Effectiveness and Safety of Dabigatran in Atrial Fibrillation Patients with Severe Obesity: a Real-World Retrospective Cohort Study

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BACKGROUND: Direct oral anticoagulants such as dabigatran are the preferred anticoagulant in treating atrial fibrillation (AF) patients due to their effectiveness and safety. Whether this applies to severely obese patients needs to be determined.

OBJECTIVE: To compare the effectiveness and safety of dabigatran with warfarin among AF patients with severe obesity.

DESIGN: Retrospective cohort study.

PARTICIPANTS: AF patients with a BMI >40kg/m^2 or a weight >120kg receiving dabigatran or warfarin between 10/01/2010 and 12/31/2019 in a large integrated health system and followed through 08/01/2020.

INTERVENTIONS: Not applicable.

MAIN MEASURES: Primary effectiveness outcome was composite thromboembolism including transient ischemic attack, ischemic stroke, or systemic embolism. Primary safety outcome was composite bleeding including gastrointestinal bleeding, intracranial bleeding, or other bleeding. Secondary outcomes included the individual outcomes and all-cause mortality. Propensity score matching (PSM) was performed to create a 1:1 matched cohort and Cox proportional hazards model was used to estimate the hazard ratio (HR) of each outcome for dabigatran users compared to warfarin users.

KEY RESULTS: A total of 6848 patients receiving either dabigatran or warfarin were identified. In a 1:1 matched cohort, dabigatran users had a HR of 0.71 (95% confidence interval (CI): 0.56–0.91) for composite thromboembolism, a HR of 1.24 (95%CI: 1.07–1.42) for composite bleeding, and a HR of 0.57 (95% CI: 0.45–0.71) for all-cause mortality when compared to warfarin users.

CONCLUSIONS: Among AF patients with a BMI >40kg/m^2 or a weight >120kg in a real-world clinical setting, dabigatran was effective in reducing the risk of thromboembolism and mortality but was associated with an increased risk of bleeding when compared to warfarin. Dabigatran may be a reasonable option for AF patients with severe obesity.

KEY WORDS: atrial fibrillation; obesity; anticoagulation; dabigatran.

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INTRODUCTION

Current guidelines recommend direct oral anticoagulants (DOAC) as the preferred anticoagulant over warfarin for stroke prevention in atrial fibrillation (AF) patients[1]. While warfarin has long been considered standard of care for anticoagulation and can reduce stroke risks by roughly 60%, several large clinical trials have established DOACs to be either non-inferior or superior to warfarin therapy in terms of efficacy and safety for AF patients[2–5]. In addition, DOACs, unlike warfarin, do not require frequent laboratory monitoring and dose adjustments to maintain therapeutic effects[6]. This has led to the progressive adoption of DOACs over the years[7,8].

Despite the increased adoption of DOACs among AF patients, DOAC use among severely obese patients has been limited given concern for limited representation of severely obese patients in clinical trials and insufficient drug concentrations with increased body weight[3–5,8–11]. The prevalence of severe obesity is ≈10% among AF patients[12,13]. In 2016, the International Society on Thrombosis and Haemostasis released guidelines recommending against the use of DOACs among patients with a body mass index (BMI) >40kg/m^2 or a weight >120kg[11]. Growing literature regarding DOACs' effectiveness among AF patients with severe obesity has been limited by homogenous populations, lack of distinction among different DOACs, and/or smaller cohort sizes[13–18]. Despite some studies supporting apixaban and rivaroxaban in patients with severe obesity, uncertainty around dabigatran remains[19–23].

If dabigatran is proven to be effective, it may allow for updated guidance and have important clinical implications on AF patients with severe obesity, especially given that dabigatran will be the first generic DOAC to enter the market. In this study, we sought to compare the effectiveness and safety of dabigatran with warfarin among AF patients with severe obesity in a large integrated health system within the USA.

METHODS

Study Setting and Population

We performed a retrospective cohort study within Kaiser Permanente Southern California (KPSC). KPSC is an integrated health system providing comprehensive care to over 4.7 million members at 15 medical centers and >200 satellite clinics throughout Southern California[24]. The patient population is racially/ethnically and socio-economically diverse, reflecting the general population of Southern California[25]. All study information collected as part of routine clinical care was electronically extracted from the electronic health record system.

We included AF patients aged ≥18 years with severe obesity who received oral anticoagulation (dabigatran, apixaban, rivaroxaban, or warfarin) between 10/01/2010 and 12/31/2019 in our study. Severe obesity was defined as a BMI >40kg/m^2 and/or weight >120kg[11]. We selected 10/2010 to begin our study period as this was when the first DOAC, dabigatran, became available within KPSC. The index date was defined as the first prescription fill date of an anticoagulant within the study period. The baseline period was defined as the preceding 12 months prior to the index date. Patients were required to have one-year continuous network insurance coverage prior to the index date (during the baseline period) with a 30-day gap allowed to be included. AF was defined by International Classification of Diseases (ICD) codes (ICD-9: 427.3x, ICD-10: I48.x) on index date or during the baseline period. Exclusion criteria included valvular heart disease ever, active renal replacement therapy and/or renal transplant prior to index date, hip or knee replacement within 6 weeks prior to index date, deep vein thrombosis, or pulmonary embolism within baseline period, and pregnancy at index date. We excluded patients with valvular heart disease given the original clinical trial only included nonvalvular AF and to minimize potential confounders using ICD codes (Appendix Table 4)[5]. The definition of valvular heart disease included rheumatic mitral stenosis, a mechanical or bioprosthetic heart valve, or mitral valve repair and was based on the prior 2014 American College of Cardiology, American Heart Association, and Heart Rhythm Society guidelines[26]. Active renal replacement therapy and/or renal transplant patients were identified based on their status within our internal KPSC Renal Business Group database. Patients who underwent hip or knee replacement or had a deep vein thrombosis or pulmonary embolism were identified based on ICD codes (Appendix Table 4)[27,28].

Our study was approved by our institutional review board (IRB# 12283) and informed consent was waived.

Exposure Ascertainment

Patients were categorized as either a DOAC or warfarin users based on prescriptions filled using pharmacy data using Generic Product Identifier (GPI) code. Any patient with a DOAC prescription filled within the study period regardless of prior warfarin use was categorized as a user of the first DOAC they were prescribed while all warfarin users could have only received warfarin. We allowed for DOAC users who were on warfarin prior, similar to the original dabigatran clinical trial[5]. We had anticipated that many patients likely would have received warfarin prior to DOAC initiation given our study period started when dabigatran first became available within our health system and wanted to maximize our dabigatran capture. We further restricted our analysis to only dabigatran and warfarin users given only a small number of apixaban (n=119) and rivaroxaban (n=67) users were identified.

Outcome Ascertainment and Follow-up

Primary effectiveness outcome was composite thromboembolism defined by a composite of transient ischemic attack, ischemic stroke, and systemic embolism. Primary safety outcome was composite bleeding defined by a composite of gastrointestinal bleeding, intracranial bleeding, and other bleeding. All outcome variables were defined by ICD codes in any encounter type (Appendix Table 4). The secondary outcomes were a transient ischemic attack, ischemic stroke, systemic embolism, gastrointestinal bleeding, intracranial bleeding, other bleeding, and all-cause mortality. Patients were followed through 08/01/2020. A patient was censored if they died, lost KPSC membership, or at the end of the follow-up period, whichever came first.

Statistical Analysis

Baseline patient characteristics were presented descriptively. Continuous variables were presented as median with interquartile range (IQR) and categorical variables as absolute numbers with percentages. Differences between baseline characteristics were compared using the χ^2 test for categorical variables and t-test for continuous variables.

A total of 28 variables listed in Table 1 including baseline demographics, co-morbidities, medication use, and risk scores including CHA_2DS_2-VASc, and HAS-BLED were used to construct a matched cohort[29,30]. All co-morbidities, including those within risk scores, were captured using ICD codes during the baseline period[31]. All medications were captured using GPI codes based on pharmacy data during the baseline period (Appendix Table 5). We used a modified HAS-BLED score with a max score of 8 after excluding labile international normalized ratio (INR) due to data limitations and given dabigatran users do not routinely have INR measurements. We defined abnormal liver and renal function based on the presence of renal and liver disease using ICD codes due to data limitations. Specifically, matching by categories defined in Table 2 was performed for the following variables: age, BMI, Charlson comorbidity index (CCI), CHA_2DS_2-VASc, and HAS-BLED.

Propensity score matching (PSM) with a caliper of 0.1 without replacement was performed to obtain a matched 1:1 cohort for analysis. The standardized difference was used to

Table 1 Baseline Characteristics of the Initial and Matched Cohort[a]

	Unmatched cohort				Matched cohort			
	All patients (*n*=6848)	**Dabigatran (*n*= 3226)**	**Warfarin (*n*= 3622)**	***P* value**	**All patients (*n*=3318)**	**Dabigatran (*n*= 1659)**	**Warfarin (*n*= 1659)**	***P* value**
Age (years)[d]	66.3 (59.2, 72.3)	66.4 (59.7, 72.0)	66.3 (58.9, 72.6)	0.93	66.9 (59.7, 72.7)	66.8 (60.1, 72.4)	67.1 (59.2, 73.1)	0.84
<65	3041 (44.4%)	1416 (43.9%)	1625 (44.9%)	0.11	1389 (41.9%)	699 (42.1%)	690 (41.6%)	0.94
65–79	3409 (49.8%)	1639 (50.8%)	1770 (48.9%)		1716 (51.7%)	855 (51.5%)	861 (51.9%)	
≥80	398 (5.8%)	171 (5.3%)	227 (6.3%)		213 (6.4%)	105 (6.3%)	108 (6.5%)	
Sex[d]				0.11				0.43
Male	4387 (64.1%)	2098 (65%)	2289 (63.2%)		2100 (63.3%)	1061 (64%)	1039 (62.6%)	
Female	2461 (35.9%)	1128 (35%)	1333 (36.8%)		1218 (36.7%)	598 (36%)	620 (37.4%)	
Race[d]				0.12				0.99
White	4512 (65.9%)	2119 (65.7%)	2393 (66.1%)		2174 (65.5%)	1083 (65.3%)	1091 (65.8%)	
Black	828 (12.1%)	364 (11.3%)	464 (12.8%)		426 (12.8%)	213 (12.8%)	213 (12.8%)	
Hispanic	1281 (18.7%)	632 (19.6%)	649 (17.9%)		609 (18.4%)	306 (18.4%)	303 (18.3%)	
Asian	78 (1.1%)	42 (1.3%)	36 (1%)		38 (1.1%)	20 (1.2%)	18 (1.1%)	
Other	149 (2.2%)	69 (2.1%)	80 (2.2%)		71 (2.1%)	37 (2.2%)	34 (2%)	
Weight	128.5(121.0, 141.3)	128.0 (121.0, 140.0)	128.9 (121.0, 142.4)	0.04	128.4 (120.9, 141.1)	128.5 (121.0, 140.8)	128.0 (120.9, 141.2)	0.91
≤120 kg	1477 (21.6%)	697 (21.6%)	780 (21.5%)	0.94	734 (22.1%)	365 (22%)	369 (22.2%)	0.87
>120 kg	5371 (78.4%)	2529 (78.4%)	2842 (78.5%)		2584 (77.9%)	1294 (78%)	1290 (77.8%)	
BMI	42.1 (39.4, 46.2)	41.9 (39.1, 45.8)	42.3 (39.6, 46.5)	<0.001	42.1 (39.5, 46.1)	42.1 (39.5, 46.0)	42.1 (39.4, 46.1)	0.56
25–29.9 kg/m^2	3 (0%)	2 (0.1%)	1 (0%)	0.009	2 (0.1%)	1 (0.1%)	1 (0.1%)	1
30–34.9 kg/m^2	345 (5%)	178 (5.5%)	167 (4.6%)		165 (5%)	84 (5.1%)	81 (4.9%)	
35–39.9 kg/m^2	1585 (23.1%)	787 (24.4%)	798 (22%)		773 (23.3%)	388 (23.4%)	385 (23.2%)	
40–44.9 kg/m^2	2826 (41.3%)	1331 (41.3%)	1495 (41.3%)		1383 (41.7%)	693 (41.8%)	690 (41.6%)	
≥45 kg/m^2	2089 (30.5%)	928 (28.8%)	1161 (32.1%)		995 (30%)	493 (29.7%)	502 (30.3%)	
Smoking[d]				0.001				0.97
Current	398 (5.8%)	178 (5.5%)	220 (6.1%)		182 (5.5%)	89 (5.4%)	93 (5.6%)	
Former	2541 (37.1%)	1151 (35.7%)	1390 (38.4%)		1227 (37%)	609 (36.7%)	618 (37.3%)	
Never	3434 (50.1%)	1696 (52.6%)	1738 (48%)		1700 (51.2%)	855 (51.5%)	845 (50.9%)	
Unknown	475 (6.9%)	201 (6.2%)	274 (7.6%)		209 (6.3%)	106 (6.4%)	103 (6.2%)	
Comorbidities								
MI[b,d]	804 (11.7%)	354 (11%)	450 (12.4%)	0.06	445 (13.4%)	220 (13.3%)	225 (13.6%)	0.80
CHF[b,d]	2619 (38.2%)	1137 (35.2%)	1482 (40.9%)	<0.001	1561 (47%)	781 (47.1%)	780 (47%)	0.97
Hypertension[d]	4307 (62.9%)	1241 (38.5%)	3066 (84.6%)	<0.001	2291 (69%)	1138 (68.6%)	1153 (69.5%)	0.57
Diabetes[d]	3574 (52.2%)	1563 (48.5%)	2011 (55.5%)	<0.001	1798 (54.2%)	899 (54.2%)	899 (54.2%)	1
Liver disease[d]	455 (6.6%)	246 (7.6%)	209 (5.8%)	0.002	242 (7.3%)	124 (7.5%)	118 (7.1%)	0.69
Renal disease[d]	2142 (31.3%)	816 (25.3%)	1326 (36.6%)	<0.001	1249 (37.6%)	616 (37.1%)	633 (38.2%)	0.54
PUD[b,d]	58 (0.8%)	20 (0.6%)	38 (1%)	0.05	31 (0.9%)	16 (1%)	15 (0.9%)	0.86
PVD[b,d]	1919 (28%)	1007 (31.2%)	912 (25.2%)	<0.001	1165 (35.1%)	586 (35.3%)	579 (34.9%)	0.80
Alcohol use[d]	189 (2.8%)	137 (4.2%)	52 (1.4%)	<0.001	98 (3%)	51 (3.1%)	47 (2.8%)	0.68
History of stroke/TIA/SE[b,d]	273 (4%)	135 (4.2%)	138 (3.8%)	0.43	150 (4.5%)	74 (4.5%)	76 (4.6%)	0.87
History of bleeding[d]	623 (9.1%)	345 (10.7%)	278 (7.7%)	<0.001	368 (11.1%)	189 (11.4%)	179 (10.8%)	0.58
GIB[b]	302 (4.4%)	178 (5.5%)	124 (3.4%)	<0.001	175 (5.3%)	96 (5.8%)	79 (4.8%)	0.19
IC bleeding[b]	20 (0.3%)	5 (0.2%)	15 (0.4%)	0.05	15 (0.5%)	5 (0.3%)	10 (0.6%)	0.20
Other bleeding	309 (4.5%)	162 (5%)	147 (4.1%)	0.06	183 (5.5%)	87 (5.2%)	96 (5.8%)	0.49
CCI[b,c,d]	2 (1, 3)	2 (1, 3)	2 (1, 3)	<0.001	2 (1, 4)	2 (1, 4)	2 (1, 4)	0.82
0–1	2578 (37.6%)	1284 (39.8%)	1294 (35.7%)	<0.001	1040 (31.3%)	518 (31.2%)	522 (31.5%)	0.79
2–3	2756 (40.2%)	1291 (40%)	1465 (40.4%)		1326 (40%)	672 (40.5%)	654 (39.4%)	
≥4	1486 (21.7%)	638 (19.8%)	848 (23.4%)		952 (28.7%)	469 (28.3%)	483 (29.1%)	
Medications								
Antiplatelet[d]	1970 (28.8%)	1055 (32.7%)	915 (25.3%)	<0.001		516 (31.1%)	491 (29.6%)	0.35

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Table 1. (continued)

	Unmatched cohort				Matched cohort			
	All patients (*n*=6848)	Dabigatran (*n*= 3226)	Warfarin (*n*= 3622)	*P* value	All patients (*n*=3318)	Dabigatran (*n*= 1659)	Warfarin (*n*= 1659)	*P* value
					1007 (30.3%)			
Antiarrhythmics[d]	512 (7.5%)	217 (6.7%)	295 (8.1%)	0.03	249 (7.5%)	124 (7.5%)	125 (7.5%)	0.95
Beta blocker[d]	4701 (68.6%)	2060 (63.9%)	2641 (72.9%)	<0.001	2267 (68.3%)	1133 (68.3%)	1134 (68.4%)	0.97
CCB[b,d]	2752 (40.2%)	1180 (36.6%)	1572 (43.4%)	<0.001	1303 (39.3%)	647 (39%)	656 (39.5%)	0.75
Diuretics[d]	4508 (65.8%)	1939 (60.1%)	2569 (70.9%)	<0.001	2250 (67.8%)	1120 (67.5%)	1130 (68.1%)	0.71
ACE-I/ARB[b,d]	4862 (71%)	2167 (67.2%)	2695 (74.4%)	<0.001	2388 (72%)	1194 (72%)	1194 (72%)	1
Antidiabetic[d]	2978 (43.5%)	1266 (39.2%)	1712 (47.3%)	<0.001	1473 (44.4%)	734 (44.2%)	739 (44.5%)	0.86
Statin[d]	4726 (69%)	2200 (68.2%)	2526 (69.7%)	0.17	2354 (70.9%)	1177 (70.9%)	1177 (70.9%)	1
PPI[b,d]	1389 (20.3%)	649 (20.1%)	740 (20.4%)	0.75	732 (22.1%)	370 (22.3%)	362 (21.8%)	0.74
Prior warfarin	4458 (65.1%)	836 (25.9%)	3622 (100%)	<0.001	2121 (63.9%)	462 (27.8%)	1659 (100%)	<0.001
CHA_2DS_2-VASc[d]	3 (2, 4)	2 (1, 4)	3 (2, 4)	<0.001	3 (2, 5)	3 (2, 4)	3 (2, 5)	0.49
0–1	1451 (21.2%)	923 (28.6%)	528 (14.6%)	<0.001	614 (18.5%)	305 (18.4%)	309 (18.6%)	0.73
2–3	2916 (42.6%)	1311 (40.6%)	1605 (44.3%)		1226 (36.9%)	624 (37.6%)	602 (36.3%)	
≥4	2481 (36.2%)	992 (30.8%)	1489 (41.1%)		1478 (44.5%)	730 (44%)	748 (45.1%)	
HAS-BLED[d]	2 (1, 2)	2 (1, 2)	2 (1, 2)	0.88	2 (1, 3)	2 (1, 3)	2 (1, 3)	0.38
<3	5230 (76.4%)	2475 (76.7%)	2755 (76.1%)	0.52	2356 (71%)	1181 (71.2%)	1175 (70.8%)	0.82
≥3	1618 (23.6%)	751 (23.3%)	867 (23.9%)		962 (29%)	478 (28.8%)	484 (29.2%)	

[a]*Data are presented as absolute number (%) or median (interquartile range)*
[b]*Abbreviations: BMI body mass index; MI myocardial infarction; CHF congestive heart failure; PUD peptic ulcer disease; PVD peripheral vascular disease; TIA transient ischemic attack; SE systemic embolism; GIB gastrointestinal bleeding; IC intracranial; CCI Charlson comorbidity index; CCB calcium channel blocker; ACE-I angiotensin-converting enzyme inhibitor; ARB angiotensin receptor blocker; PPI proton pump inhibitor*
[c]*Missing data: CCI (n=28)*
[d]*Included in propensity score matching*

quantify the balance between the variables in the two comparison groups resulting from PSM. A difference of 0.1 or less was considered as an adequate balance between the two groups[32].

A Cox regression analysis comparing dabigatran to warfarin users was performed to estimate the hazards ratio (HR) for each outcome with anticoagulant drug exposure (dabigatran or warfarin) as the exposure variable. Kaplan-Meier (KM) curves were also constructed for each outcome. Time-to-event analyses were selected given the anticipated variability in follow-up duration. Additional subgroup analysis was performed for exploratory purposes with anticoagulant drug exposure as the exposure variable for patients with a BMI ≥45 kg/m^2 and those with a BMI <45kg/m^2 within the matched cohort. A *P* value <0.05 was considered statistically significant. All statistical analyses were conducted in SAS 9.4 (SAS Institute Inc., Cary, NC).

Table 2 Cox Proportional Hazard Ratio of Each Outcome for Dabigatran Users Compared to Warfarin Users

Outcomes	Adjusted HR (95% CI)[a]	*P* value
Composite thromboembolism outcome	0.71 (0.56–0.91)	0.007
Transient ischemic attack	0.11 (0.04–0.28)	< 0.001
Ischemic stroke	0.84 (0.64–1.11)	0.22
Systemic embolism	1.25 (0.49–3.17)	0.64
Composite bleeding outcome	1.24 (1.07–1.42)	0.003
Gastrointestinal bleeding	1.59 (1.33–1.91)	< 0.001
Intracranial bleeding	0.77 (0.50–1.18)	0.23
Other bleeding	0.93 (0.78–1.12)	0.46
Death	0.57 (0.45–0.71)	< 0.001

[a]*Abbreviations: HR hazard ratio; CI confidence interval*

RESULTS

Cohort Characteristics

A total of 7034 patients who received either a DOAC or warfarin were identified. After excluding apixaban (*n*=119) and rivaroxaban (*n*=67) users, 6848 patients were included in our analysis.

Among the 6848 patients, there were 3226 (47.1%) dabigatran users and 3622 (52.9%) warfarin users. The median age was 66 (IQR: 59–72) years and there were 2461 (35.9%) female patients (Table 1). After PSM, 1659 dabigatran users and 1659 warfarin users were ultimately included in the 1:1 matched cohort. Standardized differences of all 28 variables after matching were within 0.1 (Appendix Table 6).

Within the matched cohort of 3318 patients, the median age of patients was 67 (IQR: 60–73) years and there were 1218 (36.7%) female patients. The median BMI was 42.1 (IQR: 39.5–46.1) kg/m^2 and the median weight was 128.4 (IQR: 120.9–141.1) kg. A total of 2378 (71.7%) patients had a BMI ≥40kg/m^2 and 2584 (77.9%) patients had a weight >120kg. The median CHA_2DS_2-VASc score was 3 (IQR: 2–5), and the median HAS-BLED score was 2 (IQR: 1–3). Among the 1659 dabigatran users, 462 (27.8%) patients were previously on warfarin (Table 1). Patients in the matched cohort had a greater prevalence of congestive heart failure, hypertension, renal disease, peripheral vascular disease, and history of bleeding compared to the unmatched cohort. Matched cohort patients also had a greater number of patients with CCI ≥4, CHA_2DS_2-VASc ≥4, and HAS-BLED ≥3 (Table 1).

Outcomes

The median follow-up period was 2.9 (IQR: 1.4–5.1) years. A total of 342 composite thromboembolism outcomes and 1279 composite bleeding outcomes occurred over the entire study period. The total number of events for secondary outcomes was as follows: transient ischemic attack, *n*= 62; ischemic stroke, *n*= 287; systemic embolism, *n*= 23; gastrointestinal bleeding, *n*= 724; intracranial bleeding, *n*= 114; other bleeding, *n*= 728; and all-cause mortality *n*= 712 (Appendix Table 7).

Compared to warfarin users, dabigatran users had a HR of 0.71 (95% confidence interval (CI): 0.56–0.91) for composite thromboembolism and a HR of 1.24 (95%CI: 1.07–1.42) for composite bleeding (Table 2). The KM curves are shown in Figure 1. The HRs for secondary outcomes were as followed when comparing dabigatran users to warfarin users: transient ischemic attack, 0.11 (95% CI: 0.04–0.28); ischemic stroke, 0.84 (95% CI: 0.64–1.11); systemic embolism, 1.25 (95% CI: 0.49–3.17); gastrointestinal bleeding, 1.59 (95% CI: 1.33–1.91); intracranial bleeding, 0.77 (95% CI: 0.50–1.18); other bleeding, 0.93 (95% CI: 0.78–1.12); and all-cause mortality 0.57 (95% CI: 0.45–0.71) (Table 2 and Fig. 1).

Subgroup analysis showed similar results among the 2323 (70%) patients with a BMI <45 kg/m^2 whereas among the 995 (30%) patients with a BMI ≥45 kg/m^2, associations with reduced risk of composite thromboembolism, increased risk of composite bleeding, and reduced risk of mortality when comparing dabigatran to warfarin were no longer statistically significant (Table 3).

DISCUSSION

Among AF patients with severe obesity in a real-world clinical setting, dabigatran was associated with a decreased risk of thromboembolism and increased risk of bleeding when compared to warfarin. The decreased risk of thromboembolism was primarily driven by a reduction in transient ischemic attack while the increased risk of bleeding was driven by an increase in gastrointestinal bleeding. Compared to warfarin, dabigatran was also associated with a reduction in mortality. Similar observations were seen among the subgroup with a BMI <45 kg/m^2, but the associations were no longer significant among those with a BMI ≥45 kg/m^2.

Our findings contrast with existing studies regarding dabigatran use in AF patients with severe obesity. Deitlzweig et al. found similar rates of stroke/systemic embolism and major bleeding and Briasoulis et al. also reported similar rates for ischemic stroke but lower rates of major bleeding[17,18]. There are a couple of potential explanations. Differences in effectiveness outcome may be explained by differences in the outcome definition as our study included transient ischemic attack within the composite outcomes. When examining ischemic stroke or systemic embolism alone, we found similar rates between dabigatran and warfarin users also. Another explanation, particularly with safety outcomes, may be due to differences in the population cohort, where our population had a different distribution of sex and race/ethnicity. In addition, our population had lower rates of proton pump inhibitor use and higher rates of patients with kidney disease, both of which could have contributed to increased bleeding[17,18].

Overall, our observations of dabigatran's effectiveness and safety among the less described severely obese AF population are consistent with existing reports from the general AF population. In the original Randomized Evaluation of Long-term Anticoagulation Therapy (RE-LY) trial, dabigatran 150mg was associated with reduced rates of stroke and systemic embolism while dabigatran 110mg was associated with similar rates of stroke and systemic embolism when compared to warfarin[5]. Real-world data have since reported dabigatran to be either similar or slightly better in effectiveness for ischemic strokes when compared to warfarin[33–38]. Our study showed a 29% reduction in composite thromboembolism with dabigatran use, primarily driven by a reduction in the transient ischemic attack. Our results add to the growing literature suggesting that DOAC is effective among severely obese patients[13,14,16,20].

The increased risk of bleeding we observed in our cohort was primarily driven by an increase in gastrointestinal bleeding, which was described in the original RE-LY trial[5]. The association between dabigatran and increased bleeding, particularly gastrointestinal bleeding, has since been reported in other real-world analyses[33–36,39]. Reductions in intracranial bleeding have also been reported, though we only observed a trend towards reduced intracranial bleeding[5,33–37,39]. The lack of significance may have been due to a lack of power to detect less frequent outcomes. The observation of increased bleeding in addition to the reduction in thromboembolism argues against the theoretical concern of underdosing of DOACs, or dabigatran in particular, among the severely obese[10].

We observed a significant reduction in mortality among those who received dabigatran. While the RE-LY study only observed a borderline association with reduced mortality,

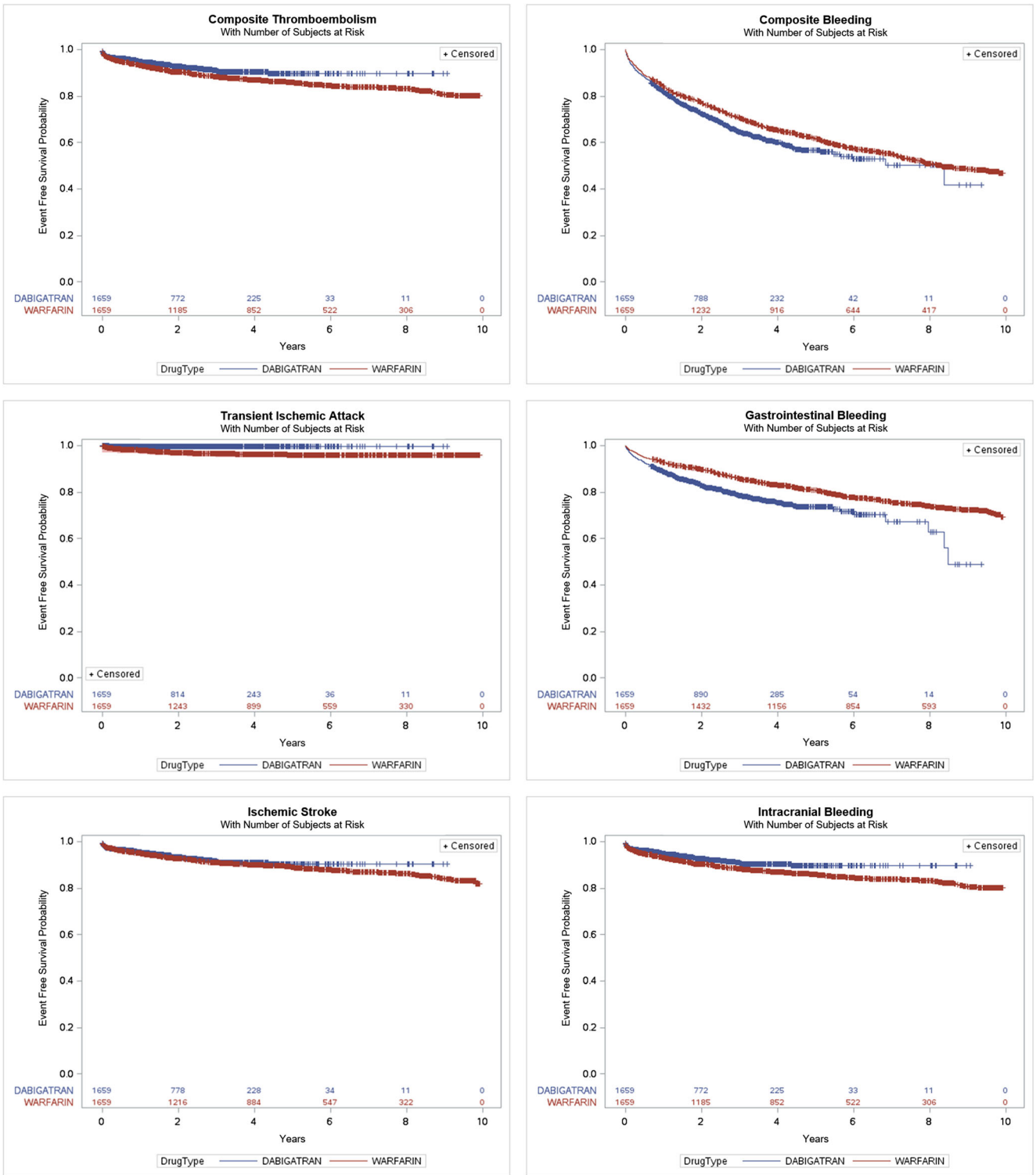

Fig. 1 Kaplan-Meier curves for effectiveness and safety outcomes and mortality.

benefits of dabigatran with regards to mortality have been reported in real-world observational studies ranging from a mortality reduction of 14–55% [5,33,35,36,38,40]. We believe the reduction in mortality was likely driven by improved outcomes with cardiovascular diseases and thromboembolisms such as those with myocardial infarction and pulmonary embolism in addition to the effectiveness outcomes in our study[38,41]. Notably, our study had a longer follow-up period compared to most existing real-world dabigatran studies and likely allowed for better capturing of longer term outcomes such as mortality[34,36,37,40].

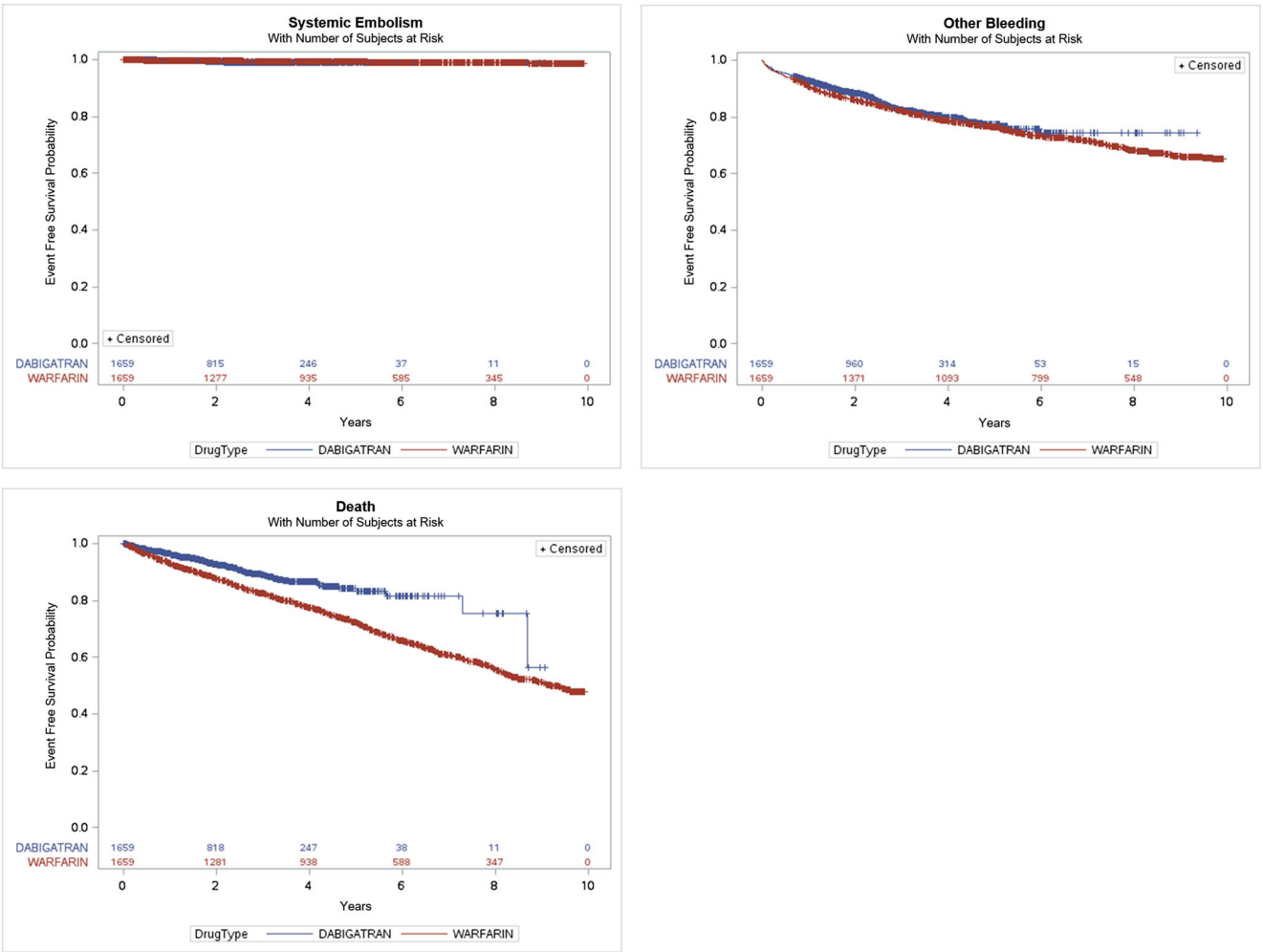

Fig. 1 continued.

Within our subgroup analysis, we observed no associations across both composite outcomes and mortality among patients with a BMI ≥45kg/m^2. This observation may suggest that dabigatran is less effective in this subgroup, though subgroup results should also be interpreted with caution as it is known that subgroup analysis is prone to both false positive and negative findings[42]. We believe the lack of associations observed in our analysis was primarily due to limited power given only 30% of our cohort were included in this subgroup.

Table 3 Subgroup Analysis by BMI ≥45 kg/m^2 and <45 kg/m^2

Outcomes	Adjusted HR (95% CI)[a]	*P* value
BMI <45 kg/m^2[2a]		
Composite thromboembolism outcome	0.62 (0.43–0.89)	0.01
Composite bleeding outcome	1.24 (1.02–1.51)	0.03
Mortality	0.61 (0.45–0.84)	0.003
BMI ≥45 kg/m^2[2a]		
Composite thromboembolism outcome	1.00 (0.45–2.23)	1
Composite bleeding outcome	1.31 (0.83–2.08)	0.25
Mortality	0.63 (0.28–1.38)	0.24

[a]*Abbreviations: BMI body mass index; HR hazard ratio; CI confidence interval*

Our findings should also be considered exploratory as matching was not reperformed within the subgroups. It does not appear that dabigatran was any less effective among patients with a BMI ≥45kg/m^2.

Our study has several strengths and adds to existing literature. We had a racially/ethnically diverse population with a good representation of both sexes. Our integrated health system with a single electronic health record system allowed for more granular clinical detail collection and likely allowed for fewer misclassifications. While we had to restrict our analysis to dabigatran only given the lack of patients on apixaban or rivaroxaban reflective of our formulary, the knowledge gap regarding dabigatran among DOACs is also higher[19,20,22]. The implications of our finding are of relevance as dabigatran will soon become the first generic DOAC.

Our study has several potential limitations that may confound the interpretation of our findings. With regards to data, we did not have information on the type and duration of AF. Over-the-counter medications, particularly aspirin and other non-steroidal anti-inflammatory drugs, may have also been incompletely captured. We did not have details on dabigatran dosage or adequate dosing in relationship to patients' kidney function, though an extended follow-up of the original RE-LY

trial showed no significant differences among those receiving dabigatran 150mg and 110mg[43]. Our study was based on prescription and fill data only and an "intention-to-treat" analysis as we did not assess adherence or changes to medications, nor the time warfarin users were in therapeutic INR range. We were unable to account for changes in patient characteristics over time and did not have outcome data on other cardiovascular or thromboembolic diseases.

With regards to analysis, roughly a quarter of our dabigatran users were previously on warfarin, which likely introduced some heterogeneity in the dabigatran group give these patients may have different underlying characteristics including likely longer periods of AF. We recognize that one of our thromboembolism outcomes, transient ischemic attack, is a diagnosis that may be prone to subjectivity, and the accuracy of outcomes by ICD code alone may be limited. We also did not account for competing risks with death, though the associations we observed remained significant and death was studied as an outcome in addition to effectiveness and safety. While larger than most severe obesity studies to date, our study had a smaller cohort compared to most real-world dabigatran studies in the general AF population and limited our ability to explore subgroups and our current subgroup analysis should be considered exploratory[14,15,20,33–37]. Finally, there may be unaccounted for biases and patient characteristics despite a well-balanced cohort after PSM.

In conclusion, dabigatran, when compared to warfarin, was effective in reducing the risk of thromboembolism and mortality but was associated with an increased risk of bleeding among AF patients with severe obesity. These observations are generally comparable to those seen among AF patients who are non-severely obese and adds to the literature suggesting that dabigatran may be a reasonable option for AF patients with severe obesity. Larger prospective studies among the severely obese AF population, particularly those with a BMI ≥45kg/m^2, are needed to further elucidate the drugs' effectiveness and safety in this population.

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Declarations:

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