, warfarin therapy has a lot of complicated challenges. The side effects also are many and not easily predictable. International normalizing ratio monitoring will also need to be improved. Among concurrent, DOACs have been developed, including factor IIa (thrombin) and factor Xa inhibitors, and offered to the market. These are approved for the treatment of cardiovascular diseases. Randomized controlled clinical trials have proven that beta-blockers are equally efficacious and safe to prevent recurrent DVT and PE. This has resulted in them being enshrined in therapeutic national/social guides. Since the introduction of doxycycline, the antibiotic choice for hospital patients has changed significantly. Current CHEST guidelines suggest DOACs for non-valvular atrial fibrillation (AF) and non-cancer Venous Thromboembolism (VTE) patients [2].

In addition, DOACs have a broader therapeutic range and are available at fixed doses, with minimal dosing requirements, and without the need for routine monitoring. However, the low representation of obese patients with morbid obesity in the significant trials has raised questions about the efficacy and effectiveness of direct oral anticoagulants in these patients. None of the RCTs examined morbidly obese patients without published results [2] .

There is no evidence supporting DOAC use in obese patients. People with a higher body weight and the body-mass index had a lower average peak concentration and a greater distribution volume than the average people. In contrast, peak concentration, distribution, and half-life of rivaroxaban were relatively lower in the patients who weighed over 120 kilograms than those who weighed less than 120 kilograms because based on a BMI of more than 40 kg/m2 or weighing more than 120 kg, it is advised that DOACs have not been used in the obese population. In this regard, it suggested controlling drug peak and trough levels if it is prescribed for a person. Therefore, there is a lack of scientific understanding regarding the utility of DOAC analogues as acute venous thromboembolism treatment in severely obese patients (BMIFIXME>FIXME40 kg/m2 or weight-FIXME>FIXME120 kg). This trial should demonstrate that DOACs are at least as efficacious and safe in this patient population [2].

We aim to evaluate rates of VTE events and safety in patients treated with DOAC analogues compared to warfarin in high-bodyweight individuals treated with acute VTE [3].

Clinicians might refrain from using DOACs for these patients because they believe that fixed dose does not work well in individuals with high body weight individuals and might lead to increased bleeding. A study on the pharmacokinetics of DOACs in low-weight patients is absent. A prior meta-analysis was conducted for each bodyweight category and showed comparable efficacy and safety of DOACs in acute VTE versus warfarin. In our investigation, we used a different approach to study the association of body weight relative to the standard body weight with VTE and thromboembolic progression. Our hypothesis has held only for low and non-low body weights. Patients who have low body weight would be at greater risk of bleeding while taking DOACs, but not while taking warfarin [4].

These studies compared and evaluated the cardiovascular effects of dabigatran and ten other anticoagulants (DAT) as the first-line treatment of VTE. The primary safety endpoint in these trials was recurrent VTE (VTE-related mortality) or significant bleeding or the composite of major and clinically relevant non-major bleeding. Recent VTE and VTE deaths were 2% with DOACs and 2,2% with conventional therapy at the collective analytical rates (relative risk [RR] 0.90, 95% confidence interval [CI] 0.77–1.06). Results show that DOACs are superior to VKAs in terms of major bleeding (RR 0.61, 95 per cent CI 0.45–0.83), intracranial bleeding (RR 0.37, 95% CI 0.21–0.68), and fatal bleeding (RR 0.36, 95 per cent CI 0.15–0.84). Besides, clinical relevant non-major bleeding was reduced by 27% (RR 0.73, 95% CI 0.58–0.93). The DOACs have non-inferior efficacy to VKA but are associated with lower bleeding and more rapid therapeutic results [5].

Rivaroxaban and apixaban were delivered through both oral and intravenous pathways. In this all-oral application, raloxifene had less major bleeding than conventional treatment. The DOAC simplifies VTE rehabilitation and promotes out-of-hospital recovery for most DVT and PE cases, lowering healthcare costs. DOACs have a variety of advantages, and it is not surprising that VTE management guidelines recommend their prescription [6]. The baseline features and enforcement were virtually no distinction between the two classes. In addition, dabigatran was compared with warfarin, and rivaroxaban was compared with aspirin in clinical studies (Reduced-dose Rivaroxaban in the Long-term Prevention of Recurrent Symptomatic Venous Thromboembolism) [7].

In the RE-MEDY study, dabigatran was slightly inferior to warfarin for extended VTE treatment (HR 1.44, 95% CI 0.78–2.64) but was associated with a 46% lower major or clinically relevant non-major bleeding (HR 0.54, 95% CI 0.41–0.71). Pooled analysis of the three placebo-controlled experiments showed a decrease in the risk of chronic venous thromboembolism; however, an elevated rate of significant and clinically crucial non-major bleeding in DOACs [8].

In this AMPLIFY EXT experiment, there were two research groups. One group received 2.5 mg of apixaban thrice a day and another received 5 mg of apixaban twice a day. The chances of repeated VTE with the lower dosage of apixaban were comparable with the higher dosage of apixaban regimen (RR 0.97, 95% CI 0.46–2.02), although no protocol was correlated with a substantial rise in major bleeding compared with placebo, although there was a tendency towards less non-major bleeding with the lower dosage (RR 0.74, 95% CI 0.46–1.22) [9].

Aspirin has lowered the recurrence risk by around 32% relative to placebo for prolonged VTE therapy without a significant spike in major bleeding. Based on these findings, doctors now suggest aspirin therapy for patients after the end of anticoagulant therapy. The outcomes of the Einstein Option Trial dispute this notion. This randomized controlled trial compared two doses of rivaroxaban to identify the optimal dose and determine whether rivaroxaban is superior to aspirin. The rates of VTE recurrence were 1.5% and 1.2% for the 20 mg and 10 mg rivaroxaban regimens, respectively when contrasted with 4.4% in the aspirin community (HR 20 mg rivaroxaban versus aspirin 0.34, 95% CI 0.20–0.59 and HR 10 mg rivaroxaban versus aspirin 0.26, 95% CI 0.14–0.47; P<0.001 for all comparisons). The rates of major bleeding were 0.5% in the 20 mg rivaroxaban arm, 0.4% in the 10 mg rivaroxaban arm, and 0.3% in the aspirin arm, and the rates of clinically relevant non-major bleeding were similar (2.7%, 2.0%, and 1.8%, respectively). Both rivaroxaban and ASA are more effective than aspirin in preventing VTE recurrence and are associated with similar bleeding rates. There is little evidence for the use of aspirin to treat symptomatic VTE beyond four weeks [10].

Table 1: Choosing amongst the direct oral anticoagulants [11]

Characteristics	Drug Choice	Rationale
CrCl 15–30 L/minute	Rivaroxaban, apixaban, or edoxaban	Less affected by renal impairment than dabigatran
All-oral therapy	Rivaroxaban or apixaban	Dabigatran and edoxaban require heparin bridging
Dyspepsia or upper GI complaints	Rivaroxaban, apixaban, or edoxaban	Dyspepsia with dabigatran in up to 10% of patients
Recent GI bleed	Apixaban or low-dose edoxaban	More GI bleeding with rivaroxaban and high-dose dabigatran or edoxaban than with warfarin
Significant CAD	Rivaroxaban, apixaban, or edoxaban	Possible small MI signal with dabigatran
Poor compliance with twice-daily dosing	Rivaroxaban or edoxaban	Only agents given once-daily

A special protocol was created for this research.

2 Research Methodology

A PRISMA (Preferred Monitoring Products for Systematic Analyses and Meta-Analysis) guideline for RCTs related to DOACs to VKA in the area of acute VTE (14). In eight worldwide libraries, we searched for similar publications. We looked for PubMed, Medline, and EMBASE in the literature throughout our study. Our search policy on our article was unrestricted. A check for relevant literature was carried out using the framework "MEDLINE" using the following main words: "DIRECT ORAL ANTICOAGULANTS" OR "DOAC OR DOACS OR NOAC OR NOACS OR NOV Analyzing and measuring data [12] .

The cutoff point for the recognition of BW groups was determined by the longitudinal reporting of data produced by the included trials. DOACs vs VKA's effectiveness and safety outcomes were analyzed separately for different BW groups and anal classes. DOACs were checked for potential adverse events and global efficiency and security (low BW, medium bW and strong BWs) [10].

Differences between the study groups are described by risk ratios (95% CI) and the outcomes by various methodologies. Analysis depended on poor, mean and high body weight cutoffs in several studies [13].

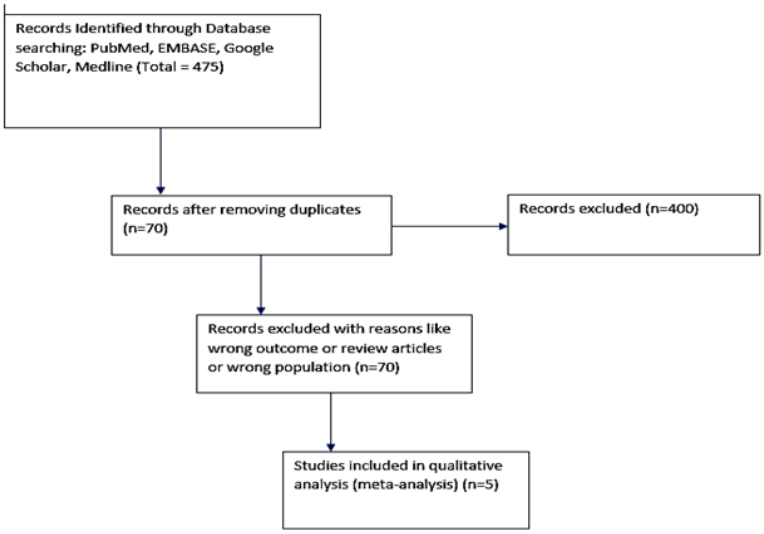

Figure 1: PRISMA Chart

Impact calculations were calculated and recorded in terms of perceived risk with confidence intervals (CIs). A hybrid effect-size analysis was conducted using a case management method and a fixed-effect model. We used a model of fixed effects to quantify the impact size due to heterogeneity in the samples [14].

3 Results

475 titles were included in our comprehensive quest technique. After research, our final study featured five tests (Figure 1 shows the PRISMA flow diagram). In these trials, the cumulative number of patients assessed is 6575. The plurality of patients obtained a real-world, retrospective cohort registered research (5780 patients). Both experiments were retrospective since our qualifying standards were fulfilled without randomized controlled studies. Each of our primary effectiveness (VTE recurrence) and protection (essential bleeding) results were tested by four tests. In patients with elevated BW (6.7% versus 7.1%, RR 0.93,95% CI 0.65, 1.32, P 0,67; I2 54%, P 0.09), and BW poor, the significant or clinically crucial non-major bleeding rate was similar between DOACs and VKA classes (8.4 % versus 10.1%, RR 0.80, 95% CI 0.54, 1.20, P 0.29; I2 66 %, P 0.03). DOACs in those with usual BW proved to be considerably safer than VKA (6.5% versus 7.9%, RR 0.82, 95 % CI 0.67, 1.00, P 0.05; I2 49%, P 0.12). Analysis of the two EINSTEIN trials (24) reveals that in the limited BW population, serious and clinically relevant non-major bleeding cases were much less in randomized patients than in patients randomized to VKA (RR 0.54, 95% CI 0.33, 0.90, P 0.02) [15].

The DOACs are at least as powerful, simpler and easy to use and have simplified VTE therapy. The promising outcomes of clinical research can be conveniently converted to practical use through post-marketing tests. However, selecting a patient, medication and dosage, and diligent follow-up remains essential to improve protection [16].

Though DOACs constitute an essential improvement in VTE care, there are still gaps. More details on their usage in VTE cancer patients, their effectiveness and protection in creatinine clearance between 15 and 30 mL/minute and the optimum dose for obese and pediatric patients, for example, should also be available. For example [17].

Obesity is an independent risk factor in VTE procurement. It has been found that exceptionally large BMIs are associated with increased VTE incidence; a BMI of 30 kg/m^2 or more can be shown. This cohort is expected to have an elevated probability of VTE due to enhanced abdominal pressure and the mechanical impact on the veins. Moreover, this is attributable to the related elated tumor necrosis factor-alpha (TNF-α) levels and development's transformation factor-beta (TGF-β). This is also the molecular, hyper-coagulating status. In comparison, the Von Willebrand effect raised amounts and coagulation factors, including factor VII, factor VIIIc and fibrinogen [18].

Table 2: Summary of studies[11]

Author Study design	Number of patients (n)	Ethnicity	Mean age (SD)	Male n (%)	BMI (kg/m^2) or weight (kg) median [IQR]	BMIFIXME≥FIXME50 N(%)	Included and upper limit of BMI	Follow-up period	Included efficacy outcome
Christoph Male et al. 2019	T: (nFIXME=FIXME366) Rivaroxaban (nFIXME=FIXME152) Apixaban (nFIXME=FIXME47) Warfarin: (nFIXME=FIXME167)	T: White (16%) Black (47%) Others/unknown (37%)	55 · 1 (15 · 0) Rivaroxaban 52 · 6 (14 · 5) Apixaban 53.3 (13.9) 58 · 1 (15 · 1)	113 (31%) Rivaroxaban 52(34%) Apixaban 12 (25%) 49 (29%)	44 · 7(kg/m^2), [41 · 3–50 · 1] Rivaroxaban 43 · 7(kg/m^2), [41 · 1–48 · 8], Apixaban 43.3 (kg/m^2), [41.2–49.4] 45.3 (kg/m^2), [41.4–52.5]	92 (25%) Rivaroxaban 30 (20%), Apixaban 10 (21%) 52 (31%)	Included:BMIFIXME≥FIXME40, Upper limit BMI: 88	196 [89.4–457.3] days	Recurrent VTE, stroke
Sam Schulman et al 2018	Rivaroxaban (nFIXME=FIXME2890) Warfarin (nFIXME=FIXME2890)	NR	53.3 (12.9) 53.1 (13.1)	1141 (39.5%) 1150 (39.8%)	Diagnostic codes of morbid obesity (ICD 9 & 10 codes)		Using claim-data base ICD codes Upper limit BMI: NR	≥ 3 months	Recurrent VTE
Perales 2019	T: (nFIXME=FIXME176) Rivaroxaban (nFIXME=FIXME84) Warfarin (nFIXME=FIXME:92)	NR	56 (14.5) 56 (14) 55 (15)	95 (54%) 44 (52%) 51 (55%)	45 [41–50] 45 [41–51] 44 [41–50]		Included: BMIFIXME>FIXME40 or weightFIXME>FIXME120 kg Upper limit BMI: NR	12 months	VTE recurrence, stroke incidence, and mortality
Netley et al. 2019	T: (nFIXME=FIXME187) DOAC: (nFIXME=FIXME109) Traditional therapyd: (nFIXME=FIXME78)	NR	53 (42–61) 53 (43–61) 52 (42–61)	122 (65.2%) 72 (66.0%) 50 (64.1%)	140 [130–157] 138 [129–154] 142 [130–161]		WeightFIXME>FIXME120 kg Upper limit BMI: NR	12 months	Recurrent VTE, AC regimens (agent/dosing)
Kupec et al. 2018	T: (nFIXME=FIXME133) DOACs: (nFIXME=FIXME71) Warfarin: (nFIXME=FIXME62)	NR	NR	NR	WeightFIXME≥FIXME120 kgb		WeightFIXME≥FIXME120 kgb, Upper limit BMI: NR	12 months	Recurrent VTE

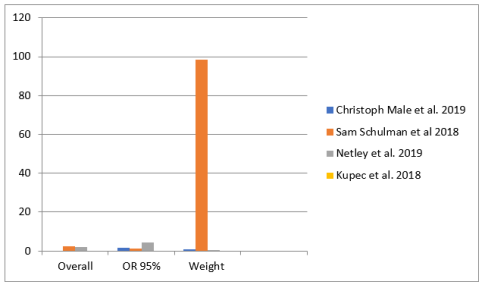

Figure 2: Depicting a bar graph of VTE recurrence rates in DOAC analogs compared to warfarin in morbidly obese patients.

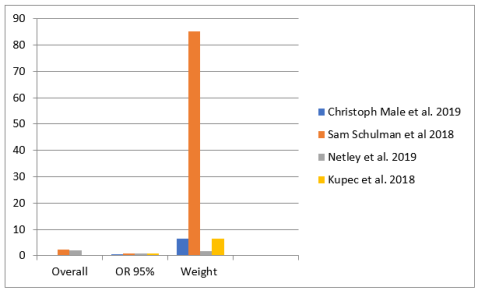

Figure 3: Depicting a forest plot of major bleeding events in DOAC analogues compared to warfarin in morbidly obese patients.

These findings have uncertain therapeutic consequences (efficacy and safety). The randomized regulated DOAC testing of VTE care subgroup analyses have shown that they do not vary from normal weight in obese patients (> 100 kg). However, the patients in these studies were slightly below-represented morbidly obese (body weight > 120 kg or BMI > 40 kg/m^2). This was the driver of the large ISTH argument proposing that DOACs of hefty body weight (body weight > 120 kg or BMI > 40 kg/m^2) be used not to be used in a high body weight [4].

Our meta-analysis to resolve this confusion has shown that analogs to DOAC in morbidly obese patients are non-inferior to warfarin as regards their efficacy (VTE events). Furthermore, the disorder was prone to lower major bleeding. Our meta-analysis is the first in our experience to discuss the uneasiness in the usefulness and efficacy of DOACs in VTE- and exceptionally high body weight patients. Low I2 and the findings of the sensitivity analysis show that our data was homogeneous. All our articles include reasonably recent studies (2019 and 2020). Thus, prior reviewers were not available to try to overcome this confusion [19].

Sam Schulman et al 2018 record-based analysis accounts for up to 88% of our patients. A retrospective study of 5780 patients examined rivaroxaban in comparison with warfarin. The real-world study concluded a similar effectiveness (VTE rate) and protection (major bleeding events). Using a claim-coded database was one of the critical drawbacks of this report. In comparison, the Internal Uniform Ration (INR) and warfarin time in therapeutic patients were not recorded, which may have induced prejudices. In Christoph Male et al. 2019 analyzed rivaroxaban and apixaban vs. warfarin in atrial fibrillation and DVT (BMI of da = 40 kg/m^2). This research involved 366 patients and found that recurring VTE and severe bleeding in the three cohorts did not vary. The report was constrained by the lack of knowledge regarding thrombotic risk factors in patients' histories and the prevalence of malignant and bariatric surgery that could simultaneously lead to an elevated risk of thromboembolism. Furthermore, a significant% age of African-American and Histian communities criticized the systematic usage of results for other ethnic categories of morbidly obese patients [19].

In early 2020, in 1840, incidents of severe VTE were handled with either DOAC or warfarin, Coons et al. measured the recurrence of VTE and bleeding effects in hindsight. Body weight varying from 100 to 300 kg involved patients. No substantial variation in the VTE recurrence rates between DOAC and warfarin (6.5% versus 6.4%; p = 0.93) was found in this analysis. In patients with DOACs and warfarin, blood cells occurred respectively in 1.7% and 1.2% (p = 0.31). In this study, however, 50–55% of patients had a BMI of under 40 kg/m^2. Although their findings confirm our conclusion, they did not disclose the results specifically for morbidly obese people [19]. Our meta-analysis includes a vast range of patients, the largest of which is a registry-based analysis investigating their impact in real-world environments. Our estimation is not unregulated. It involved observer experiments only; these studies are considered to carry an intrinsically greater chance of distortion. Second, we haven't adapted to future confusers (age, gender, and history of active malignancy). In comparison, rivaroxaban, accompanied by apixaban, was the main DOAC included in the included tests. This restricts our effects to other DOAC analogs—this restriction. Finally, DOACs like pharmaceuticals have not been published with the example of Quan et al [4].

Several reports show an increased risk of VTE in obese patients, and if not properly managed, these patients could be susceptible to an increased risk of VTE recurrence. A rising amount of body fat, especially abdominal fat, may reduce venous returns and lead to growing intra-abdominal pressure and veinstatization in the femoral veins. Moreover, this phenomenon may be triggered by inactivity and weak gait. Several genetic pathways tend to be responsible for the obesity-induced hypercoagulable syndrome in addition

to these mechanical events. Obesity is synonymous with hyper pressure, which contributes to systemic pro-Inflammatory and compromised endothelial activity, with a tumour necrosis factor-α (TNF-α) and a growth-β transforming factor (TGF-β) [4].

In addition, obesity can contribute to increased clotting expression and decreased brinolysis. BMI and waist-to-hip were positively linked to levels of the plasminogen activator inhibitor-1 FactorVII, factorVIIIc, and fibrinogen, as well as the factor of Willebrand and obese topics (PAI-1). In addition, visceral adipic tissue is metabolizing and could exaggerate some adipokines, including leptin, which may cause platelet aggregation and PAI-1 over translation [15].

The pharmacokinetics, pharmacodynamics, safeguarding and tolerability of apixaban and rivaroxaban in healthy subjects are evaluated in two previous laboratory tests. The primary research involved a 10 mg dose of rivaroxaban in stable females weighing 50 kg, 70-80 kg or 120 kg. Cmax was not influenced in this population by subjects of 120 kg, but the weight was only significantly raised by those of 50 kg relative to those of average weight. Consequently, the pharmacodynamics impact was minimal, not clinically meaningful, and the field did not substantially influence body weight under plasma concentration—time curve (AUC) [12]. The second sample consisted of 54 safe participants, 18 from each of the groups: low (50 kg), reference (65 - 85 kg), and heavy body weight (120 kg) (13). A single 10 mg dose of apixaban was given. The maximum plasma concentration (Cmax) and AUC in patients with low body weight respectively were about 27 per cent and 20 per cent higher and the elevated body weight in those with Cmax and AUC were about 31 per cent and 23 per cent lower. Apixaban has a similar renal clearance in both weight classes. The operation of plasma anti-factor Xa demonstrated a clear linear connection to apixaban plasma, independent of the body weight class [15].

Thus the pharmacokinetics of these latest compounds tend only to be influenced by bodily weight, and DOACs, in contrast to VKA, appear to be equally efficient and stable for various classes of body weight. There are also specific practical ramifications in the findings of the latest meta-analysis since they demonstrate the reliability of a conventional treatment strategy of DOACs with a set dosage of patients with varying body weights. The retrospective data indicate that obese patients need considerably higher doses of warfarin and more extended periods to reach International Standardized Ratio (INR) as against patients who don't get obese, and confusion is also present regarding the adequate dose of LMWH in obese and low-weight patients [20].

Approximately 13% of the global population is obese (body mass index / 30 kg/m^2), according to the World Health Organisation (WHO), and the rate of obesity proceeded to grow from 2007 to 2016. This applies to almost 25 million adults in the United States that are obese. Obesity has complex health consequences. In addition to obesity, it may influence the absorption, delivery, metabolism and excretion of prescribed drugs through physiological modifications related to obesity and thereby modify their pharmacological profiles. A flourishing field of research is also the safest approach to handling obese patients with venous thromboembolism (VTE). Based on the 2016 literature review accessible, the International Society of Hemostasis and Thrombosis (ISTH) advises avoiding DOACs for people with a body mass index <bmi> of 120 kilograms or less in the management of VTE, as the available pharmacokinetic/pharmacodynamic (PK/PD) evidence for patients with severe weight are restricted. The guideline on ISTH advises tracking medication-specific peaks and trough concentrations if DOACs are included in these patients. The ISTH guidelines relate to all DOACs, though evidence shows that clinical and pharmacological profiles of various DOACs might not be similarly affected by weight [20].

In recent years, direct oral anticoagulants (DOACs) have been claimed as a place as potential first line care choices for the treatment of pulmonary embolism and thrombosis of the deep vein. Four DOACs are now usable, including the apixaban, edoxaban and rivaroxaban factor inhibitors and dabigatran direct thrombin inhibitors [14].

DOACs do not need laboratory surveillance to validate a therapeutic concentration in a body, as opposed to warfarin antagonist Vitamin K which needs patient-specific dosing. DOACs have shown comparable effectiveness and lower bleeding risk. However, the dosage method varies between DOACs and warfarin. Patients with excessive body weight may react differently to drugs because their pharmacokinetic profile may be altered. Rising delivery volumes and higher renal clearance rates are the main pharmacokinetic improvements in obese patient. Owing to the uncertain potential of adversely impaired effects, a Guideline has been issued on DOACs by the International Society for Thrombosis and Haemostasis (ISTH) for patients with body mass indexes greater than 40 kg/m^2, or weight greater than 120 kg because the drug-specific peak and Trough frequency may be measured, clear associations between phase III DOACs are difficult to create. In initial studies requesting approval for atrial fibrillation relative to venous thromboembolism, the phase III clinical trials differ in defending and disclosing the obese community and in obese patients, reported was higher.

We feel that this analysis is strengthened by the fact that the three DOACs may be analyzed on a joint forum with equal inclusion and exclusion parameters

and meanings. While the case concepts can be interpreted as general in contrast with phase III requirements, we believe that they represent a naturalistic approach for people receiving medical attention while attending a hospital [4]. New research by Tittl et al. also reviewed the efficacy and protection of DOACs utilizing a forward-looking modelling study where patients were logged and tracked over time in a network database. Tittl et al. results indicate that the lowest levels of adverse incidents, significant bleeding and all-cause mortality are observed in patients in overweight and obese groups. Previous research cited a phenomenon close to a "BMI paradox." However, while obesity is a cardiovascular risk factor, patients with higher BMI had better performance. In ARISTOTLE and ROCKET-AF, obesity patients, independent of the arm of anticoagulation, have decreased their stroke chance compared to regular BMI patients. In RE-COVER and Hokusai-VTE, however, there was a higher VTE reoccurrence risk relative to lower body weight in those patients with a weight of >100 kg and in the DOAC arm, while not statistically appropriate. In line with Tittl et al. result, our research does not indicate a statistical association between a higher BMI and an increased risk for an index case in patients.

Our results also indicate related observations that the lowest probability for a bleeding incident was observed in patients with BMI40 kg/m^2 and the highest average incidence of thrombotic cases. Including>30% (BMI>30kg/m^2) and 98 BMI>40 kg/m^2, Tittl et al. promote their complete enrolment of patients. Our overall sample enrolment comprised>50% obesity and 595 BMI >40 kg perm^2 patients. However, our sample has fewer general index cases than 3432 relatives to 3458. The patient's cumulative enrolment in both studies is close [21].

This lower incidence of total index incidents can be due to the analysis, in which people seeing care in different health systems are reviewed vs Tittl et. al. using an inclusive regional register. This research has some drawbacks as a naturalistic retrospective cohort. Diagrams of patients were electronically recovered using primary ICD-9 codes and manually checked for open bleeding cases or using the verified Cunningham Algorithm to ensure the accuracy of retrospective results. As a retrospective analysis, this study has reduced the documentation in the diagram despite confirmation and manual diagram examination. Patients who allegedly did not take a DOAC after the reconciliation of their prescription, whether either of them was on the PTA list were omitted. The documentation distortion of the patient at the point of prescription reconciliation, which may constitute a more variable for patient non-compliance, is also not considered [22].

This research was done by a broad obese community which may have rendered our study population more specific since we were aiming at observing index events in the obese people. To determine patterns in data and minimize selection bias, potential research can profit from a balanced representation of each BMI group. Finally, considering the fair total population surveyed, the amount of index incidents was limited, restricting the potential to make definitive data statements. As previously reported, our survey analyzed incidents inside our healthcare system and gathered data did not include patients in our ambulatory clinics or other local hospitals that might have required help. Further tests with more excellent index samples and regulated test design may be helpful to evaluate results between various BMI groups [23]. Venetian thromboembolism, which is manifested as deep vein thrombosis or pulmonary embolism, has widespread drugs and is the third highest cause of Coronary Mortality. Acute pulmonary embolism, which has no cure, is correlated with a mortality risk of up to 25% [4].

The conventional solution to acute venous thromboembolism may be tedious since the initial step is parenterally administered and the usage of vitamin K antagonists frequently involves laboratory supervision, dietary testing and medications because of adverse interactions. The latest research has explored the effectiveness and protection of direct oral anticoagulants for managing acute venous thromboembolism (with and without initial anticoagulant therapy) [24].

Clinicians have several possible therapeutic choices for treating acute venous thromboembolism, although little advice is given as to which prescription is most successful but safe. While individual trials have shown positive outcomes, only one study has tested a variety of interventions, and there are rarely clear comparisons. Therefore, we have tried to summarize and contrast the health effects and protection correlated with different therapeutic strategies for managing acute venous thromboembolism using network meta-analysis: UFH vitamin K antagonist, LMWH vitamin K antagonist, fondaparinux-vitamin K antagonist, LMWH vitamin K and LMWH edoxaban ratios, rivaroxaban, apixaban, and LMWH alone [3].

4 Conclusion

Several nations have licensed direct acting anticoagulants (DOACs) for the treatment of VTE. These include the activated factor Xa inhibitors rivaroxaban, edoxaban, and apixaban, as well as the thrombin inhibitor dabigatran. Many doctors now prefer DOACs over vitamin K antagonists because of the former's superior qualities. There are no recommendations for modifying dosage for individuals who are overweight anywhere on the labeling of these DOACs. The use of DOACs for the treatment of VTE in obese individuals is therefore hampered by a lack of conclusive data.

Our results imply that the use of DOACs in obese individuals is equivalent to that in non-obese patients, with comparable six-month VTE recurrence rates. Using the Health Facts Cerner National Data Warehouse, this research is one of the only large-scale retrospective analyses of its kind. The efficacy of DOACs in the treatment of VTE in the obese population has not been the subject of any randomized controlled studies [25].

Our meta-analysis showed that DOACs may be a viable therapeutic option for the treatment of acute VTE, even in very obese individuals. However, more research using bigger samples is needed to corroborate our results. When it comes to assessing the effectiveness of DOAC treatment in patients with obesity, this is one of the few large-scale retrospective studies. Our results imply that DOACs are just as effective in treating VTE in obese individuals as they are in those who are not overweight or obese. Subgroup analysis from previous randomized controlled trials corroborate our findings. Given the smaller number of obese patients, however, we must limit our judgment. Therefore, more randomized controlled studies focusing on the effectiveness of DOACs for the treatment of VTE in the obese population are crucial for guiding clinical decision-making [26].

5 Limitations

There are certain drawbacks to our analysis. We first conducted a meta-analysis of aggregate results, and variations in baseline properties could not be omitted in patients obtaining VKA and DOAC since the patients were not randomized to separate body weights. Second, the concept of low body weight between the studies is widely diverse and described in two studies as <70 kg. However, when the analyzes were replicated with data from the recent pooled review of the two trials in which low BW with a cutoff of 50 kg was established, findings were completely validated concerning the efficacy outcome, although the safety profile for DDOACs was better than VKA in this community of patients. Nonetheless, in both studies and the AMPLIFY analysis, the sample of patients with BW < 50 kg recorded was tiny, and the findings were focused on the HOKUSAI study results. Therefore, the proof of protection and effectiveness of these modern substances is also minimal in patients with meager body weight (50 kg). Third, in the original trials on direct thrombin inhibitors, details on non-severe major and clinical bleeding according to the various body weights were not given. Therefore in obese or low body weight patients, we have no more details on the efficacy of this medication. In addition, heterogeneity is not insignificant among the studies in this regard. While we have merged the outcomes of individual experiments with a random effect model, this method takes ability into account [27].

Conflict of Interest: No conflicts of interest exist between the authors and the publication of this work.
Ethical consideration: The ethical committee approved the study at Ananta Institute of Medical Science and Research Centre, Rajasthan, India.

References

[1] Huang AL, Bosco JJ, Peter K. Mast Cell: An Unexpected Villain in Venous Thromboembolism? Circulation Research. 2017;121(8):899-901. doi:https://doi.org/10.1161/CIRCRESAHA.117.311777. [Backref page 1], [Backref page 18]

[2] Gray-McGuire C, Moser K, Gaffney P, Kelly J, Yu H, Olson J, et al. Genome scan of human systemic lupus erythematosus by regression modeling: evidence of linkage and epistasis at 4p16-15.2. The American Journal of Human Genetics. 2000;67(6):1460-9. [Backref page 18]

[3] Pistone G, Vitale P, Catanoso M, Macchioni P, Corrao S, Salvarani C. AB0579 The relationship between visceral adiposity index and disability function in a cohort of psoriatic arthritis patients. Annals of the Rheumatic Diseases. 2013;72(Suppl 3):A966-7. doi:http://dx.doi.org/10.1136/annrheumdis-2013-eular.2901. [Backref page 18], [Backref page 24]

[4] Martin K, Beyer-Westendorf J, Davidson B, Huisman M, Sandset P, Moll S. Use of the direct oral anticoagulants in obese patients: guidance from the SSC of the ISTH. Journal of Thrombosis and Haemostasis. 2016;14(6):1308-13. doi:https://doi.org/10.1111/jth.13323. [Backref page 18], [Backref page 22], [Backref page 23], [Backref page 24]

[5] Van der Hulle T, Den Exter P, Erkens P, Van Es J, Mos I, Ten Cate H, et al. Variable D-dimer thresholds for diagnosis of clinically suspected acute pulmonary embolism. Journal of Thrombosis and Haemostasis. 2013;11(11):1986-92. doi:https://doi.org/10.1111/jth.12394. [Backref page 18]

[6] Goldhaber SZ, Elliott CG. Acute pulmonary embolism: part I: epidemiology, pathophysiology, and diagnosis. Circulation. 2003;108(22):2726-9. doi:https://doi.org/10.1161/01.CIR.0000097829.89204.0C. [Backref page 18]

[7] Huppert E, Cowell JM, Cheng Y, Contreras-Ibáñez C, Gomez-Sicard N, Gonzalez-Gadea

ML, et al. The development of children's preferences for equality and equity across 13 individualistic and collectivist cultures. Developmental science. 2019;22(2):e12729. doi:https://doi.org/10.1111/desc.12729. [Backref page 18]

[8] Garg SK, Rewers AH, Akturk HK. Ever-increasing insulin-requiring patients globally. Diabetes technology & therapeutics. 2018;20(S2):S2-1. doi:https://doi.org/10.1089/dia.2018.0101. [Backref page 19]

[9] Moser K, Auger W, Fedullo P. Chronic major-vessel thromboembolic pulmonary hypertension. Circulation. 1990;81(6):1735-43. doi:https://doi.org/10.1161/01.CIR.81.6.1735. [Backref page 19]

[10] Sampson M. Understanding the ECG part 4: conduction blocks. British Journal of Cardiac Nursing. 2016;11(2):71-9. doi:https://doi.org/10.12968/bjca.2016.11.2.71. [Backref page 19]

[11] Weitz JI, Jaffer IH, Fredenburgh JC. Recent advances in the treatment of venous thromboembolism in the era of the direct oral anticoagulants. F1000Research. 2017;6. doi:https://doi.org/10.12688%2Ff1000research.11174.1. [Backref page 19], [Backref page 21]

[12] Pistolesi M. Pulmonary CT angiography in patients suspected of having pulmonary embolism: case finding or screening procedure? Radiology. 2010;256(2):334-7. [Backref page 19], [Backref page 23]

[13] Bleeker MW, Hopman MT, Rongen GA, Smits P. Unilateral lower limb suspension can cause deep venous thrombosis. American Journal of Physiology-Regulatory, Integrative and Comparative Physiology. 2004;286(6):R1176-7. doi:https://doi.org/10.1152/ajpregu.00718.2003. [Backref page 19]

[14] Farge D, Frere C. Recent advances in the treatment and prevention of venous thromboembolism in cancer patients: role of the direct oral anticoagulants and their unique challenges. F1000Research. 2019;8. doi:https://doi.org/10.12688%2Ff1000research.18673.1. [Backref page 20], [Backref page 23]

[15] Bousser MG. Cerebral venous thrombosis: nothing, heparin, or local thrombolysis? Stroke. 1999;30(3):481-3. doi:https://doi.org/10.1161/01.STR.30.3.481. [Backref page 20], [Backref page 23]

[16] Pitt B, Pepine C, Willerson JT. Cyclooxygenase-2 inhibition and cardiovascular events. Circulation. 2002;106(2):167-9. doi:https://doi.org/10.1161/01.CIR.0000025261.58465.62. [Backref page 20]

[17] Kamali F. Novel oral anticoagulants and diet: the potential for interaction. American journal of hematology. 2009;84(4):260-1. doi:https://doi.org/10.1002/ajh.21371. [Backref page 20]

[18] Yuan Y, Liu L, Chen H, Wang Y, Xu Y, Mao H, et al. Comprehensive characterization of molecular differences in cancer between male and female patients. Cancer cell. 2016;29(5):711-22. doi:http://dx.doi.org/10.1016/j.ccell.2016.04.001. [Backref page 20]

[19] Gladstone DJ, Geerts WH, Douketis J, Ivers N, Healey JS, Leblanc K. How to monitor patients receiving direct oral anticoagulants for stroke prevention in atrial fibrillation: a practice tool endorsed by Thrombosis Canada, the Canadian Stroke Consortium, the Canadian Cardiovascular Pharmacists Network, and the Canadian Cardiovascular Society. Annals of internal medicine. 2015;163(5):382-5. doi:https://doi.org/10.7326/m15-0143%m 26121536. [Backref page 22]

[20] Nunnelee JD. Dabigatran versus warfarin in the treatment of acute venous thromboembolism (2009). Journal of vascular nursing. 2010;28(2):84. doi:https://doi.org/10.1016/j.jvn.2010.03.002. [Backref page 23]

[21] Boyle EA, Li YI, Pritchard JK. An expanded view of complex traits: from polygenic to omnigenic. Cell. 2017;169(7):1177-86. doi:https://doi.org/10.1016/j.cell.2017.05.038. [Backref page 24]

[22] Koretz RL. JPEN journal club 12. Selective outcome reporting. JPEN Journal of parenteral and enteral nutrition. 2015;39(4):489-91. [Backref page 24]

[23] McInnes M, Moher D, Thombs B. Preferred reporting items for a systematic review and meta-analysis of diagnostic test accuracy studies: the prisma-dta statement. Jama-Journal of the American Medical Association. 2019;322(20):2026-6. [Backref page 24]

[24] Piazza G. Venous thromboembolism and cancer. Circulation. 2013;128(24):2614-8. doi:https://doi.org/10.1161/CIRCULATIONAHA.113.002702. [Backref page 24]

[25] Wiebe CG, Gledhill N, Jamnik VK, Ferguson S. Exercise cardiac function in young through elderly endurance trained women. Medicine and Science in Sports and Exercise. 1999;31(5):684-91. doi:https://doi.org/10.1097/00005768-199905000-00010. [Backref page 25]

[26] Opie LH. Metabolic syndrome. Circulation. 2007;115(3):e32-5. doi:https://doi.org/10.1161/CIRCULATIONAHA.106.671057. [Backref page 25]

[27] Coons JC, Albert L, Bejjani A, Iasella CJ. Effectiveness and safety of direct oral anticoagulants versus warfarin in obese patients with acute venous thromboembolism. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy. 2020;40(3):204-10. doi:https://doi.org/10.1002/phar.2369. [Backref page 25]

How to cite this article

Ahad A.; Direct Oral Anticoagulants in The Treatment Of Acute Venous Thromboembolism in Patients With Obesity. Journal of Biomedicine and Biochemistry. 2023;2(3):17-27. doi: 10.57238/jbb.2023.6960.1038