

Contents lists available at ScienceDirect

Annals of Medicine and Surgery



Systematic Review / Meta-analysis

Safety and efficacy of direct oral anticoagulants in comparison with warfarin across different BMI ranges: A systematic review and meta-analysis

Talal Almas^{a,*}, Faeez Muhammad^b, Laiba Siddiqui^b, Batool Shafi^b, Rabbia Gul^b, Rafiya Altaf^b, Zaeem Abbasi^b, Ghulam Mustafa^b, Arham Iqbal^b, Amatul Rehman Durdana^b, Maham Dilawar^b, Adeena Musheer^b, Kaneez Fatima^b

^a Department of Medicine, RCSI University of Medicine and Health Sciences, Dublin, Ireland

^b Department of Medicine, Dow University of Health Sciences, Karachi, Pakistan

A R T I C L E I N F O	A B S T R A C T
Keywords: DOAC (direct oral anticoagulants) Warfarin BMI (Body mass index) Safety Efficacy	<i>Background:</i> Many publications have compared various outcomes defining safety and efficacy of DOACs across different BMI ranges. Our meta-analysis compares warfarin and DOACs for its treatment effects over different BMI ranges. <i>Methods:</i> A systematic search was conducted from inception to May 2021 on PubMed, Scopus and Embase databases. The data was extracted and pooled using a random effects model. Our study consisted of patients being treated for VTE and AF, across different BMI categories. For the comparison of DOAC, risk ratios (RR) with 95% confidence intervals (CIs) were used, whilst for the second comparison between warfarin and DOACs odds ratios (OR) were used. <i>Results:</i> In our first comparison, 12 studies ($n = 254,908$ patients) were included. For our second comparison, six studies ($n = 109,609$ patients) were included. Major bleeding events in the underweight group were higher than normal weight [RR: 1.89 (1.10, 3.23); $P = 0.02$; $I^2 = 0\%$]. Overweight patients were related with reduced rates of VTE than in patients with normal BMI [RR: 0.86 (0.76, 0.97); $P = 0.02$; $I^2 = 0\%$]. In comparison with patients receiving warfarin, DOACs had significantly reduced risk of major bleeding in normal weight, overweight and obese [OR: 0.64 (0.49, 0.83); $P = 0.0007 I^2 = 90\%$]. <i>Conclusion:</i> The risk of VTE reduces with an increasing BMI, hence there could be a possible obesity paradox in patients with anticoagulation therapy. In comparison to warfarin, DOACs proved to be the safer option by having a reduced risk of bleeding across all BMI categories.

1. Introduction

Venous thromboembolism (VTE) and atrial fibrillation (AF) have a prevalence of approximately 10 million cases annually and a reported 59.7 million cases in 2019 alone, respectively [1,2]. Warfarin therapy has proven its effectiveness in previous years in the prevention of such thromboembolic events [3]. In recent years, the emergence of direct oral anticoagulants (DOACs) has not only shown further efficacy but has overcome several limitations associated with warfarin use [4]. DOAC's offer a further elaborate form of therapy due to their rapid onset of action that does not require bridging with parenteral anticoagulants, along with any dietary restrictions nor continual international

normalized ratio (INR) laboratory monitoring [5]. Further advantages of DOAC's include the provision of a large therapeutic window with low drug-drug interactions, predictable pharmacodynamics and the ease of switching patients from low molecular weight heparins (LMWH) and warfarin therapy onto DOAC drug regimens [6].

Despite the wide usage and advantages of DOAC's, there is inadequate evidence in regard to their effect across patients of varying body mass index (BMI) categories. Obesity is associated with a 6.2-fold increased risk for VTE, and is a risk factor for developing AF [7,8]. Thus many of the VTE and AF patients account for obese patients, in addition to patients with a normal BMI. Therefore, because lack of corroboration still remains in the comparison between DOAC's and

* Corresponding author. RCSI University of Medicine and Health Sciences, 123 St. Stephen's Green, Dublin 2, Ireland. *E-mail address:* talalamas.almas@gmail.com (T. Almas).

https://doi.org/10.1016/j.amsu.2022.103610

Received 1 March 2022; Received in revised form 7 April 2022; Accepted 7 April 2022 Available online 14 April 2022

2049-0801/© 2022 The Authors. Published by Elsevier Ltd on behalf of IJS Publishing Group Ltd. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).



warfarin therapy for obese patients, further investigation is required. The "obesity paradox" has been demonstrated in several studies in which DOAC's had a greater efficacy in individuals with a higher BMI in comparison to those with a lower BMI [9]. However further analysis on patients of all categories of BMI on different DOACs (apixaban, rivaroxaban, dabigatran and ximelagatran) requires in-depth investigation. Thus, this systematic review and meta-analysis aims to establish better treatment options specific to BMI categories by exploring two comparisons (I) the safety and efficacy of DOAC's in patients with AF or VTE with different BMI categories and (II) the safety and efficacy of DOAC and warfarin in patients with AF or VTE across different BMI categories.

2. Methods

This systematic review and meta-analysis was conducted in accordance with PRISMA guidelines [10]. The methods of this study adequately adhere to the AMSTAR checklist [11]. An institutional review board (IRB) approval was not required for this study as the data used is publicly available.

2.1. Search strategy

In order to retrieve all relevant articles, a literature review was conducted from inception to May 2021 on PubMed and Scopus using two formulated search strings. The two different search strings were constructed based on the two different criteria of this study, using key terms: atrial fibrillation, venous thromboembolism, deep-vein thrombosis, pulmonary embolism, DOAC, VKA, warfarin, rivaroxaban, apixaban, edoxaban and dabigatran arranged with various configurations. The first search string covered the comparison for the safety and efficacy outcomes of different DOAC's across different BMI categories, in VTE or AF patients. The second search string covered the comparison for the safety and efficacy outcomes of DOACs and warfarin across different BMI categories, in VTE or AF patients. All articles were then transferred to EndNote X7 for the removal of duplicate studies. Two reviewers (FM and LS) screened remaining articles on the basis of title and abstract before conducting a full text screening.

2.2. Study selection

Studies were included if the given criteria was fulfilled: (1) observational cohorts (retrospective or prospective) or RCTs; (2) patients with VTE and/or AF across different BMI categories (underweight (<18.5 kg/m²), normal weight (18.5–24.9 kg/m²), overweight (25.0–29.9 kg/m²), obese class I (30.0–34.9 kg/m²), obese class II (35.0–39.9 kg/m²) and obese class III (\geq 40 kg/m²)), who were \geq 18 years old and were treated with one or more specific DOAC mentioned and/or warfarin; (3) demonstrated safety (bleeding) and/or efficacy (stroke/VTE recurrence) outcomes after use of DOAC. Studies were excluded if the given was present: (1) patients with other underlying disorders/risk factors (e.g., diabetes, surgery, cancer) (2) patients with other interventions besides the use of DOAC (e.g., cardioversion, heparin, aspirin).

2.3. Data extraction

Members of the review team extracted data based on baseline characteristics and key safety and efficacy outcomes. Outcomes of interest include major bleeding events, and VTE recurrence or stroke. Major bleeding events can be defined as fatal bleeding, bleeding into a critical organ (retroperitoneal, intracranial, intraocular, intraspinal), bleeding requiring surgical revision or angiographic embolization, and bleeding with a fall in hemoglobin of 2 g/dL or documented blood transfusion of 2 or more units according to International Society on Thrombosis and Haemostasis [12]. VTE or stroke was measured based on clinical symptoms.

2.4. Statistical analysis

The analysis for the data obtained for both comparisons was done using RevMan 5.4.

Outcomes associated with DOAC therapy across patients with different BMI were pooled using a random effects model. For the dichotomous outcomes comparing each BMI (UW, OW, obese, obese I, obese II-III) with a normal BMI, the risk ratios (RR) and their 95% confidence intervals (CIs) were used. The subgroup analysis compared the different types of DOACs for a specific BMI. Outcomes as a result of DOAC or warfarin therapy in patients with different BMI were also pooled using a random effects model. For the dichotomous outcomes comparing DOAC with warfarin, the odds ratio (OR) and their 95% CIs were used. For both comparisons, to assess heterogeneity, an I2 statistic of >75% reported severe heterogeneity. The subgroup analysis compared the different BMI categories on DOAC or warfarin therapy. A p-value of <0.05 was considered significant. Forest plots visualize the pooled data for both comparisons.

3. Results

3.1. Literature search and study characteristics

The literature search consisted of two search strings. The first search string, which focused on finding articles for the safety and efficacy of different DOACs across different BMI categories in VTE and AF patients, revealed a total of 2189 studies. Following the exclusion of articles, only 12 met the inclusion criteria. These consisted of 254,908 patients in total who were on one of four DOACs -rivaroxaban, apixaban, dabigatran or ximelagatran. The studies include clinical trials, retrospective, and prospective cohort studies. The second search string focused on related articles for the safety and efficacy of DOACs vs warfarin across different BMI categories in VTE and AF patients and obtained 1561 studies. After the exclusion of several articles, six remained. They contained a total of 109,609 patients undergoing DOAC or warfarin therapy. Three of these articles were cohort studies and the remaining three were randomized clinical trials. Characteristics of each study, relevant to the metaanalysis are described in Table 3 and 4 An overview of the literature search is available in the PRISMA flow charts 1 and 2.

3.2. Results of meta-analysis

The results of the meta-analysis of the data extracted from the relevant studies are presented in detailed forest plots in Fig. 1–12.

3.2.1. Major bleeding events in patients with different BMIs on DOAC therapy (Figs. 1–5)

Major bleeding events in underweight patients were overall significantly higher than in patients with a normal weight [p = 0.02; RR: 1.89 (1.10, 3.23); I² = 0%]. However, events in overweight patients were not significantly different than in patients with a normal weight [p = 0.19; RR: 0.88 (0.73, 1.07); I² = 58%]. Bleeding in obese class I patients was also not significantly different than in patients with a normal BMI [p = 0.83; RR: 0.98 (0.83, 1.16); I² = 17%]. There was no statistical significance in the difference of bleeding events between obese class I patients and patients with a normal weight [p = 0.17; RR: 0.65 (0.35, 1.20); I² = 86%]. Lastly, there was no significant difference in major bleeding events in obese class II-III and normal BMI [p = 0.21; RR: 0.77 (0.51, 1.16); I² = 55%].

3.2.2. VTE recurrence or stroke in patients with different BMIs on DOAC therapy (Figs. 6–10)

There was no significant difference for the recurrence of VTE or stroke between underweight and normal weight patients [p = 0.32; RR: 2.12 (0.48, 9.30); I² = 85%], however a subgroup analysis revealed a significantly higher rate of VTE recurrence or stroke in the study with

	Underw	eight	Normal W	/eight		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year	M-H, Random, 95% Cl
3.1.1 Rivaroxaban								
XAPASS	15	540		4392	93.1%	1.94 [1.11, 3.38]		
Subtotal (95% CI)		540		4392	93.1%	1.94 [1.11, 3.38]		◆
Total events	15		63					
Heterogeneity: Not ap	plicable							
Test for overall effect:	Z = 2.33	$\langle \mathbf{P}=0,$	02)					
3.1.2 Mixed								
Park - 2017	1	62	9	753	6.9%	1.35 [0.17, 10.48]	2017	
Subtotal (95% CI)		62		753	6.9%	1.35 [0.17, 10.48]		
Total events	1		9					
Heterogeneity: Not ap	plicable							
Test for overall effect:	Z = 0.29	$\langle \mathbf{P}=0,$	77)					
Total (95% CI)		602		5145	100.0%	1.89 [1.10, 3.23]		◆
Total events	16		72					
Heterogeneity: Tau ² =	• 0.00; Ch	r ² = 0.1	1, df = 1 (P = 0.74	l); l ² = 07	<u> </u>		hay also a should be
Test for overall effect:		-						0.01 0.1 1 10 100'
Test for subgroup diff					Favours Underweight Favours Normal			

Fig. 1. Major bleeding events in underweight patients on different DOACs.

	Overwe	eight	Normal V	Veight		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year	M-H, Random, 95% Cl
2.2.1 Apixaban								
DOUCETTE-2015	26	165	6	32	4.5%	0.64 [0.36, 1.66]	2015	+
ARISTOTLE (Sandhu - 2016)	115	6687	72	4035	14.5%	0.96 [0.72, 1.29]	2016	
AMPLIFY	33	999	35	725	9.6X	0.68 [0.43, 1.09]	2021	
Subtotal (95% CI)		7851		4792	28.6%	0.87 [0.69, 1.10]		◆
Total events	174		113					
Heterogeneity: Tau ² = 0.00; ($Chl^2 = 1.54$	0, df = 3	2 (P = 0.4)	7); 1² = 0	×			
Test for overall effect: $Z = 1.1$	14 (P = 0.3)	26)						
2.2.2 Rivaroxaban								
DOUCETTE-2015	32	170	11	25	8.0%	0.43 [0.25, 0.74]	2015	
EINSTEIN DVT/PE	18	1603	15	1257	5.8%			
ROCKET-AF (Balla - 2017)	314	5529	179	3274	18.4%	1.04 [0.87, 1.24]	2017	+
Subtotal (95% CI)		7302		4556	32.2%	0.77 [0.43, 1.36]		◆
Total events	364		205					-
Heterogeneity: Tau ² = 0.20; ($Chl^{2} = 9.54$	0. df = 3	2 (P = 0.0)	09); l ² =	79%			
Test for overall effect: Z = 0.5			•					
2.2.3 Dabigatran								
RE-LY (Connolly - 2009)	60	372	36	234	12.0%	0.99 [0.68, 1.44]	2009	_ _
RE-DUAL	59	372	54	234	13.3%			
Subtotal (95% CI)		744	-	468	25.3%			•
Total events	119		92					-
Heterogeneity: Tau ² = 0.04; ($Chl^2 = 2.10$	0, df = :	1 (P = 0.1)	5); ř = 5	2%			
Test for overall effect: Z = 1.0								
2.2.4 Ximelagatran								
SPORTIF (Proletti - 2016)	61	164	47	164	13.6%	1.30 [0.95, 1.77]	2016	-
Subtotal (95% CI)		164		164	13.8%			◆
Total events	61		47					
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.6		10)						
Total (95% CI)		16061		9980	100.0%	0.88 [0.73, 1.07]		•
Total events	718		457					
Heterogeneity: Tau ² = 0.04; ($Chl^{2} = 18.$	87, df =	8 (P = 0.0	02); l ² =	58X			0.01 0.1 1 10 100
Test for overall effect: Z = 1.3	31 (P = 0.3)	19)	a n. 2013	100 M				Favours Overweight Favours Normal
Test for subgroup differences	: Cht ² = 5.	53, df -	= 3 (P = 0.	14), l ² =	45.7%			ravours overweight ravours norffal
	-							

Fig. 2. Major bleeding events in overweight patients on different DOACs.

mixed DOAC's (rivaroxaban, apixaban, dabigatran) therapy as compared to the study with only rivaroxaban therapy $[p = 0.01; I^2 = 84.5\%]$. VTE recurrence in overweight patients was overall significantly lower than in patients with a normal BMI $[p = 0.02; RR: 0.86 (0.76, 0.97); I^2 = 0\%]$. Obese class I and normal weight patients had no significant difference in recurrence of VTE or stroke $[p = 0.35; RR: 0.76 (0.42, 1.37); I^2 = 85\%]$. Obese class II-III patients did not have a significant difference in VTE recurrence or stroke when compared to

normal weight patients [p = 0.54; RR: 0.87 (0.57, 1.34); $I^2 = 58\%$], subgroup analysis reported a significant difference in events of VTE recurrence or stroke between studies that used apixaban, rivaroxaban and dabigatran [p = 0.01; $I^2 = 77\%$].

3.2.3. Major bleeding events with DOAC or warfarin therapy across BMI categories (Fig. 11)

Major bleeding events reported to be significantly higher in patients

	Obe	se	Normal V	Veight		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year	M-H, Random, 95% Cl
1.2.1 Apixaban								
DOUCETTE-2015	132	7134	72	4035	24.3%	1.04 [0.76, 1.38]	2015	+
ARISTOTLE (Sandhu - 2016)	6	55	6	39	2.3%		2016	
Subtotal (95% CI)		7189		4074	26.6%	1.01 [0.77, 1.33]		•
Total events	138		78					
Heterogeneity: Tau ² = 0.00; (1 (P = 0.5	0);	×			
Test for overall effect: $Z = 0.0$	07 (P = 0.9)	94)						
1.2.2 Rivaroxaban								
DOUCETTE-2015	13	59	11	25	5.9%	0.50 [0.26, 0.96]	2015	- _
ROCKET-AF (Balla - 2017)	279	5199	179	3274	43.1%	0.98 [0.82, 1.18]	2017	•
XAPASS	7	499	70	4410	4.3%	0.88 [0.41, 1.91]	2020	
Subtotal (95% CI)		5757		7709	53.2%	0.82 [0.55, 1.22]		◆
Total events	299		260					
Heterogeneity: Tau ² = 0.07; ($Cht^2 = 3.84$	4, df = :	2 (P = 0.1)	5); i ² = 4	6%			
Test for overall effect: $Z = 0.5$	97 (P = 0.3)	33)						
1.2.3 Ximelagatran								
SPORTIF (Projetti - 2016)	56	164	47	164	20.2%	1.19 [0.86, 1.64]	2016	
Subtotal (95% CI)		164		164	20.2%	1.19 [0.86, 1.64]		◆
Total events	56		47					
Heterogeneity: Not applicable								
Test for overall effect: $Z = 1.0$	07 (P = 0.2	29)						
Total (95% CI)		13110		11947	100.0%	0.98 [0.83, 1.16]		•
Total events	493		385					
Heterogeneity: Tau ² = 0.01; (Chf ² = 6.04	4, df = :	5 (P = 0.3	0); ř = 1	7%		L.	0.01 0.1 1 10 100
Test for overall effect: Z = 0.2	21 (P = 0.1)	83)					v	Favours Obese Favours Normal Weight
Test for subgroup differences	$: Cht^2 = 2.$.04, df -	= 2 (P = 0)	.36), l ² =	2.2%			ravours obese Tavours Norman Weight

Fig. 3. Major bleeding events in obese patients on different DOACs.

	Obe	ese	Normal	Weight		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year	M-H, Random, 95% CI
4.2.1 Apixaban								
AMPLIFY	1	575	5	725	6.4%	0.25 [0.03, 2.15]	2021	
COHEN-2021	152	23344	564	112024	29.6%	1.29 [1.08, 1.55]	2021	+
Subtotal (95% CI)		23919		112749	36.0%	0.82 [0.19, 3.46]		
Total events	153		569					
Heterogeneity: Tau ² = 0.7			= 1 (P =	0.14); l ²	55%			
Test for overall effect: Z =	0.27 (P	= 0.79)						
4.2.2 Rivaroxaban								
EINSTEIN DVT/PE	2	822	15	1257	11.0%	0.20 [0.05, 0.89]	2016	
Subtotal (95% CI)		822	_	1257	11.0%	0.20 [0.05, 0.89]		
Total events	2		15					
Heterogeneity: Not applica	ble							
Test for overall effect: Z =	2.12 (P	= 0.03)						
4.2.3 Dabigatran								
RE-LY (Connolly - 2009)	37	260	38	234	26.6%	0.88 [0.58, 1.33]	2009	
RE-DUAL	27	260	54	234	26.4%	0.45 [0.29, 0.69]	2020	
Subtotal (95% CI)		520		468	53.0%	0.63 [0.33, 1.21]		
Total events	64		92					
Heterogeneity: Tau ² = 0.1	8; Chf ² =	4.80, df	= 1 (P =	0.03); l ²	79%			
Test for overall effect: Z =	1.39 (P	= 0.16)						
Total (95% CI)		25261		114474	100.0%	0.65 [0.35, 1.20]		•
Total events	219		676					
Heterogeneity: Tau ² = 0.3	2; Cht ² =	27.60, 4	if = 4 (P	< 0.0001)	; i ² = 66;	ĸ		0.01 0.1 1 10 100
Test for overall effect: Z =	1.39 (P	= 0.17)						Favours Obese I Favours Normal
Test for subgroup differen	ces: Chl ²	= 2.20,	df = 2 (P	= 0.33), (² = 9.1%			ravours obeser ravours normal

Fig. 4. Major bleeding events in obese class I patients on different DOACs.

on warfarin therapy as opposed to DOAC therapy across normal weight, overweight and obese [p = 0.0007; OR: 0.64 (0.49, 0.83); I² = 90%].

90%].

4. Discussion

3.2.4. VTE recurrence or stroke with DOAC or warfarin therapy across BMI categories (Fig. 12)

There was no significant difference in the recurrence of VTE or stroke in patients using DOAC and warfarin therapy across normal weight, overweight and obese patients $[p = 0.96; OR: 1.01 (0.77, 1.31); I^2 =$

The primary findings of this meta-analysis, derived from the plots of major bleeding events and VTE recurrence/stroke across BMI classes, include an increased risk of VTE and bleeding events associated with underweight patients in contrast to normal weight, overweight and

	Obesity	11-111	Normal	Weight		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year	M-H, Random, 95% Cl
5.2.1 Apixaban								
AMPLIFY	2	362	5	725	5.6%	0.80 [0.16, 4.11]	2021	
COHEN-2021	106	19751	564	112024	37.8%	1.07 [0.87, 1.31]	2021	+
Subtotal (95% CI)		20113		112749	43.3%	1.06 [0.86, 1.30]		◆
Total events	108		569					
Heterogeneity: Tau ² = 0.0	10; Chl ² =	0.12, di	'= 1 (P =	0.73); l ²	= 0%			
Test for overall effect: Z =	0.57 (P -	0.57)						
5.2.2 Rivaroxaban								
	~							
EINSTEIN DVT/PE Subtotal (95% CI)	5	462 462	15	1257 1257	12.0% 12.0%	0.91 [0.33, 2.48] 0.91 [0.33, 2.48]	2016	
	-	402		1237	12.0%	0.91 [0.55, 2.46]		
Total events	5		15					
 Heterogeneity: Not applica Test for overall effect: Z = 		0.00						
lest for overall effect: 2 =	0.19 (* •	• 0.05)						
5.2.3 Dabigatran								
RE-LY (Connolly - 2009)	13	112	38	234	22.7%	0.71 [0.40, 1.29]	2009	
RE-DUAL	11	112	54	234	22.0%	0.43 [0.23, 0.78]	2020	_ _
Subtotal (95% CI)		224		468	44.6%	0.55 [0.33, 0.92]		◆
Total events	24		92					-
Heterogeneity: $Tau^2 = 0.0$	$4; Chl^2 =$	1.45, di	= 1 (P =	0.23); P	31×			
Test for overall effect: Z =	2.27 (P -	0.02)						
Total (95% CI)		20799		114474	100.0%	0.77 [0.51, 1.16]		•
Total events	137		676					
Heterogeneity: $Tau^2 = 0.1$			= 4 (P =	0.07); ۲	= 55X			0.01 0.1 1 10 100
Test for overall effect: Z =								Favours Obese II-III Favours Normal
Test for subgroup differer	ces: Chi ²	= 5.37,	df = 2 (P	= 0.07), I	f = 62.8	6		

Fig. 5. Major bleeding events in obese class II-III patients on different DOACs.

	Underw	eight	Normal W	/eight		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year	M–H, Random, 95% Cl
3.2.1 Rivaroxaban								
XAPASS Subtotal (95% CI)	9	542 542	70	4410 4410	51.9% 51.9%	1.05 [0.53, 2.08] 1.05 [0.53, 2.08]		*
Total events	9		70					
Heterogeneity: Not ap	olicable							
Test for overall effect:		$\langle P = 0 \rangle$	90)					
3.2.2 Mixed								
Park – 2017 Subtotal (95% CI)	6	62 62	16	753 753	48.1X 48.1%	4.55 [1.85, 11.22] 4.55 [1.85, 11.22]		
Total events	6		16					
Heterogeneity: Not ap	plicable							
Test for overall effect:	z = 3.30	$(\mathbf{P}=0)$	0010)					
Total (95% CI)		604		5163	100.0%	2.12 [0.48, 9.30]		
Total events	15		66					
Heterogeneity: Tau ² =	0.97; Ch	l ² = 6.8	0, df = 1 (P = 0.00)9); I ² = 6	35%		0.01 0.1 1 10 100
Test for overall effect:								0.01 0.1 1 10 100 Favours Underweight Favours Normal
Test for subgroup diff	ferences: (Chl² = 6	.46, df = 1	$(\mathbf{P}=0)$	01), i² =	84.5 %		ravours onderweight Favours Norman

Fig. 6. VTE recurrence/stroke in underweight patients on different DOACs.

obese patients. In the plots comparing DOACs to warfarin, analysis of the safety outcomes signifies an overall reduced risk of bleeding in oral anticoagulants, especially in normal weight patients. In general, an obesity paradox can be interpreted as our results indicate that the efficacy commensurates with the increasing BMI.

Our conclusive findings insinuate that the underweight BMI is more susceptible to high risks of VTE and bleeding when using anticoagulants, which remains consistent with prior meta-analyses [13]. Although more research needs to be done to confirm the hypothesis that being underweight is an independent risk factor for AF, it could still be interpreted by these plausible mechanisms. Firstly, low body weight is directly associated with poor systemic inflammation and endothelial function, which further gives rise to platelet aggregation and adhesion, contributing to embolism and ultimately, death [14,15]. Consequently, patients show an escalation in angiotensin 2 levels, which may cause fibrosis of the heart valve [16]. Another probable theory suggests that stripping away the favorable repercussions adipose tissue possesses causes adiponectin levels to paradoxically rise in lean humans causing the development of AF [17]. An apparent observation in underweight patients is malnourishment which could potentially cause illnesses due to a nutrient and vitamin deficiency [18]. Low body weight patients also show profound effects on heartbeat irregularities leading to significantly greater risk of coronary heart disease, which increases the possibility of AF [19]. Even though we have substantial evidence to authenticate our hypothesis, the studies involved present with questionable reliability. For example, the XAPASS study may have pre-existing bias towards the underweight group developing AF owing to the fact that the patients were older and had lower creatinine clearance levels compared to the other BMI groups. Another contributory cause may be the previously presented medical history of stroke; all these factors contribute to a

	Overwe	-	Normal \	-		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year	M-H, Random, 95% Cl
2.1.1 Apixaban								
DOUCETTE-2015	3	22	1	8	0.3%	1.09 [0.13, 9.03]	2015	
ARISTOTLE (Sandhu – 2016)	84	6702	59	4052	14.2%	0.86 [0.62, 1.20]	2016	
AMPLIFY	27	985	16	693	4.1%	1.19 [0.64, 2.19]	2021	_ -
Subtotal (95% CI)		7709		4753	18.6%	0.93 [0.70, 1.24]		•
Total events	114		76					
Heterogeneity: Tau ² = 0.00; (cht ² = 0.8	5, df = 3	2 (P = 0.6	5); i ² = 0	×			
Test for overall effect: Z = 0.5	0 (P = 0.6	\$1)						
2.1.2 Rivaroxaban								
DOUCETTE-2015	7	107	2	16	0.7%	0.52 [0.12, 2.30]	2015	
EINSTEIN DVT/PE	35	1608	28	1266	6.4%	0.98 [0.60, 1.61]		
ROCKET-AF (Balla - 2017)	226	5535	166	3289	40.4%	0.81 [0.67, 0.98]		
XAPASS	33	2161	63	4393	8.9%	1.06 [0.70, 1.62]	2020	
Subtotal (95% CI)		9411		8964	56.4%	0.86 [0.73, 1.01]		•
Total events	301		259					
Heterogeneity: $Tau^2 = 0.00$; (Test for overall effect: $Z = 1.6$			3 (P = 0.5	5);	×			
2.1.3 Dabigatran								
RE-LY (Connolly - 2009)	59	372	54	234	14.1%	0.69 [0.49, 0.96]	2009	
RE-DUAL	3	372	3	234	0.6%	0.63 [0.13, 3.09]	2020	
Subtotal (95% CI)		744		468	14.7%	0.68 [0.50, 0.95]		•
Total events	62		57					
Heterogeneity: $Tau^2 = 0.00$; (Test for overall effect: $Z = 2.2$			L (P = 0.9	1);	×			
2.1.4 Ximelagatran								
SPORTIF (Proletti – 2016) Subtotal (95% CI)	33	90 90	32	90 90	10.2% 10.2%	1.03 [0.70, 1.52] 1.03 [0.70, 1.52]	2016	★
Total events	33		32					
Heterogeneity: Not applicable Test for overall effect: $Z = 0.1$		88)						
Total (95% CI)		17954		14275	100.0%	0.86 [0.76, 0.97]		•
Total events	510		424					
Heterogeneity: Tau ² = 0.00; (7. df = 1) (P = 0.7	4); ² = 0	×			has als a she a
Test for overall effect: Z = 2.4								
Test for subgroup differences			a /a					Favours Overweight Favours Normal

Fig. 7. VTE recurrence/stroke in overweight patients on different DOACs.

	Obes	se	Normal \	Weight		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year	M-H, Random, 95% Cl
1.1.1 Apixaban								
DOUCETTE-2015	0	6	1	6	0.3%	0.33 [0.02, 7.14]	2015	
ARISTOTLE (Sandhu – 2016) Subtotal (95% CI)	66	7153 7161	59	4038 4046	21.0X 21.2%	0.63 [0.45, 0.90] 0.63 [0.44, 0.89]	2016	★
Total events	66		60					
Heterogeneity: $Tau^2 = 0.00; 6$ Test for overall effect: $Z = 2.6$			l (P = 0.6	6);	×			
1.1.2 Rivaroxaban								
DOUCETTE-2015	3	47	2	16	0.9%	0.51 [0.09, 2.79]	2015	
ROCKET-AF (Balla - 2017)	179	5206	166	3289	59.8%	0.68 [0.55, 0.84]	2017	=
XAPASS	7	497	63	4392	4.2%	0.98 [0.45, 2.13]	2020	
Subtotal (95% CI)		5750		7697	64.9%	0.69 [0.57, 0.85]		•
Total events Heterogeneity: Tau ² = 0.00; 6 Test for overall effect: Z = 3.6			231 2 (P = 0.6	3);	×			
1.1.3 Ximelagatran								
SPORTIF (Proletti – 2016) Subtotal (95% CI)	25	90 90	33	90 90	13.6% 13.8%		2016	
Total events	25		33					
Heterogeneity: Not applicable Test for overall effect: $Z = 1.2$		21)						
Total (95% CI)		13001		11833	100.0%	0.69 [0.59, 0.81]		•
Total events	260		324					
Heterogeneity: $Tau^2 = 0.00$; (Test for overall effect: $Z = 4.5$ Test for subgroup differences	9 (P < 0.0	00001)					Ċ	0.01 0.1 1 10 10 Favours Obese Favours Normal

Fig. 8. VTE recurence/stroke in obese patients on different DOACs.

	Obese I \	Weight	Normal	Weight		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M–H, Random, 95% CI
4.1.1 Apixaban							
AMPLIFY	9	568	16	693	17.6%	0.69 [0.31, 1.54]	
COHEN-2021	160	23344	655	112024	25.8%	1.32 [1.12, 1.55]	=
Subtotal (95% CI)		23912		112717	43.4%	1.08 [0.60, 1.95]	•
Total events	189		671				
Heterogeneity: Tau ² = 0.1		-	1 (P = 0	.12); i² =	58%		
Test for overall effect: Z =	0.25 (P =	0.80)					
4.1.2 Rivaroxaban							
EINSTEIN DVT/PE	10	825	28	1266	19.0%	0.55 [0.27, 1.12]	_ _
Subtotal (95% CI)		825		1266	19.0%	0.55 [0.27, 1.12]	-
Total events	10		28				-
Heterogeneity: Not applica	able						
Test for overall effect: Z =	1.64 (P =	0.10)					
4.1.3 Dabigatran							
RE-DUAL	8	260	6	221	14.5%	1.13 [0.40, 3.22]	
RE-LY (Connolly - 2009)	27	260	54	234	23.1%	0.45 [0.29, 0.69]	
Subtotal (95% CI)		520		455	37.6%	0.63 [0.26, 1.50]	-
Total events	35		60				
Heterogeneity: Tau ² = 0.2	:6; Chl ² = 2	.58, df =	1 (P = 0	.11); 🖻 =	61%		
Test for overall effect: Z =	1.04 (P =	0.30)					
Total (95% CI)		25257		114438	100.0%	0.76 [0.42, 1.37]	•
Total events	234		759				-
Heterogeneity: $Tau^2 = 0.3$		6.48, df		0.0001):	² = 85%		
Test for overall effect: Z =							0.01 0.1 1 10 100 100
Test for subgroup differen		,	= 2 (P =	0.31), P	- 13.6X		Favours Obese I Favours Normal

Fig. 9. VTE recurrence/stroke in obese class I patients on different DOACs.

	Obesity	y II-III	Normal	Weight		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	Year	M-H, Random, 95% Cl
5.1.1 Apixaban								
AMPLIFY	7	349	16	693	14.6%	0.87 [0.36, 2.09]	2021	
COHEN-2021	125	19751	655	112024	36.5X	1.08 [0.89, 1.31]	2021	+
Subtotal (95% CI)		20100		112717	51.3%	1.07 [0.89, 1.29]		♦
Total events	132		671					
Heterogeneity: Tau ² = 0.0	0; Chf ² =	0.23, di	i = 1 (P =	0.63); 12	= 0%			
Test for overall effect: Z =	0.73 (P	= 0.47)						
5.1.2 Rivaroxaban								
EINSTEIN DVT/PE	13	427	28	1266	20.7%	1.38 [0.72, 2.63]		
Subtotal (95% CI)		427		1266	20.7%	1.38 [0.72, 2.63]		◆
Total events	13		28					
Heterogeneity: Not applica								
Test for overall effect: Z =	0.97 (P	= 0.33)						
5.1.3 Dabigatran								
RE-LY (Connolly - 2009)	11	112	54	234	21.9%	0.43 [0.23, 0.78]	2009	
RE-DUAL	2	112	6	234	6.2%	0.70 [0.14, 3.40]		
Subtotal (95% CI)		224	•	468	28.1%	0.45 [0.26, 0.80]		•
Total events	13		60					•
Heterogeneity: $Tau^2 = 0.0$		0.32. di		0.57); l ²	- 0%			
Test for overall effect: Z =					•••			
Total (95% CI)		20751		114451	100.0%	0.87 [0.57, 1.34]		+
Total events	158		759					
Heterogeneity: $Tau^2 = 0.1$	2; Cht ² =	9.49, di	f = 4 (P =	0.05); 12	- 58%			0.01 0.1 1 10 100
Test for overall effect: Z =								0.01 0.1 1 10 100 Favours Obese II-III Favours Normal
Test for subgroup differen	ces: Chl ²	= 8.91,	df = 2 (P	= 0.01),	² = 77.65	4		Favours Obese II-III Favours Normal
		-						

Fig. 10. VTE recurrence/stroke in obese class II-III patients on different DOACs.

much higher risk of thromboembolism in AF patients [20]. Drug metabolism also differs from patient to patient due to varying BMIs. The reduced renal and hepatic clearance in UW patients could be a possible explanation for the increased bleeding as they result in a longer half-life of the drug producing a more dangerous impact [21,22]. Due to all of these adverse effects, a rational option would be to decrease dosages of DOACs in UW patients, however reduced doses of medication have shown to have an ineffective impact on the risks of bleeding in multivariate analysis [23].

Our investigation revealed that the associated risk of VTE recurrence/stroke was lower in overweight and obese patients on anticoagulation therapy compared to normal weight. The studies used to derive this data are divided into subgroups by specifically naming the DOACs used; dabigatran shows the most significant advocation of

	DOA	Cs	Warfa	arin		Odds Ratio		Odds Ratio
Study or Subgroup	Events		Events		Weight	M-H, Random, 95% CI	Year	M-H, Random, 95% Cl
1.1.2 Normal weight BMI	18.5-24.9							
ARISTOTLE-2016	72	4035	147	4035	11.6%	0.48 [0.36, 0.64]	2016	+
RE-DUAL-PCI	95	394	126	400	11.3%	0.69 [0.51, 0.94]	2020	-
Subtotal (95% CI)		4429		4435	22.9%	0.57 [0.40, 0.82]		•
Total events	167		273					
Heterogeneity: Tau ² = 0.04	4; Chi ² = 2.	83, df =	1 (P = 0.0	19); I ² = 6	5%			
Test for overall effect: Z = 3	3.07 (P = 0	.002)						
1.1.3 overweight BMI 25-2	29.9							
ARISTOTLE-2016	115	6687	156	6687	12.1%	0.73 [0.57, 0.93]	2016	+
RE-DUAL-PCI	128	677	203	770	12.0%	0.65 [0.51, 0.84]		-
Subtotal (95% CI)		7364		7457	24.1%	0.69 [0.58, 0.82]		♦
Total events	243		359					
Heterogeneity: Tau ² = 0.00); Chi ² = 0.	44, df =	1 (P = 0.5	i1); l ² = 0	96			
Test for overall effect: $Z = -$	4.14 (P < 0	.0001)						
1.1.4 obese BMI 30-39								
ARISTOTLE-2016	132	7134	153	7134	12.2%	0.86 [0.68, 1.09]	2016	-
Charlene Kalani 2019	2	90	3	90	1.8%	0.66 [0.11, 4.04]		
ISAAC J.PERALES-2019	7	84	2	92	2.2%	4.09 [0.83, 20.28]	2019	
Kazuhiko Kido 2020	103	4384	139	4281	11.9%	0.72 [0.55, 0.93]	2020	-
RE-DUAL-PCI	82	667	129	603	11.4%	0.52 [0.38, 0.70]	2020	-
OLIVIA S. COSTA-2020	1329	35613	3151	35613	13.4%	0.40 [0.37, 0.43]	2020	•
Subtotal (95% CI)		47972		47813	52.9%	0.66 [0.44, 1.00]		•
Total events	1655		3577					
Heterogeneity: Tau ² = 0.19			= 5 (P < 0	.00001);	I ² = 92%			
Test for overall effect: Z = 1	1.96 (P = 0	1.05)						
Total (95% CI)		59765		59705	100.0%	0.64 [0.49, 0.83]		•
Total events	2065		4209					
Heterogeneity: Tau ² = 0.13	3; Chi² = 91	1.79, df=	= 9 (P < 0	.00001);	I² = 90%		_	.01 0.1 1 10 100
Test for overall effect: Z = 3	•						0	Favours DOACs Favours WARFARIN
Test for subgroup differen	ces: Chi²:	= 0.87, d	f= 2 (P =	0.65), I ^z	= 0%			



reduced VTE in overweight patients compared to normal weight, whilst rivaroxaban takes the lead in reducing occurrence of VTE in obese patients. Even though a staggering significance is implied for the risks of developing VTE, the small number of studies bring up arguable validity. Moreover, our initial hypothesis of reduced risk of VTE in obese patients is weakened once the insignificant effects of BMI groups on bleeding and risks of adverse effects (incidence of VTE and bleeding) in the divided obese classes (obese classes I, II and III) are taken into consideration. Overall, an anomaly may be observed in obese patients.

The obesity paradox is a commonly seen trend in individual studies with many possible clarifications stating the underlying causes for this contradiction. Firstly, obese patients tend to present with a higher number of comorbidities which increases their requirement for intervention and drug therapies. The medications for these pre-existing diseases could induce a beneficial effect on the cardiovascular system which would decrease the adverse effects triggered by the anticoagulants [24,25]. Secondly, obesity tends to be correlated with a better metabolic reserve which leads to an increased endurance against the increased metabolic stress that accompanies diseases [26]. Moreover, the fore-mentioned critically high levels of renin-angiotensin II system in underweight patients are reversed in obese patients, hence contributing to safer outcomes [27]. Another defense mechanism for AF patients may be the decreased levels of natriuretic peptide in obese patients which are common promoters of stroke and mortality [28]. Coupled with this mechanism, is the increased production of tumor necrosis factor- α receptors in adipose tissue, which could aid in diffusion of inflammation and arrhythmogenic substrates [29]. Finally, heightened levels of lipoproteins generated by adipose tissue may tie up with the circulating lipopolysaccharides produced during inflammation, cleansing and inhibiting them from stimulating a procoagulant state [30]. Other reasons may include the common fault of conferred selection bias or unmeasured potential risk factors.

Several studies have proposed modifiable factors that exacerbate the adverse effects of obesity paradox in AF patients. For instance, a prior study by Wu et al. [31] reflects an evident obesity paradox in elderly compared to younger patients, which signifies a greater shift with increasing age. The effect of age on the paradox for coronary heart diseases, especially AF is still deemed arguable, hence further investigation is required to confirm this phenomenon. In addition, studies have also shown that patients with comparatively good well-maintained cardiorespiratory fitness suggest advantageous prognosis amongst the coronary heart disease patients. The previous findings demonstrate that cardiorespiratory fitness may also mitigate the obesity paradox in AF considering the observations on coronary heart disease and HF [32,33]. Therefore, indicating that high levels of physical activity is directly associated with decreased risk of AF for all BMI classifications.

Our meta-analysis also investigated the outcomes of warfarin and DOACs in relation to different BMI categories, determining DOACs as the

	DOACs		Warfarin		Odds Ratio			Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year	M-H, Random, 95% CI
2.1.2 Normal weight								
RE-LY-2009	269	9131	183	9131	10.4%	1.48 [1.23, 1.79]	2009	+
ARISTOTLE-2016	59	4052	83	4052	9.3%	0.71 [0.50, 0.99]	2016	
RE-DUAL-PCI	61	387	45	370	8.6%	1.35 [0.89, 2.05]	2020	<u>t</u>
Subtotal (95% CI)		13570		13553	28.2%	1.13 [0.70, 1.82]		•
Total events	389		311					
Heterogeneity: Tau ² = 0.15; Chi ² = 14.30, df = 2 (P = 0.0008); l ² = 86%								
Test for overall effect: Z = 0.51 (P = 0.61)								
2.1.3 Overweight								
RE-LY-2009	208	8962	120	8962	10.1%	1.75 [1.40, 2.20]	2009	+
ARISTOTLE-2016	84	6702	90	6702	9.6%	0.93 [0.69, 1.26]	2016	+
RE-DUAL-PCI	91	617	117	770	9.6%	0.97 [0.72, 1.30]	2020	
Subtotal (95% CI)		16281		16434	29.3%	1.17 [0.76, 1.81]		•
Total events	383		327					
Heterogeneity: Tau ² = 0.13; Chi ² = 15.07, df = 2 (P = 0.0005); I ² = 87%								
Test for overall effect: Z = 0	1.73 (P = 0).47)						
2.1.4 Obese								
ARISTOTLE-2016	66	7159	86	7159	9.4%	0.77 [0.55, 1.06]	2016	
ISAAC J.PERALES-2019	2	84	4	92	1.9%	0.54 [0.10, 3.01]	2019	
Charlene Kalani 2019	3	90	2	90	1.8%	1.52 [0.25, 9.30]	2019	
Kazuhiko Kido 2020	65	4421	75	4311	9.3%	0.84 [0.60, 1.18]	2020	
RE-DUAL-PCI	87	667	68	613	9.3%	1.20 [0.86, 1.69]	2020	+
OLIVIA S. COSTA-2020	650	35613	987	35613	10.8%	0.65 [0.59, 0.72]	2020	•
Subtotal (95% CI)		48034		47878	42.4%	0.82 [0.64, 1.06]		•
Total events	873		1222					
Heterogeneity: Tau ² = 0.05; Chi ² = 14.01, df = 5 (P = 0.02); I ² = 64%								
Test for overall effect: Z = 1.54 (P = 0.12)								
Total (95% CI)		77885		77865	100.0%	1.01 [0.77, 1.31]		•
Total events	1645		1860					
Heterogeneity: Tau ² = 0.16; Chi ² = 109.79, df = 11 (P < 0.00001); l ² = 90% 0.01 0.1 1 10 100								
Test for overall effect: Z = 0.05 (P = 0.96) 0.01 0.1 1 10 100 Favours DOACs Favours WARFARIN								
Test for subgroup differences: Chi ² = 2.72, df = 2 (P = 0.26), l ² = 26.5%								

Fig. 12. VTE recurrence or stroke in DOAC or warfarin therapy.

superior treatment. We defined a BMI of 18.5–24.9 kg/m² as normal weight and showed that DOACs had significantly more beneficial safety outcomes in normal weight AF patients. On the contrary, obese and overweight patients favored neither, DOACs or warfarin, showing no modifications in their bleeding related outcomes. Overall, the total effect of oral anticoagulants across all BMIs resulted in safer outcomes with reduced risk of bleeding; however, they were non-inferior to warfarin in terms of efficacy. More investigation should be done debating whether warfarin or NVKAs are the better choice for high risk VTE patients. According to the linked studies, DOACs remain to be the preferable choice regardless, due to their rapid onset of action, standard dosages without the need of titration, lack of requirement of routine check-ups, and limited interactions with food and associated drugs [34-57].

4.1. Limitations

Many limitations were acknowledged in our study, consequently further studies should take into account these restrictions when collecting data. Primarily, the association between BMI and AF and VTE outcomes may have been modified by several factors involving age, sex, exercise, and cardiorespiratory fitness. Secondly, BMI is not a true measurement of body adiposity hence, taking into consideration the obesity paradox in patients with HF and coronary heart disease, the BMI might not have evaluated the body fat and other body compositions accurately. In the plots involving warfarin, comparison to individual DOACs could not be performed due to limited data available which could have further altered the overall results. Additionally, the safety outcome, all-cause mortality was not included in this study; thus, the connection between BMI and death in patients remains dubious. Secondly, substantial heterogeneity occurred amongst the subgroups (Rivaroxaban trial patients had higher average CHA2DS2-VASc score and mechanisms of Dabigatran may differ in contrast to other DOACs) resulting in inconclusive insignificant results. This warrants future trials to specify the data according to the type of data as well, so the safety and efficacy of the individual DOAC's can be evaluated and assessed under variety of clinical settings. The data collected for the meta-analysis did not provide measurements of activated factor X levels, thus it is not evaluated by the study and could possibly affect the outcomes. The study does not evaluate the different dosages given to different groups of BMI. Furthermore, our results are regarded as hypothesis generating as they are based on post hoc analysis such as RCTs and observational studies. Finally, we were unable to assess the effect of preceding comorbidities (cancer or chronic renal disease) or pre-diagnosed medications (cardiac associated or anti diabetic) on AF patients due to the lack of extensive statistics

Annals of Medicine and Surgery 77 (2022) 103610

5. Conclusion

In conclusion, our study demonstrates that a reduced risk of VTE is associated with an increasing BMI. There could be a possible obesity/ lean paradox in AF patients with anticoagulation therapy but follow-up studies should ensure validation before prescribing medication. Finally, the safety outcome, across diverse BMI, of DOACs proved to be more favorable than warfarin in normal weight, overweight, and obese patients.

Ethical approval

N/A.

Sources of funding

None to declare.

Author contributions

Talal Almas - Conceptualization and Designing Study.

Faeez Muhammad – Into and Methods (Manuscript writing), Data Collection, Baseline Characteristics, Forest Plots (DOAC vs Warfarin)

Laiba Siddiqui – Intro and Methods (Manuscript Writing), Data Collection.

Batool Shafi – Forest Plots (DOAC for different BMIs), Data Collection.

Rabbia Gul – Manuscript writing (Abstract, Discussion, Limitations, Conclusion), Data Collection.

Rafiya Altaf - Manuscript writing (Abstract, Discussion, Limitations, Conclusion), Data Collection.

Zaeem Abbasi – Forest Plots (DOAC vs Warfarin), Data Collection. Ghulam Mustafa - Forest Plots (DOAC vs Warfarin), Data Collection. Arham Iqbal - Forest Plots (DOAC vs Warfarin), Data Collection. Amatul Rehman Durdana – Manuscript editing, Data Collection. Maham Dilawar - Forest Plots (DOAC for different BMIs), Data

Collection.

Adeena Musheer – Manuscript editing, formatting. Kaneez Fatima - Conceptualization and Designing Study.

Registration of research studies

1. Name of the registry:

2. Unique Identifying number or registration ID:

3. Hyperlink to your specific registration (must be publicly accessible and will be checked):

Guarantor

Batool Shafi - batoolshafi@gmail.com.mailto:batoolshafi@gmail.com

Consent

N/A.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Declaration of competing interest

None to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amsu.2022.103610.

References

- World Thrombus Day, World Thrombus Day. https://www.worldthrombosisday. org/issue/vte/#footnote1, 2021.
- [2] J. Kornej, E.J. Benjamin, J.W. Magnani, Atrial fibrillation: global burdens and global opportunities, Heart (2021 Jan 28), https://doi.org/10.1136/heartjnl-2020-318480 heartjnl-2020-318480, Epub ahead of print. PMID: 33509978.
- [3] A.I. Franco Moreno, R.M. Martín Díaz, M.J. García Navarro, Direct oral anticoagulants: an update, Med. Clin. 151 (5) (2018 Sep 14) 198–206, https://doi. org/10.1016/j.medcli.2017.11.042. English, Spanish, Epub 2017 Dec 30. PMID: 29295790.
- [4] A.J. Camm, G.Y. Lip, R. De Caterina, et al., ESC Committee for Practice Guidelines (CPG). 2012 focused update of the ESC guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation. developed with the special contribution of the European heart Rhythm Association, Eur. Heart J. 33 (21) (2012 Nov) 2719–2747, https://doi.org/ 10.1093/eurheartj/ehs253. Epub 2012 Aug 24. Erratum in: Eur Heart J. 2013 Mar; 34(10):790. Erratum in: Eur Heart J. 2013 Sep;34(36):2850-2747. PMID: 22922413.
- [5] M.N.D. Di Minno, A. Russolillo, Di Minno, et al., Direct anticoagulant drugs to overcome limitations of vitamin K antagonists, Criti. Appraisal. Data. Artial. Fibrillation. Patient. Expert. Opinion. Emerging. Drug. 18 (1) (2013) 9–23, https:// doi.org/10.1517/14728214.2013.777427.
- [6] Y.H. Mekaj, A.Y. Mekaj, S.B. Duci, et al., New oral anticoagulants: their advantages and disadvantages compared with vitamin K antagonists in the prevention and treatment of patients with thromboembolic events, Therapeut. Clin. Risk Manag. 11 (2015 Jun 24) 967–977, https://doi.org/10.2147/TCRM.S84210. PMID: 26150723; PMCID: PMC4485791.
- [7] C. Hotoleanu, Association between obesity and venous thromboembolism, Med. Pharm. Rep. 93 (2) (2020 Apr) 162–168, https://doi.org/10.15386/mpr-1372. Epub 2020 Apr 22. PMID: 32478322; PMCID: PMC7243888.
- [8] V. Vyas, P. Lambiase, Obesity and atrial fibrillation: Epidemiology, Pathophysiology and Novel therapeutic opportunities, Arrhythmia Electrophysiol. Rev. 8 (1) (2019 Mar) 28–36, https://doi.org/10.15420/aer.2018.76.2. PMID: 30918664; PMCID: PMC6434511.
- [9] Y. Zhou, J. Ma, W. Zhu, Efficacy and safety of direct oral anticoagulants versus warfarin in patients with atrial fibrillation across BMI categories: a systematic review and meta-analysis, Am. J. Cardiovasc. Drugs 20 (1) (2020 Feb) 51–60, https://doi.org/10.1007/s40256-019-00362-4. PMID: 31342343.
- [10] M.J. Page, J.E. McKenzie, P.M. Bossuyt, I. Boutron, T.C. Hoffmann, C.D. Mulrow, et al., The PRISMA 2020 statement: an updated guideline for reporting systematic reviews, Int. J. Surg. 88 (2021) 105906.
- [11] B.J. Shea, B.C. Reeves, G. Wells, M. Thuku, C. Hamel, J. Moran, D. Moher, P. Tugwell, V. Welch, E. Kristjansson, D.A. Henry, Amstar 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both, BMJ 358 (2017 Sep 21) j4008.
- [12] R.D. Lopes, J.H. Alexander, S.M. Al-Khatib, et al., ARISTOTLE Investigators. Apixaban for reduction in stroke and other ThromboemboLic events in atrial fibrillation (ARISTOTLE) trial: design and rationale, Am. Heart J. 159 (3) (2010) 331–339.
- [13] C.B. Weir, A. Jan, BMI classification Percentile and cut off Points. 2021 may 9 [Internet], in: StatPearls, StatPearls Publishing, Treasure Island (FL, 2021 Jan., PMID: 31082114.
- [14] J.P. Higgins, D.G. Altman, P.C. Gøtzsche, et al., Cochrane bias methods group; cochrane statistical methods group. The cochrane collaboration's tool for assessing risk of bias in randomised trials, BMJ 343 (2011 Oct 18) d5928, https://doi.org/ 10.1136/bmj.d5928. PMID: 22008217; PMCID: PMC3196245.
- [15] J.P.T. Higgins, S.G. Thompson, J.J. Deeks, et al., Measuring inconsistency in metaanalyses, BMJ 327 (7414) (2003) 557–560, https://doi.org/10.1136/ bmj.327.7414.557.
- [16] W. Zhu, R. Wan, F. Liu, et al., Relation of body mass index with adverse outcomes among patients with atrial fibrillation: a meta-analysis and systematic review, J. Am. Heart Assoc. 5 (9) (2016 Sep 9), e004006, https://doi.org/10.1161/ JAHA.116.004006. PMID: 27613773; PMCID: PMC5079045.
- [17] Y. Higashi, S. Sasaki, K. Nakagawa, et al., Low body mass index is a risk factor for impaired endothelium-dependent vasodilation in humans: role of nitric oxide and oxidative stress, J. Am. Coll. Cardiol. 42 (2) (2003 Jul 16) 256–263, https://doi. org/10.1016/s0735-1097(03)00630-2. PMID: 12875761.
- [18] K. Nakajima, H. Yamaoka, K. Morita, et al., Elderly people with low body weight may have subtle low-grade inflammation, Obesity 17 (4) (2009 Apr) 803–808, https://doi.org/10.1038/oby.2008.596. Epub 2009 Jan 8. PMID: 19131938.
- [19] G. Novo, D. Guttilla, G. Fazio, et al., The role of the renin-angiotensin system in atrial fibrillation and the therapeutic effects of ACE-Is and ARBS, Br. J. Clin. Pharmacol. 66 (3) (2008 Sep) 345–351, https://doi.org/10.1111/j.1365-2125.2008.03234.x. PMID: 18782141; PMCID: PMC2526238.
- [20] F. Macheret, T.M. Bartz, L. Djousse, et al., Higher circulating adiponectin levels are associated with increased risk of atrial fibrillation in older adults, Heart 101 (17) (2015 Sep) 1368–1374, https://doi.org/10.1136/heartjnl-2014-307015. Epub 2015 Apr 8. PMID: 25855796; PMCID: PMC5161822.

- [21] D.W. Park, Y.H. Kim, S.C. Yun, et al., J. Association of body mass index with major cardiovascular events and with mortality after percutaneous coronary intervention, Circ. Cardiovasc. Interv. 6 (2) (2013 Apr) 146–153, https://doi.org/ 10.1161/CIRCINTERVENTIONS.112.000062. Epub 2013 Mar 26. PMID: 23532553.
- [22] D. Park, J.H. Lee, S. Han, Underweight: another risk factor for cardiovascular disease?: a cross-sectional 2013 Behavioral Risk Factor Surveillance System (BRFSS) study of 491,773 individuals in the USA, Medicine (Baltim.) 96 (48) (2017 Dec), e8769, https://doi.org/10.1097/MD.000000000008769. PMID: 29310352; PMCID: PMC5728753.
- [23] M.J. Brill, J. Diepstraten, A. van Rongen, et al., Impact of obesity on drug metabolism and elimination in adults and children, Clin. Pharmacokinet. 51 (2012) 277–304.
- [24] R. Jain, S.M. Chung, L. Jain, et al., Implications of obesity for drug therapy: limitations and challenges, Clin. Pharmacol. Ther. 90 (2011) 77–89.
- [25] Park, C.S., Choi, E.-K., et al. Increased risk of major bleeding in underweight patients with atrial fibrillation who were prescribed non-vitamin K antagonist oral anticoagulants. Heart Rhythm 14, 501–507. https://doi.org/10.1016/j.hrthm.20 16.12.036.
- [26] Y. Murakawa, T. Ikeda, S. Ogawa, et al., Impact of body mass index on real-world outcomes of rivaroxaban treatment in Japanese patients with non-valvular atrial fibrillation, Heart Ves. 35 (8) (2020 Aug) 1125–1134, https://doi.org/10.1007/ s00380-020-01587-z. Epub 2020 Apr 6. PMID: 32253531; PMCID: PMC7332477.
- [27] R. Nieuwlaat, M.H. Prins, J.Y. Le Heuzey, et al., Prognosis, disease progression, and treatment of atrial fibrillation patients during 1 year: follow-up of the Euro Heart Survey on atrial fibrillation, Eur. Heart J. 29 (9) (2008 May) 1181–1189, https:// doi.org/10.1093/eurheartj/ehn139. Epub 2008 Apr 7. PMID: 18397874.
- [28] T.B. Horwich, G.C. Fonarow, M.A. Hamilton, et al., The relationship between obesity and mortality in patients with heart failure, J. Am. Coll. Cardiol. 38 (3) (2001 Sep) 789–795, https://doi.org/10.1016/s0735-1097(01)01448-6. PMID: 11527635.
- [29] Z.J. Wang, Y.J. Zhou, B.Z. Galper, et al., Association of body mass index with mortality and cardiovascular events for patients with coronary artery disease: a systematic review and meta-analysis, Heart 101 (20) (2015 Oct) 1631–1638, https://doi.org/10.1136/heartjnl-2014-307119. Epub 2015 May 29. PMID: 26025084.
- [30] M.A. Weber, J.M. Neutel, D.H. Smith, Contrasting clinical properties and exercise responses in obese and lean hypertensive patients, J. Am. Coll. Cardiol. 37 (1) (2001 Jan) 169–174, https://doi.org/10.1016/s0735-1097(00)01103-7. PMID: 11153733.
- [31] Z. Hijazi, L. Wallentin, A. Siegbahn, et al., N-terminal pro-B-type natriuretic peptide for risk assessment in patients with atrial fibrillation: insights from the ARISTOTLE Trial (Apixaban for the Prevention of Stroke in Subjects with Atrial Fibrillation), J. Am. Coll. Cardiol. 61 (22) (2013 Jun 4) 2274–2284, https://doi. org/10.1016/j.jacc.2012.11.082. Epub 2013 Apr 3. PMID: 23563134.
- [32] S.H. Lee, Y.C. Chen, Y.J. Chen, et al., Tumor necrosis factor-alpha alters calcium handling and increases arrhythmogenesis of pulmonary vein cardiomyocytes, Life Sci. 80 (19) (2007 Apr 17) 1806–1815, https://doi.org/10.1016/j.lfs.2007.02.029. Epub 2007 Mar 1. PMID: 17383682.
- M. Rauchhaus, A.J. Coats, S.D. Anker, The endotoxin-lipoprotein hypothesis, Lancet 356 (9233) (2000 Sep 9) 930–933, https://doi.org/10.1016/S0140-6736 (00)02690-8. PMID: 11036910.
- [34] S. Wu, Y. Yang, J. Zhu, et al., Impact of age on the association between body mass index and all-cause mortality in patients with atrial fibrillation, J. Nutr. Health Aging 21 (10) (2017) 1125–1132, https://doi.org/10.1007/s12603-016-0863-2.
- [35] W. Zhu, R. Wan, F. Liu, et al., Relation of body mass index with adverse outcomes among patients with atrial fibrillation: a meta-analysis and systematic review, J. Am. Heart Assoc. 5 (9) (2016), e4006, https://doi.org/10.1161/ JAHA.116.004006.
- [36] A. Elagizi, S. Kachur, C.J. Lavie, et al., An Overview and update on obesity and the obe- sity paradox in cardiovascular diseases, Prog. Cardiovasc. Dis. 61 (2) (2018) 142–150, https://doi.org/10.2147/VHRM.S168946.
- [37] A.H. Malik, S. Yandrapalli, W.S. Aronow, et al., Meta-analysis of direct-acting oral anticoagulants compared with warfarin in patients >75 years of age, Am. J. Cardiol. 123 (2019) 2051–2057, https://doi.org/10.1016/j.amjcard.2019.02.060.
- [38] A.H. Malik, S. Yandrapalli, W.S. Aronow, et al., Oral anticoagulants in atrial fibrillation with valvular heart disease and bioprosthetic heart valves, Heart 105 (2019) 1432–1436, https://doi.org/10.1136/heartjnl-2019-314767.
- [39] C.S. Park, E.-K. Choi, H.M. Kim, et al., Increased risk of major bleeding in underweight patients with atrial fibrillation who were prescribed non-vitamin K antagonist oral anticoagulants, Heart Rhythm 14 (2017) 501–507, https://doi.org/ 10.1016/j.hrthm.2016.12.036.

- [40] Y. Murakawa, T. Ikeda, S. Ogawa, et al., Impact of body mass index on real-world outcomes of rivaroxaban treatment in Japanese patients with non-valvular atrial fibrillation, Heart Ves. 35 (2020) 1125–1134, https://doi.org/10.1007/s00380-020-01587-z.
- [41] G. Boriani, C.T. Ruff, J.F. Kuder, et al., Relationship between body mass index and outcomes in patients with atrial fibrillation treated with edoxaban or warfarin in the ENGAGE AF-TIMI 48 trial, Eur. Heart J. 40 (2019) 1541–1550, https://doi.org/ 10.1093/eurheartj/ehy861.
- [42] R.K. Sandhu, J. Ezekowitz, U. Andersson, et al., The 'obesity paradox' in atrial fibrillation: observations from the ARISTOTLE (apixaban for reduction in stroke and other thromboembolic events in atrial fibrillation) trial, Eur. Heart J. 37 (2016) 2869–2878, https://doi.org/10.1093/eurheartj/ehw124.
- [43] S.J. Connolly, M.D. Ezekowitz, S. Yusuf, et al., Dabigatran versus warfarin in patients with atrial fibrillation, N. Engl. J. Med. 361 (2009) 1139–1151, https:// doi.org/10.1056/nejmoa0905561.
- [44] R.D. Caterina, A. Procopio, J.-L.L. Sendon, et al., Comparison of dabigatran Plus a P2Y12 inhibitor with warfarin-based Triple therapy across body mass index in RE-DUAL PCI, Am. J. Med. 133 (2020) 1302–1312, https://doi.org/10.1016/j. amjmed.2020.03.045.
- [45] S.R. Balla, D.D. Cyr, Y. Lokhnygina, et al., Relation of risk of stroke in patients with atrial fibrillation to body mass index (from patients treated with rivaroxaban and warfarin in the rivaroxaban once Daily oral direct factor xa inhibition compared with vitamin K Antagonism for prevention of stroke and embolism trial in atrial fibrillation trial), Am. J. Cardiol. 119 (2017) 1989–1996, https://doi.org/10.1016/ j.amjcard.2017.03.028.
- [46] M.C. Vedovati, A. Riera-Mestre, M.H. Prins, et al., Treatment of venous thromboembolism with rivaroxaban in relation to body weight, Thromb. Haemostasis 116 (2016) 739–746, https://doi.org/10.1160/TH16-02-0087.
- [47] A. Cohen, J. Sah, T. Lee, et al., Effectiveness and safety of apixaban vs. Warfarin in venous thromboembolism patients with obesity and morbid obesity, J. Clin. Med. 10 (2021) 200, https://doi.org/10.3390/jcm10020200.
- [48] A.T. Cohen, S. Pan, W. Byon, et al., Efficacy, safety, and Exposure of apixaban in patients with high body weight or obesity and venous thromboembolism: insights from AMPLIFY, Adv. Ther. 38 (2021) 3003–3018, https://doi.org/10.1007/ s12325-021-01716-8.
- [49] M. Proietti, D.A. Lane, G.Y. Lip, Relation of nonvalvular atrial fibrillation to body mass index (from the SPORTIF trials), Am. J. Cardiol. 118 (2016) 72–78, https:// doi.org/10.1016/j.amjcard.2016.04.013.
- [50] K. Doucette, H. Latif, A. Vakiti, et al., Efficacy and safety of direct-acting oral anticoagulants (DOACs) in the overweight and obese, Adv. Hematol. 2020 (2020) 1–7, https://doi.org/10.1155/2020/3890706.
- [51] S.J. Connolly, M.D. Ezekowitz, S. Yusuf, et al., RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation, N. Engl. J. Med. 361 (12) (2009 Sep 17) 1139–1151, https://doi.org/10.1056/ NEJMoa0905561. Epub 2009 Aug 30. Erratum in: N Engl J Med. 2010 Nov 4;363 (19):1877. PMID: 19717844.
- [52] Roopinder K. Sandhu, Justin Ezekowitz, Ulrika Andersson, et al., The 'obesity paradox' in atrial fibrillation: observations from the ARISTOTLE (apixaban for reduction in stroke and other thromboembolic events in atrial fibrillation) trial, Eur. Heart J. 37 (Issue 38) (7 October 2016) 2869–2878, https://doi.org/10.1093/ eurhearti/ehw124.
- [53] R. De Caterina, A. Procopio, J.L. Lopez Sendon, et al., Comparison of dabigatran Plus a P2Y12 inhibitor with warfarin-based Triple therapy across body mass index in RE-DUAL PCI, Am. J. Med. 133 (11) (2020 Nov) 1302–1312, https://doi.org/ 10.1016/j.amjmed.2020.03.045. Epub 2020 May 7. PMID: 32389658.
- [54] I.J. Perales, K. San Agustin, J. DeAngelo, et al., Rivaroxaban versus warfarin for stroke prevention and venous thromboembolism treatment in Extreme obesity and high body weight, Ann. Pharmacother. 54 (4) (2020 Apr) 344–350, https://doi. org/10.1177/1060028019886092. Epub 2019 Oct 31. PMID: 31672028.
- [55] O.S. Costa, J. Beyer-Westendorf, V. Ashton, D. Milentijevic, et al., Effectiveness and safety of rivaroxaban versus warfarin in obese nonvalvular atrial fibrillation patients: analysis of electronic health record data, Curr. Med. Res. Opin. 36 (7) (2020 Jul) 1081–1088, https://doi.org/10.1080/03007995.2020.1762554. Epub 2020 May 13. PMID: 32347755.
- [56] C. Kalani, E. Awudi, T. Alexander, et al., Evaluation of the efficacy of direct oral anticoagulants (DOACs) in comparison to warfarin in morbidly obese patients, Hosp. Pract. 47 (4) (2019 Oct) 181–185, https://doi.org/10.1080/ 21548331.2019.1674586. Epub 2019 Nov 5. PMID: 31580732.
- [57] K. Kido, M. Shimizu, T. Shiga, et al., Meta-analysis comparing direct oral anticoagulants versus warfarin in morbidly obese patients with atrial fibrillation, Am. J. Cardiol. 126 (2020 Jul 1) 23–28, https://doi.org/10.1016/j. amjcard.2020.03.048. Epub 2020 Apr 8. PMID: 32345473.