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ORIGINAL ARTICLE

Influence of body mass index on clinical outcomes in venous thromboembolism: Insights from GARFIELD-VTE

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Abstract

Background: There is limited information on the influence of body mass index (BMI) on clinical outcomes in patients with venous thromboembolism (VTE).

Objectives: Investigate the influence of BMI on baseline characteristics, treatment patterns, and 24-month outcomes in VTE patients.

Methods: GARFIELD-VTE is a prospective, non-interventional study of 10 869 patients with objectively confirmed VTE. Patients were grouped according to BMI:

A complete list of investigators is given in the Supplemental material.

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<18.5 (underweight; *n* = 214); 18.5–24.9 (normal; *n* = 2866); 25.0–29.9 (overweight; *n* = 3326); ≥30 (obese; *n* = 3073).

Results: Compared with patients with a normal BMI, obese patients were more frequently Caucasian (77.4% vs. 57.9%), treated in the outpatient setting (30.4% vs. 23.1%), and had previous VTE (17.5% vs. 11.7%). Active cancer was associated with lower BMI (underweight: 30.4%, normal: 13.5%, overweight: 9.4%, obese: 7.0%). At baseline, overweight and obese patients less often received parenteral therapy alone (16.7% and 14.4%) compared with those with an underweight or normal BMI (30.8% and 21.6%). Obese patients more commonly remained on anticoagulants for ≥2-years compared to those with a normal BMI (52.3% vs. 37.7%). After 24-months, the risk of all-cause mortality was lower in overweight and obese patients than in those with normal BMI (adjusted hazard ratio [95% CI]; 0.75 [0.63–0.89] and 0.59 [0.49–0.72], respectively). Underweight patients more often experienced major bleeding (2.45 [1.41–4.26]) and all-cause mortality (1.90 [1.43–2.53]) than patients with a normal BMI. Recurrent VTE was comparable among groups.

Conclusion: Underweight VTE patients have the highest risk of mortality and major bleeding. The risk of mortality in obese VTE patients is lower than that in VTE patients with a normal BMI.

KEYWORDS
anticoagulation, body mass index, obesity, pulmonary embolism, venous thromboembolism

1 | INTRODUCTION

Venous thromboembolism (VTE), encompassing both deep vein thrombosis (DVT) and pulmonary embolism (PE), is the third most common cause of cardiovascular death worldwide.[1,2] VTE is associated with a number of important risk factors, including prior history of VTE, older age, and obesity.[3] Indeed, a linear relationship between body mass index and the risk of VTE risk has been reported.[4,5] Obesity, particularly obesity class II [BMI 35–39.9] and III [BMI ≥40], has been established as an independent and moderate risk factor for both initial and recurrent VTE.[6-10] Furthermore, obesity may interact with other risk factors to increase the risk of VTE.[11,12]

The influence of BMI on clinical outcomes in patients with VTE is poorly understood. Some studies have revealed a counterintuitive "obesity paradox" whereby the mortality rate is lower in obese patients than in those with a normal BMI.[13,14] Additionally, obesity has been identified as a minor persistent risk factor for recurrent VTE. However, data regarding the impact of different BMI categories on outcomes in patients with VTE are limited.

Anticoagulants are the mainstay of VTE treatment. Although direct oral anticoagulants (DOACs) are prescribed more often than vitamin K antagonists (VKAs), the optimal anticoagulant for those with a high or low BMI has not been well established. Indeed, the International Society on Thrombosis and Hemostasis (ISTH) advises caution when using DOACs for morbidly obese patients due to the limited efficacy and safety data currently available.[15,16]

The Global Anticoagulant Registry in the FIELD – venous thromboembolism (GARFIELD-VTE) is a non-interventional, global, prospective registry designed to observe therapeutic strategies and clinical outcomes in VTE patients worldwide. In this study, baseline characteristics, anticoagulation patterns, and 24-month outcomes (all-cause mortality, recurrent VTE, and major bleeding) are compared among patients within four BMI categories as defined by the World Health Organization (underweight, normal, overweight, and obese). An additional analysis subcategorizes obese patients into obesity class I, class II, and class III.

ESSENTIALS

- We investigated the effect of BMI on treatment patterns and 2-year outcomes in VTE patients
- Discontinuation of therapy was higher in patients with normal BMI compared to obese patients
- Underweight patients had the highest risk of mortality and major bleeding
- Obese VTE patients had a lower mortality risk compared to VTE patients with normal BMI

2 | METHODS

2.1 | Study design and participants

The GARFIELD-VTE registry (ClinicalTrials.gov identifier: NCT02155491) design has been previously published.[17] The registry enrolled 10 685 VTE patients ≥18 years of age from 415 sites

between May 2014 and January 2017 across 28 countries worldwide. Patients were considered eligible if an objective diagnosis of VTE was made within ±30 days of entry into the registry. Exclusion criteria included patients not treated with anticoagulation therapy at baseline, patients without a BMI measurement, and those with missing or inconsistent outcome records.

2.2 | Selection of study sites

The national coordinating investigator identified the care settings they believed most accurately represented the management of VTE patients in their country. The contract research organization provided a list of sites that reflected these care settings before contacting a random sample of sites for each care setting. Sites that agreed to participate were recruited after a qualification telephone call. Investigators were required to complete an educational program providing guidance on patient screening, enrolment, and follow-up in the registry.

2.3 | Data collection

Patient data were collected using an electronic case report form (eCRF) designed by eClinicalHealth Services, Stirling, UK and were submitted electronically via a secure website to the registry-coordinating center at the Thrombosis Research Institute (TRI), London, UK. TRI was responsible for ensuring complete and accurate data collection from the medical records of enrolled patients. The GARFIELD-VTE protocol mandates that 10% of all eCRFs are verified with source documentation, that electronic audit trails are available for all data modifications, and that critical variables are subjected to additional audit. The data were extracted from the study database in October 2020.

2.4 | Ethics statement

The registry is conducted in accordance with the Declaration of Helsinki and guidelines from the International Conference on Harmonisation on Good Clinical Practice (GCP) and Good Pharmacoepidemiological Practice (GPP) and adheres to all applicable national laws and regulations. Independent ethics committees for each participating country and the hospital-based institutional review board approved the design of the registry. All patients provided written informed consent to participate.

2.5 | Clinical outcomes

The clinical outcomes analyzed in this study included all-cause mortality, recurrent VTE, and major bleeding. Major bleeding events were defined as clinically overt bleeding associated with a critical site, transfusion of 2 or more units of red blood cells, a fall in hemoglobin of ≥2g/dl, or fatal outcome. Any bleeding, myocardial infarction (MI)/acute coronary syndrome (ACS), and stroke/ transient ischemic attack (TIA) were also recorded. The earliest event for each outcome was considered for this analysis.

2.6 | BMI categories

BMI categories were classified based upon definitions by the World Health Organization (WHO). Patients were categorized into four BMI groups; underweight (<18.5 kg/m^2), normal (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2), and obese (≥30 kg/m^2). Obese patients were further subcategorized into three classes: obese class I (30.0–34.9 kg/m^2), obese class II (35.0–39.9 kg/m^2), and obese class III (≥40 kg/m^2).

2.7 | Statistical analysis

Continuous variables are reported using medians and interquartile range (IQR). Categorical variables are summarized as frequency counts and percentage. Unadjusted incidence rates at 2-years follow-up, and 95% confidence intervals (CIs) were estimated using Poisson regression. Time-to-event analyses of outcomes were performed using Cox proportional hazard models.

A range of covariates were assessed as potential risk factors for all outcomes, and those found to be associated were incorporated into the analysis. Hazard ratios (HRs) across BMI categories were adjusted for covariates associated with each outcome (Table S1). Model assumptions were tested to evaluate the adequacy of the observed data. To assess the impact of cancer at baseline, outcomes across BMI categories were estimated first after exclusion of patients with active cancer and then after exclusion of those with active cancer or a history of cancer. Patients were classified as having active cancer if it was diagnosed and/or they were receiving treatment for cancer ≤90 days before VTE diagnosis and up to 30 days after VTE diagnosis. Patients were classified as having a history of cancer if they were diagnosed with cancer or were receiving cancer treatment >90 days before VTE diagnosis. New cancer was considered a cancer event or active cancer treatment >30 days after VTE diagnosis.

Cumulative incidence plots were estimated to account for the competing risk of mortality on recurrent VTE and major bleeding. Missing values were imputed using the multivariate imputation by chain equations method.[18] The association between BMI treated as a continuous variable with main clinical outcomes was evaluated through restrictive cubic splines to capture non-linear relationships and interaction effects. Statistical analyses were conducted using R statistical software and SAS (version 9.4) statistical software.[19] In all cases, the threshold for assessing statistical significance for two-sided tests was set at level $\alpha = .05$.

3 | RESULTS

3.1 | Baseline characteristics

An objective diagnosis of VTE was confirmed in 10 679 patients within the GARFIELD-VTE registry. Of these patients, 9479 had a recorded BMI value and were eligible for analysis; 214 (2.3%) underweight, 2866 (30.2%) normal weight, 3326 (35.1%) overweight, and 3073 (32.4%) obese (of which 1824 [59.4%] class I, $n = 769$ [25.0%] class II and $n = 480$ [15.6%] class III [Figure 1]). The median age was comparable among groups. Underweight, normal, and obese patients were more often female (60.7%, 51.5%, and 56.2%, respectively), whereas overweight patients were less likely to be female (41.3%). Obese patients were more often Caucasian and more often diagnosed in an outpatient setting compared with lower BMI categories. Full baseline characteristics are provided in Table 1.

The diagnosis of DVT alone decreased as BMI values increased (underweight: 71.5%, normal: 62.5%, overweight: 61.4%, and obese: 57.9%), whereas PE with or without DVT increased with increasing BMI (28.5%, 37.5%, 38.6%, and 42.1%, respectively). DVT was most often detected in the lower limbs in all BMI categories (89.9%, 90.6%, 93.3%, and 94.0%, respectively).

Active cancer was more common in underweight patients compared with those with a normal, overweight, or obese BMI (30.4%, 13.5%, 9.4%, 7.0%, respectively). Transient risk factors including acute medical illness (11.2%, 6.9%, 5.2%, 5.6%) and hospitalization (21.5%, 13.6%, 11.8%, 11.5%), and predisposing risk factors including chronic immobilization (8.9%, 6.6%, 5.1%, 5.4%) and a history of cancer (33.2%, 15.4%, 13.0%, 10.3%) were also more prominent in underweight patients. Conversely, long-haul travel (0.5%, 4.5%, 5.1%, 5.2%), trauma to the lower limb (4.7%, 7.8%, 8.7%, 7.3%), and hormone replacement therapy (0.9%, 1.5%, 1.4%, 2.1%) were less frequent in underweight patients. The prevalence of a previous diagnosis of VTE and a family history of VTE increased with increasing BMI. Surgery, chronic heart failure and thrombophilia were comparable among groups (Table 2).

3.2 | VTE treatment patterns

After diagnosis, the proportion of patients commencing anticoagulation was comparable among groups (Figure 2). Obese patients and overweight patients were less likely to be given parenteral therapy alone (14.4% and 16.7%, respectively) compared with those with an underweight or normal BMI (30.8% and 21.6%, respectively). VKA prescription (with or without parenteral therapy) was comparable across groups, whereas DOAC use (with or without parenteral therapy) was lower in underweight patients (32.2%) compared with normal, overweight, and obese patients (46.6%, 50.5%, and 48.8% respectively).

Anticoagulation discontinuation was least frequent in obese patients. At 24-months follow-up, persistent use of DOACs and

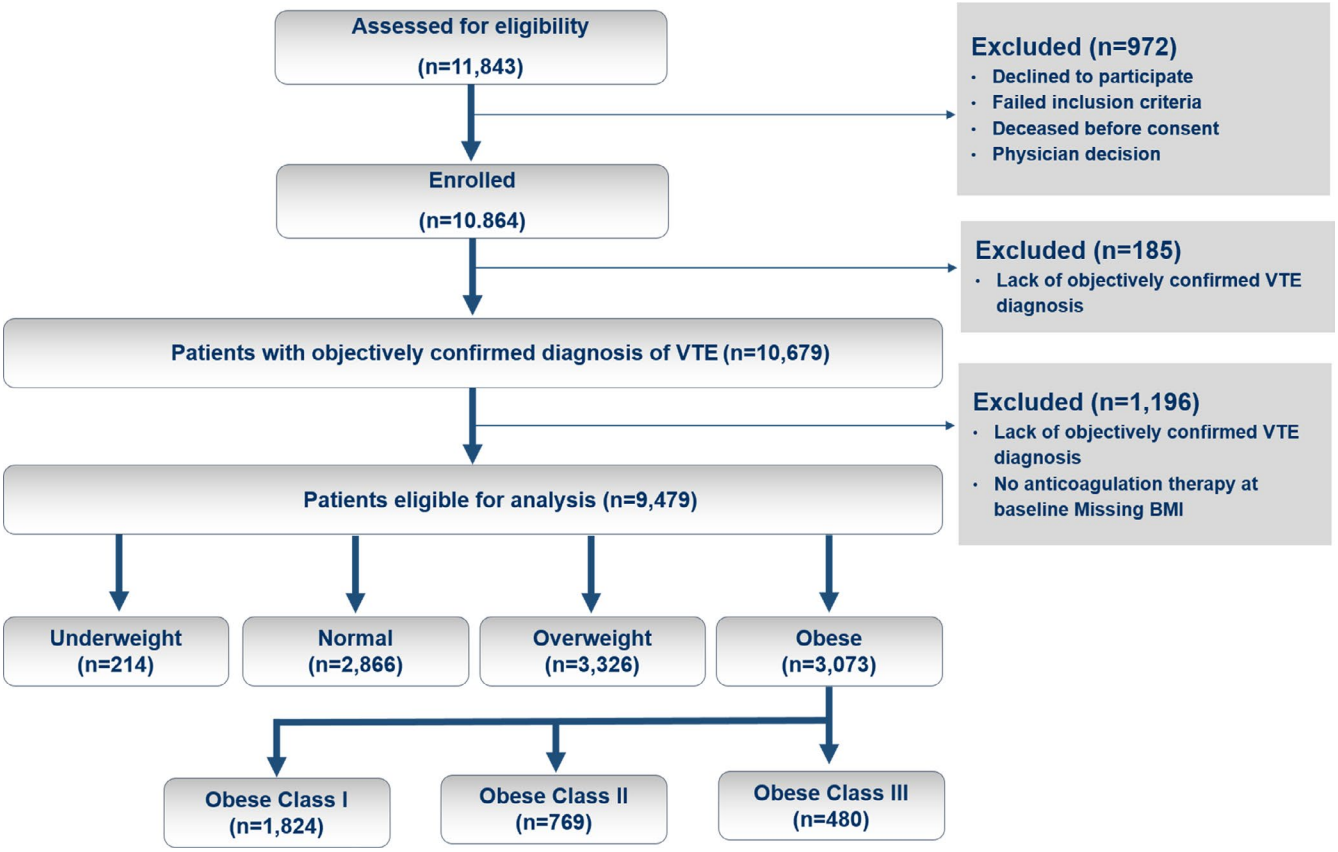


FIGURE 1 Study population flowchart

TABLE 1 Baseline characteristics by BMI category

	Underweight ($n = 214$)	Normal ($n = 2866$)	Overweight ($n = 3326$)	Obese ($n = 3073$)
Female, *n* (%)	130 (60.7)	1475 (51.5)	1374 (41.3)	1728 (56.2)
Age, Median (IQR)	61.9 (42.9, 73.1)	59.6 (42.7, 72.5)	61.2 (48.5, 72.8)	58.9 (46.0, 68.8)
Body mass index, median (IQR), kg/m^2	17.4 (16.4, 18.0)	22.9 (21.3, 24.1)	27.4 (26.2, 28.6)	34.0 (31.6, 37.5)
Ethnicity, n (%)				
Asian	104 (50.7)	857 (32.1)	534 (17.3)	225 (7.7)
Black	25 (12.2)	128 (4.8)	107 (3.5)	183 (6.2)
Caucasian	68 (33.2)	1546 (57.9)	2254 (73.1)	2274 (77.4)
Other	8 (3.9)	137 (5.1)	189 (6.1)	257 (8.7)
Missing	9	198	242	134
Smoking, *n* (%)				
Ex-smoker	46 (21.8)	570 (20.2)	815 (24.9)	681 (22.6)
Current smoker	37 (17.5)	522 (18.5)	502 (15.3)	440 (14.6)
Missing	3	47	49	55
VTE type, *n* (%)				
DVT	153 (71.5)	1791 (62.5)	2042 (61.4)	1780 (57.9)
PE ± DVT	61 (28.5)	1075 (37.5)	1284 (38.6)	1293 (42.1)
Site of DVT, *n* (%)				
Upper limb	14 (7.89)	154 (7.0)	132 (5.1)	98 (4.3)
Lower limb	160 (89.9)	2003 (90.6)	2419 (93.3)	2165 (94.0)
Caval vein	4 (2.3)	53 (2.4)	42 (1.6)	39 (1.7)
Missing	36	656	733	771
Unilateral or bilateral DVT, *n* (%)				
Left	99 (55.6)	1212 (54.8)	1336 (51.6)	1260 (54.7)
Right	55 (30.9)	829 (37.5)	1079 (41.6)	922 (40.1)
Both	24 (13.5)	169 (7.6)	176 (6.8)	120 (5.2)
Missing	36	656	735	771
Type of DVT, *n* (%)				
Isolated distal	41 (19.2)	573 (20.0)	691 (20.8)	574 (18.7)
Proximal ± distal DVT	97 (45.3)	1031 (36.0)	1184 (38.6)	1062 (34.6)
Care setting, *n* (%)				
Hospital	172 (80.4)	2203 (76.9)	2407 (72.4)	2139 (69.6)
Outpatient setting	42 (19.6)	663 (23.1)	919 (27.6)	934 (30.4)
Physician specialty, *n* (%)				
Vascular medicine	75 (35.0)	1263 (44.1)	1631 (49.1)	1414 (46.0)
General practitioner	13 (6.1)	102 (3.6)	112 (3.4)	120 (3.9)
Internal medicine (Hematology and Intensive Care)	109 (50.9)	1232 (43.0)	1326 (39.9)	1327 (43.2)
Emergency medicine	2 (0.9)	64 (2.2)	69 (2.1)	74 (2.4)
Cardiology	15 (7.0)	204 (7.1)	186 (5.6)	136 (4.4)
Missing	0	1	2	2
Creatinine clearance, median (IQR), ml/min	63.1 (41.4, 92.0)	79.7 (57.4, 104.9)	90.9 (65.7, 118.3)	113.5 (82.5, 150.6)
CKD stage (eGFR), *n* (%)				
I – Normal (≥90)	99 (52.1)	1003 (40.9)	878 (31.2)	686 (26.2)
II – Mild (60–89)	58 (30.5)	989 (40.3)	1276 (45.3)	1232 (47.1)

(Continues)

TABLE 1 (Continued)

	Underweight ($n = 214$)	Normal ($n = 2866$)	Overweight ($n = 3326$)	Obese ($n = 3073$)
III – Moderate (30–59)	25 (13.2)	353 (14.4)	548 (19.5)	571 (21.8)
IV – Severe (15–29)	4 (2.1)	46 (1.9)	56 (2.0)	64 (2.4)
V – Failure (<15)	4 (2.1)	61 (2.5)	57 (2.0)	61 (2.3)
Missing	24	414	511	459
Haemoglobin, median (IQR), g/dl	10.6 (9.0, 12.1)	12.6 (11.0, 14.0)	13.3 (11.8, 14.5)	13.3 (11.8, 14.6)
Missing	31	436	507	442
Platelets, median (IQR), 10^9/L	240.0 (182.0, 331.0)	236.0 (187.0, 300.0)	225.0 (179.0, 288.0)	230.0 (186.0, 290.0)
Platelet categories [10^9/L] (%)				
Thrombocytopenia (<150)	31 (16.1)	272 (11.0)	329 (11.6)	247 (9.3)
Normal (150–450)	147 (76.2)	2078 (83.8)	2408 (84.7)	2311 (87.1)
Thrombocytosis (≥450)	15 (7.8)	131 (5.3)	106 (3.7)	95 (3.6)
Missing	21	385	483	420

TABLE 2 Risk factors associated with VTE in BMI categories

	Underweight ($n = 214$)	Normal ($n = 2866$)	Overweight ($n = 3362$)	Obese ($n = 3073$)
Persistent provoking risk factors, *n* (%)				
Active cancer	65 (30.4)	387 (13.5)	314 (9.4)	215 (7.0)
Transient provoking risk factors, *n* (%)				
Acute medical illness	24 (11.2)	197 (6.9)	173 (5.2)	172 (5.6)
Hospitalization	46 (21.5)	389 (13.6)	391 (11.8)	352 (11.5)
Long-haul travelling	1 (0.5)	128 (4.5)	170 (5.1)	160 (5.2)
Surgery	26 (12.1)	364 (12.7)	416 (12.5)	394 (12.8)
Trauma to the lower limb	10 (4.7)	224 (7.8)	290 (8.7)	223 (7.3)
Hormone replacement therapy	2 (0.9)	44 (1.5)	47 (1.4)	63 (2.1)
Oral contraception	7 (3.3)	205 (7.2)	118 (3.5)	153 (5.0)
Predisposing risk factors, *n* (%)				
Chronic heart failure	8 (3.7)	78 (2.7)	97 (2.9)	128 (4.2)
Chronic immobilization	19 (8.9)	190 (6.6)	171 (5.1)	166 (5.4)
Family history of VTE	7 (3.3)	146 (5.1)	212 (6.4)	214 (7.0)
History of cancer	71 (33.2)	441 (15.4)	432 (13.0)	317 (10.3)
Known thrombophilia	7 (3.3)	113 (3.9)	101 (3.0)	68 (2.2)
Previous VTE	14 (6.5)	335 (11.7)	510 (15.3)	539 (17.5)

VKAs was highest in obese patients (28.7% and 17.7%, respectively) compared with underweight (14.4% and 8.7%), normal (22.5% and 12.5%), and overweight patients (25.4% and 13.8%). Parenteral therapy use at 24-months was comparable among groups.

3.3 | Clinical outcomes

At 24-months, the incidence rates [95% CI] of all-cause mortality and major bleeding were higher in underweight patients (24.72 [19.56–31.25] and 6.19 [3.85–9.95] per 100 person years) and lower in obese patients (3.48 [3.02–4.01] and 1.65 [1.34–2.03] per 100 person years) compared with normal weight patients (7.36 [6.63–8.17] and 1.97 [1.60–2.41] per 100 person years). The rate of recurrent VTE was similar among groups (Table S2).

Adjusted HRs [95% CI] revealed that both all-cause mortality and major bleeding remained higher in underweight patients than in those with a normal BMI (1.90 [1.43–2.53] and 2.45 [1.41–4.26]) at 24-months. All-cause mortality was lower in overweight (0.75 [0.63–0.89]) and obese (0.59 [0.49–0.72]) patients than in those

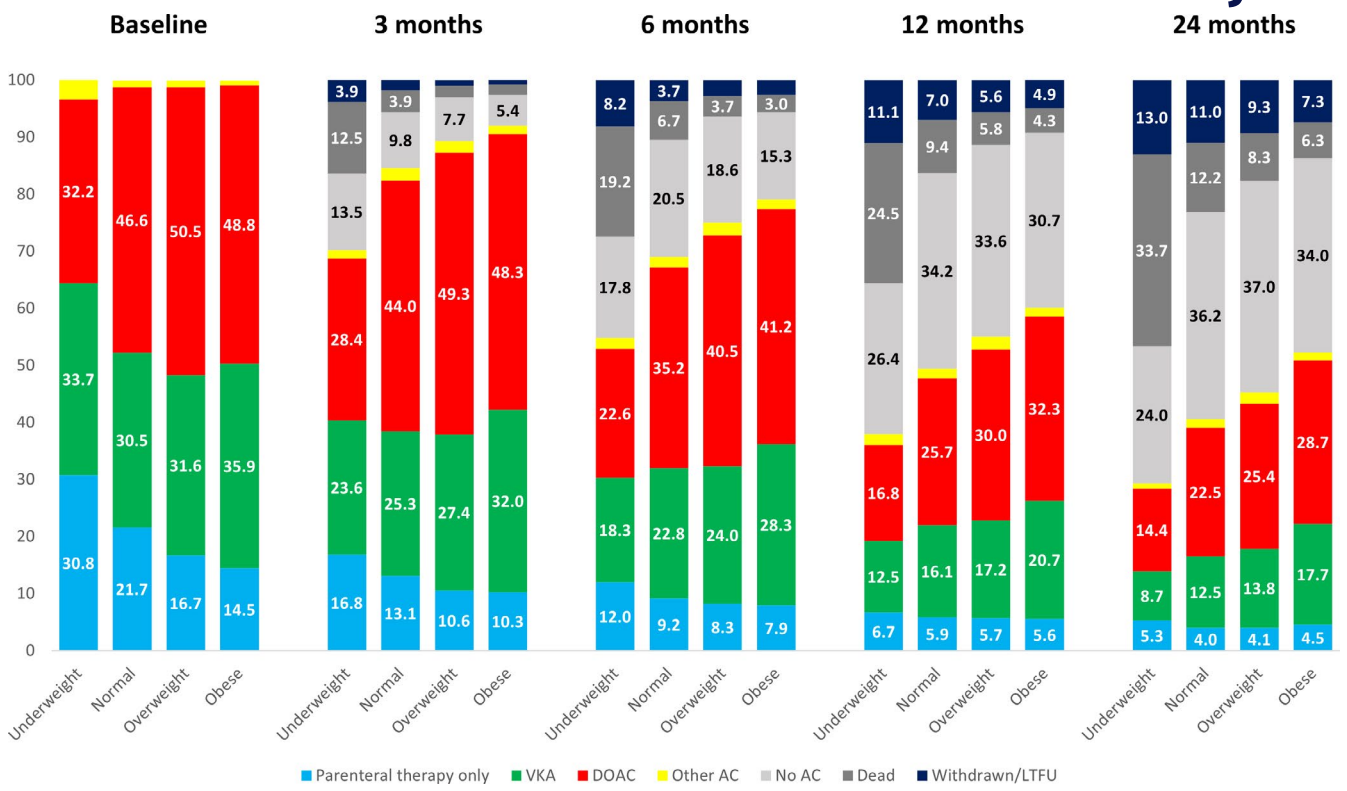


FIGURE 2 Anticoagulation treatment patterns over 24-months' follow-up in VTE patients varying bodyweight. Baseline refers to the first 30 days after VTE diagnosis. AC, anticoagulant; DOAC, Direct oral anticoagulant; LTFU, lost to follow-up; VKA, Vitamin K antagonist

with a normal BMI (Figure 3). Cumulative incidence curves for outcomes are displayed in Figure S1. The interaction between BMI as a continuous variable and treatment was not significant for primary outcomes (mortality: $p = .1305$, VTE: $p = .3839$, major bleeding: $p = .6556$; Figure 4). To better examine the impact of cancer, outcomes were determined after excluding patients with active cancer at baseline; underweight patients remained at increased risk of mortality and major bleeding (HR: 2.21 [1.41–3.46] and 2.72 [1.32–5.61], respectively; Figure S2). Similarly, after exclusion of patients with active cancer and a history of cancer at baseline, underweight patients still were at a higher risk of all-cause mortality and major bleeding (HR: 2.60 [1.49–4.53] and 2.63 [1.10–6.27], respectively; Figure S3). The most common cause of mortality was cancer-related in all BMI categories (55.7%, 52.7%, 54.0%, 48.7%, respectively). The proportions of cancer-related deaths were similar across BMI categories after exclusion of patients with active cancer at baseline (Table S3). Cardiac-related mortality was more frequent in obese (8.8%) and overweight (9.1%) patients than in patients with a normal (5.1%) or underweight BMI (4.3%). The most common sites of major bleeding were the upper and lower gastrointestinal tract (Table S4). Compared with patients with a normal BMI, any bleeding and MI/ACS were not significantly impacted by BMI. The risk of stroke/TIA was lower in overweight patients (0.43 [0.25–0.75]; Figure 3).

3.4 | Obesity sub-study

Of the 3073 obese patients with objectively confirmed VTE, 1824 (59.4%) were classified as obesity class I, 769 (25.0%) as obesity class II, and 480 (15.6%) as obesity class III (Figure 1). The median age of class I patients was slightly higher than that of class II and III patients (60.3, 58.7, and 54.1 years, respectively). Class II and III patients were more often female (62.5% and 70.0%, respectively) than class I patients (49.9%). The distribution of baseline characteristics is provided in Table S5. The distributions of VTE type, VTE site, and VTE risk factors were comparable among obesity groups (Table S6). The percentage of obesity according to geographical location is provided in Figure 5.

The unadjusted rate of all-cause mortality was highest in obesity class II (4.14 [3.20–5.37]) compared with class I (3.35 [2.78–4.03]) and class III (2.96 [2.01–4.34]). Major bleeding was less frequent in class I patients (1.36 [1.01–1.82]) than in class II (2.23 [1.56–3.19]) and class III patients (1.86 [1.14–3.04]; Table S7). Recurrent VTE was comparable among obesity groups. After adjustment, these differences among obesity classes were no longer significant (Figure 6). Any bleeding was higher in class III patients (HR [95% CI]: 1.39 [1.06–1.81]). Event rates (per 100 person-years) for all-cause mortality, recurrent VTE, and major bleeding by country are provided in Figure S4.

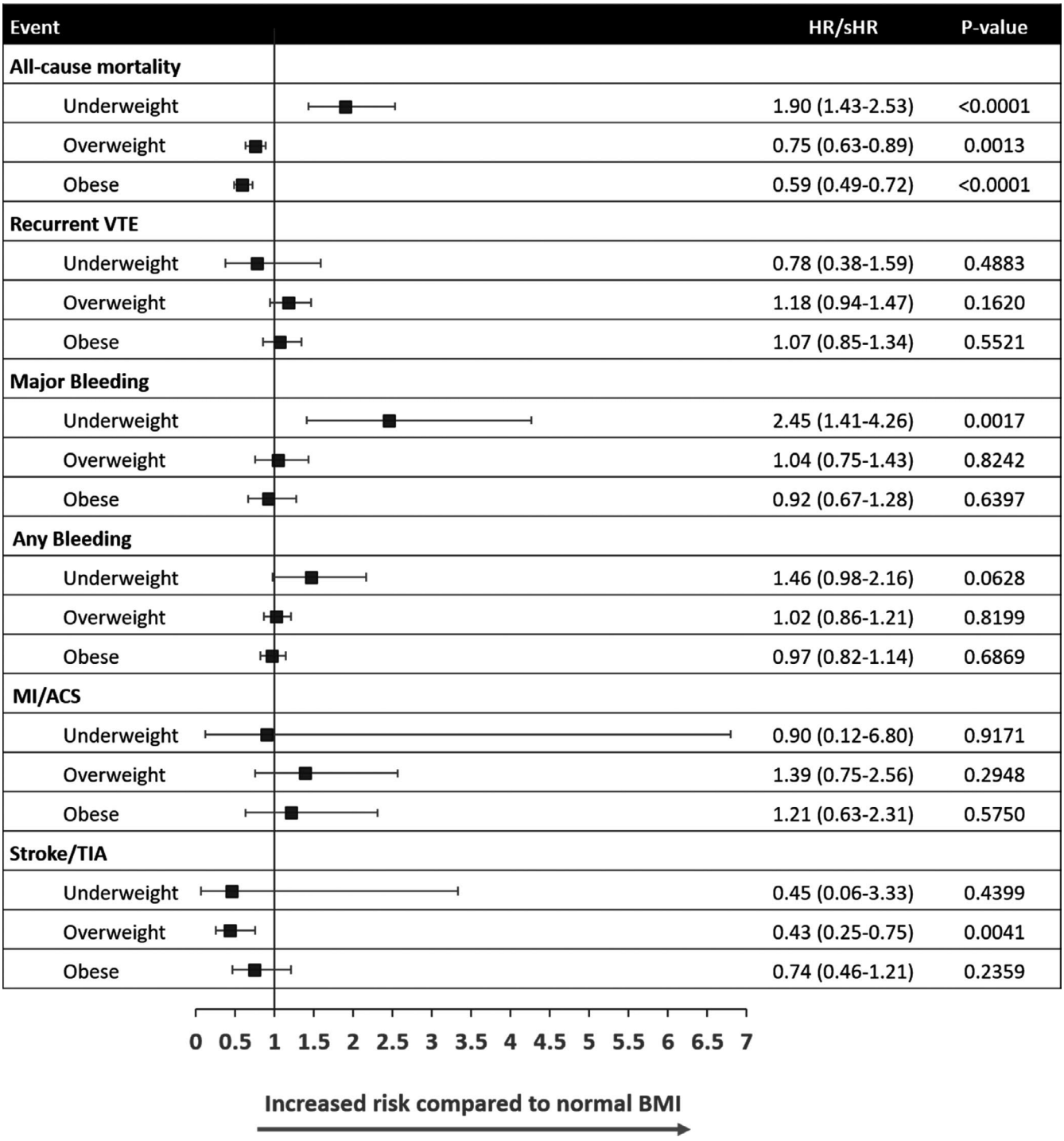


FIGURE 3 Adjusted hazard ratios with 95% CIs for 24-month outcomes in VTE patients with different BMIs (normal: reference group. Hazard ratios were adjusted for associated covariates described in Table S1). VTE, venous thromboembolism; TIA, transient ischemic attack; MI, myocardial infarction; ACS, acute coronary syndrome; HR, hazard ratio; CI, confidence interval

4 | DISCUSSION

In this large, global observational study of VTE, almost 70% of patients were overweight or obese, consistent with the concept that a high BMI is a risk factor for VTE[6] and with the finding of a similar distribution of VTE patients by BMI in the RIETE registry.[13] Overweight and obese patients most frequently received DOACs.

Paradoxically, all-cause mortality was least frequent in obese patients. Among obesity classes I-III, there was no difference in primary outcomes and no significant interaction was established between BMI and treatment. Underweight patients comprised the smallest proportion of participants in GARFIELD-VTE, reflecting the reduced risk of VTE associated with a low BMI.[20] However, underweight patients were most likely to have active cancer, a history of

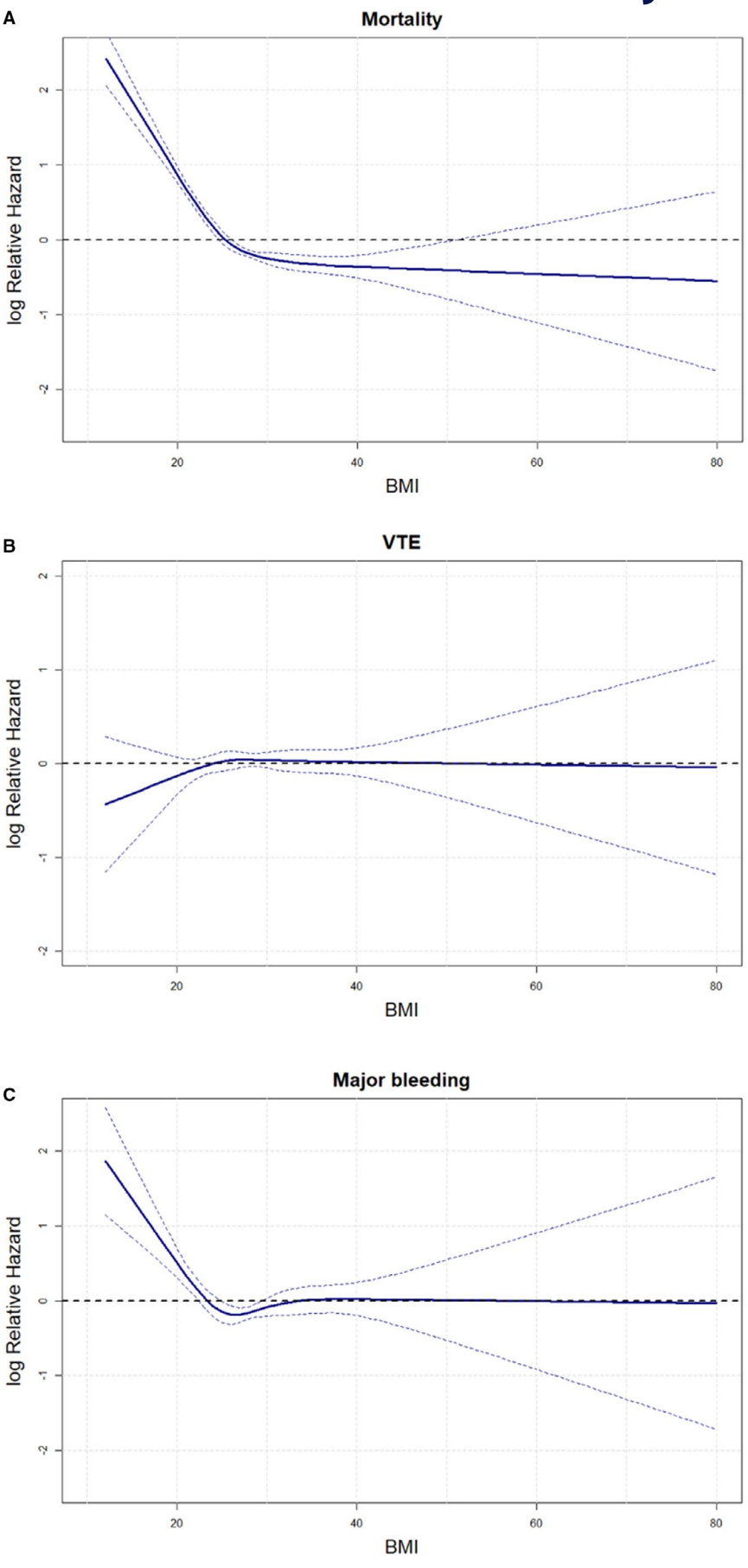


FIGURE 4 Relative risk and 95% CIs as a function of BMI for (A) all-cause mortality, (B) recurrent VTE, and (C) major bleeding. Negative values indicate a risk reduction compared to the sample average. Positive values indicate an increased risk compared to the sample average. Interaction *p*-values for mortality: $p = .1305$; VTE: $p = .3839$; and major bleeding: $p = .6556$

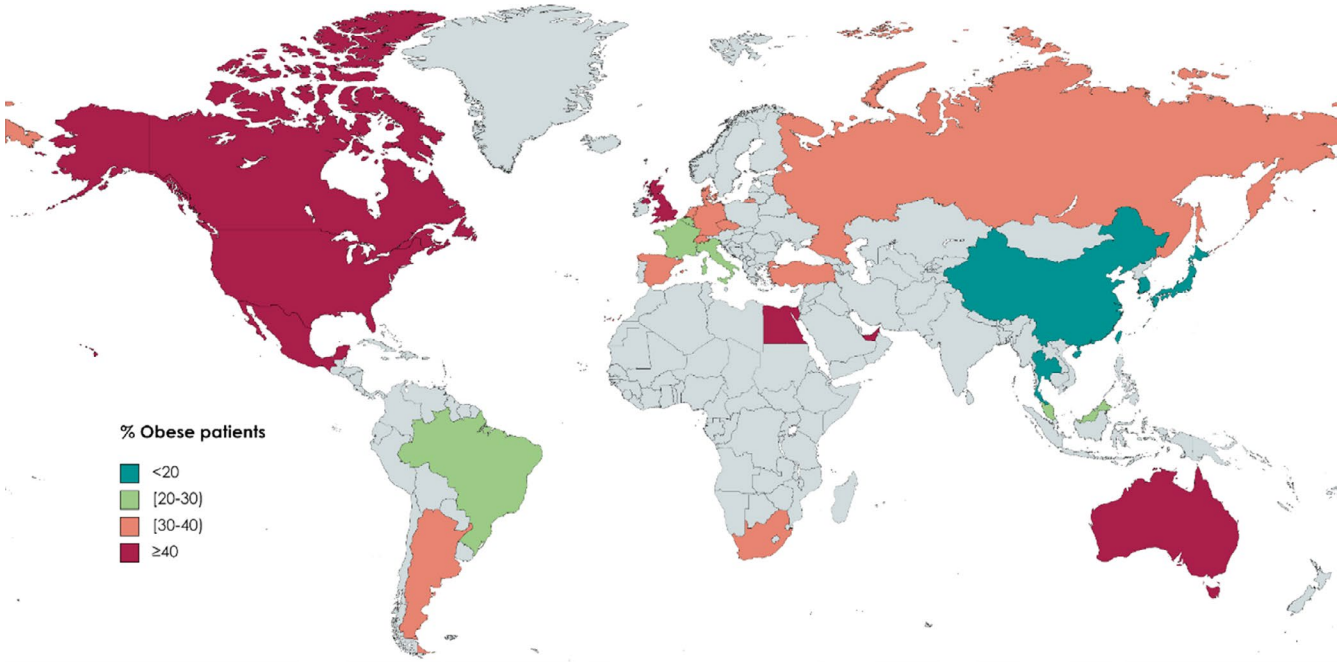


FIGURE 5 Distribution of obese patients according to country

cancer, and acute medical illness. Underweight patients were also most often prescribed parenteral therapy alone and had the highest risk of all-cause mortality and major bleeding, even when patients with active cancer at baseline were excluded.

The proportion of patients with PE rather than DVT was greater with each increasing BMI category. This finding is consistent with previous reports that higher BMI is associated with PE,[21] with obese patients more than twice as likely to experience PE as their counterparts with a normal body weight.[22] Therefore, obesity may be more of a risk factor for PE than for DVT,[23] consistent with the reduced proportion of patients with DVT in the higher BMI cohorts in GARFIELD-VTE.

The proportion of patients having undergone recent (≤3 months) surgery was comparable across BMI categories. A history of prior VTE was more prevalent as BMI increased, possibly reflecting an interaction with high BMI. In contrast, acute illness, hospitalization, and immobilization were more frequently observed in those with an underweight BMI, possibly due to the higher proportion of patients with active cancer or a history of cancer in that group. These potential interactions are consistent with previous reports that BMI interacts with other risk factors such as prior VTE, recent surgery, malignancy, and immobilization to increase the risk of VTE.[6,11]

Current guidelines recommend anticoagulation therapy for a minimum of 3 months in patients with VTE. Treatment beyond 3 months is considered for patients with unprovoked VTE, VTE provoked by major persistent risk factors such as active cancer, and for patients with recurrent VTE.[24,25] Recent guidelines also suggest consideration of extended anticoagulation therapy in patients with VTE provoked by minor persistent risk factors such as obesity.[22] This may explain why anticoagulation discontinuation was less frequent in obese patients than in those in the lower BMI categories.

Optimal treatment for those with a high or low BMI is unclear. DOAC use was higher in patients with an overweight or obese BMI, despite ISTH guidance to use caution when prescribing DOACs for patients with morbid obesity.[15,16] In contrast, underweight patients were substantially more likely to receive parenteral therapy, possibly reflecting the greater proportion of patients with active cancer or a history of cancer in that BMI category. Despite differences in treatments across the various BMI categories, rates of recurrent VTE were similar. However, the rate of major bleeding was highest in underweight patients and lowest in obese patients. Conflicting results have been reported on the association between BMI and major bleeding with VKAs. Higher rates of bleeding in obese individuals than in those with a normal BMI are reported in some studies, but not in others.[26,27] In contrast, studies with DOACs report no association between BMI and rates of bleeding.[28,29]

Despite the link between high BMI and a range of chronic conditions, obesity is often associated with a reduced risk of mortality.[30] The risk of mortality has been inversely correlated with BMI, and a BMI of ≥30 kg/m^2 has been reported to be one of the best indicators for survival in patients with VTE.[14,31] Some studies suggest that the obesity paradox may reflect, in part, confounder 'masking' of mortality risk. For example, obesity acquired in old age may allow patients to present without detrimental obesity-related complications that would develop over time. Furthermore, sudden weight loss due to illness in old age is a predictor for mortality, which may falsely suggest that elderly obese patients are protected. In our study, obese patients had the lowest risk of all-cause mortality after adjustment for a range of potential confounders, thereby confirming the obesity paradox. In contrast, obese patients had similar rates of all other outcomes compared with those with a normal BMI. Except for any bleeding, which was higher in patients with class III obesity, no outcome differences were noted across obesity classes.

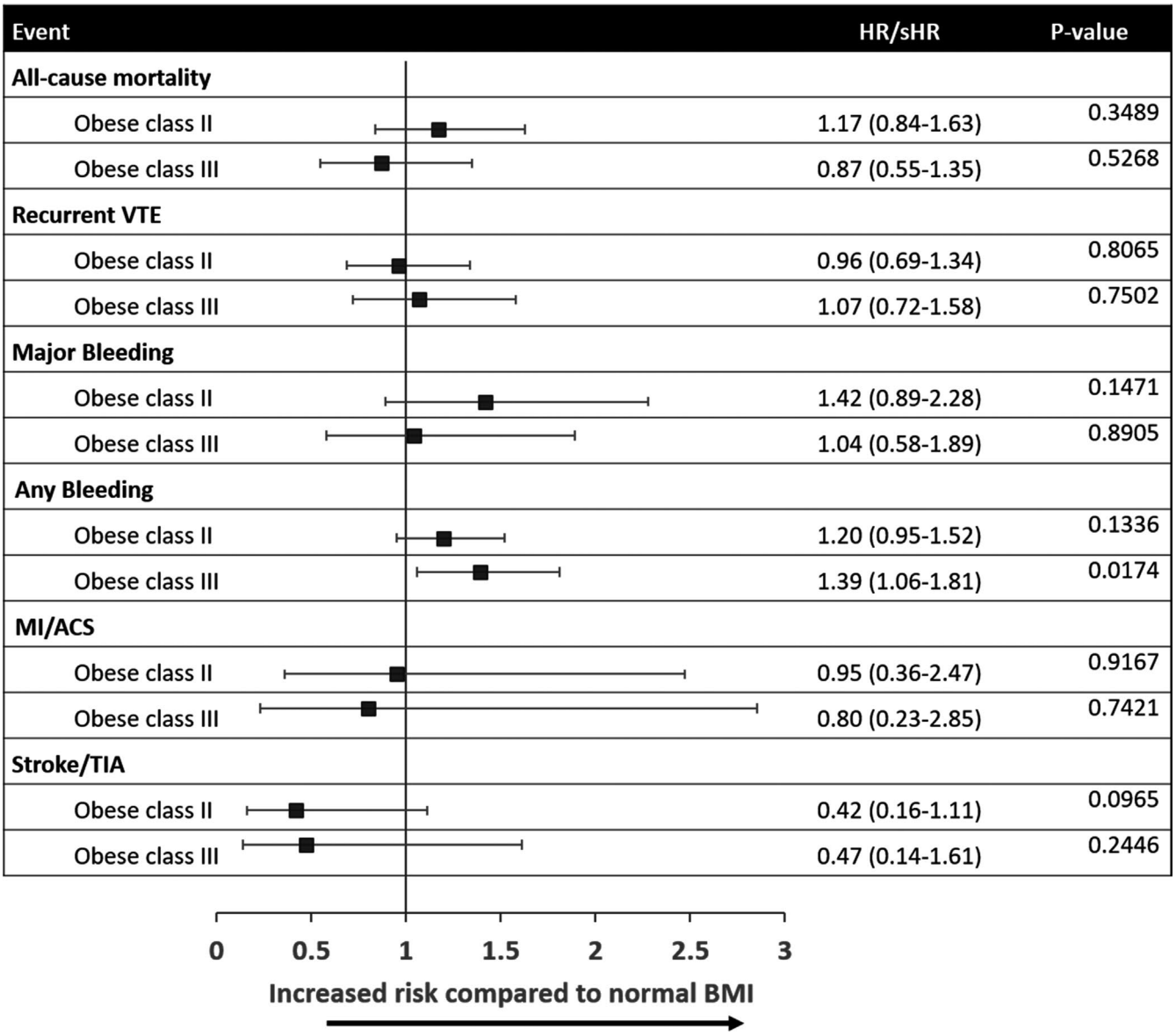


FIGURE 6 Adjusted hazard ratios with 95% CIs for 24-month outcomes after VTE diagnosis with difference obesity class (normal: reference group. Hazard ratios were adjusted for associated covariates described in Table S1). VTE, venous thromboembolism; TIA, transient ischemic attack; MI, myocardial infarction; ACS, acute coronary syndrome; HR, hazard ratio; CI, confidence interval. Reference group = obesity class I

Underweight patients demonstrated the highest rate of all-cause mortality, likely reflecting concurrent illnesses in patients within this category. In support of this concept, underweight patients more often presented with acute medical illness and were more frequently hospitalized at baseline. Underweight patients were more likely to experience major bleeding, indicating that anticoagulation strategies for this group require further optimization.

4.1 | Limitations

Limitations include the non-randomized collection of data and the absence of central adjudication of outcome events. In addition, despite the size of the study, the number of underweight patients in this analysis is small. Finally, although little absent data was observed throughout, there is a possibility that the cause of missing data was not random, and thus imputation has the potential to introduce bias.

5 | CONCLUSIONS

In summary, GARFIELD-VTE indicates that current anticoagulation practices vary according to BMI. All-cause mortality was lowest in obese patients and highest in underweight patients, reflecting the existence of the obesity paradox. Major bleeding was highest in underweight patients, suggesting that further research is needed to

determine the optimal treatment regimens for patients with extreme BMIs.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

Jeffrey I. Weitz, Walter Ageno, Alexander G. G. Turpie, Sylvia Haas, Shinya Goto, Samuel Z. Goldhaber, Pantep Angchaisuksiri, Gloria Kayani, Sebastian Schellong, Henri Bounameaux, Lorenzo G. Mantovani, Paolo Prandoni and Ajay K. Kakkar all contributed to the concept, design, and conduct of the study. Alfredo E. Farjat conducted the statistical analysis. All authors contributed to data interpretation. Jeffrey I. Weitz wrote the manuscript. All authors critically reviewed the manuscript. Ajay K. Kakkar and Gloria Kayani handled funding and supervised the registry.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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