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Pre-hospital use of direct oral anticoagulants agents is associated with a lower risk of major bleeding events in critically ill patients: A single academic center experience

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ABSTRACT

Background: The last decade has witnessed significant advancements in direct oral anticoagulants (DOACs), transforming the landscape of anticoagulation therapy. With the uptrend in DOACs use, critical care physicians are encountering more patients with pre-hospital DOACs prescription. Safety and real world outcomes-related data on DOACs use in critically ill patients are scarce.
Objective: We assess the risk of major bleeding (MB) events and patient-centered outcomes with pre-hospital use of direct oral anticoagulant agents (DOACs) compared to warfarin therapy.
Methods: Observational study in a single large academic center from January 1st, 2012, through May 4th, 2018. We included adult critically ill patients with warfarin or one of the DOACs, as active medications at the time of hospital admission. The primary outcome was major bleeding (MB), based on the ISTH criteria
Results: 99,481 patients were screened; 558 and 3037 patients were included in the final analysis for the DOAC and warfarin groups, respectively. Multivariable analysis showed that the pre-hospital use of DOACs was associated with lower odds for major bleeding events, GI bleeding, need for endoscopic intervention, hemorrhagic shock, any blood transfusion; but higher odds of intracranial bleeding, as compared to warfarin use. There was no difference in hospital length of stay or ICU-free days.
Conclusions: Pre-hospital use of DOACs among critically ill patients is associated with lower major bleeding events, GI bleeding, need for endoscopic intervention, and blood transfusion but a higher risk for intracranial bleeding.

Introduction

The last decade has witnessed significant advancements in direct oral anticoagulants (DOACs), transforming the landscape of anticoagulation therapy. Dabigatran was the first DOAC to gain approval in 2011 by the Food and Drug Administration (FDA).[1] Apixaban, rivaroxaban, edoxaban and betrixaban soon followed. Randomized controlled trials have demonstrated the noninferiority of DOACs to warfarin for stroke prevention in nonvalvular atrial fibrillation and treatment of venous thromboembolism.[1–5] Based on the robust evidence, clinical practice guidelines strongly recommend using DOACs over warfarin for various cardiovascular indications.[6–8]

Due to the predictable pharmacokinetics and ease of use, trends have been toward increased use of DOACs than warfarin. Using the United States Medicare beneficiaries database, Wheelock et al. reported that DOAC prescriptions increased from 14.1% in 2013 to 57.3 % in 2018 for all anticoagulant prescriptions.[9] Similarly, one study from the United Kingdom reported an increase in the prescription of DOACs from 9% in 2014 to 74% in 2019.[10] Another study reported an uptrend in DOACs prescriptions from 16.5 % in 2015 to 61.8% in 2019 of all oral

Abbreviation: DOAC, direct oral anticoagulants; LOS, length of stay; ICU, intensive care unit; VKA, vitamin k antagonist; AF, atrial fibrillation; LMWH, low molecular weight heparin; VTE, venous thromboembolism; EMR, electronic medical record; MAP, mean arterial pressure.

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anticoagulant prescriptions.[11]

With the uptrend in DOACs use, critical care physicians are encountering more patients with pre-hospital DOACs prescription. In our recently published single-center experience, the number of intensive care unit admissions with pre-hospital DOAC use went up from 8 in 2012 to 177 in 2017.[12] Unfortunately, critically ill patients were excluded from randomized controlled trials and most observational studies.[13] Therefore, data on how pre-hospital DOACs use impacts patient-centered outcomes in critically ill patients is lacking.

In this study, we aimed to evaluate the impact of pre-hospital DOACs use compared to pre-hospital warfarin therapy on patient-centered outcomes during critical illness.

Methods

We performed a retrospective chart review exploring the prescribing practices, morbidity, and clinical outcomes with pre-hospital DOAC and warfarin therapy for patients admitted to the ICU at Mayo Clinic, Rochester, MN, USA, from January 2012 through May 2018. This timeline was selected due to the more prevalent use of DOACs since their introduction in 2012. The study was approved by the Mayo Clinic Institutional Review Board (IRB #18-011674, approved on 12/12/2019 under the IRB request titled "*Safety of direct oral anticoagulant (DOAC) use in critically Ill patients*"). Due to the design of the study, the informed consent was waived. However, the patients that refused the Minnesota research authorization were excluded from this study. The entirety of the research methodology was performed per the ethical standards of the Mayo Clinic institutional review board committee (based on the Helsinki Declaration of 1975). Preliminary results were presented at the American Thoracic Society annual conference, Washington D.C., USA; May 2023.[14]

Inclusion criteria included all adult (≥18-year-old) patients admitted to either medical or surgical ICUs with a DOAC (apixaban, rivaroxaban, dabigatran, or edoxaban) or warfarin listed as one of the active medications in the medical record at the time of index hospital admission. Patients who were prescribed either one of the DOACs or warfarin as an outpatient but were not taking it at the time of hospital admission were also excluded. This was confirmed through medication reconciliation performed by a clinical pharmacist upon admission to the ICU (standard practice at ICU admission). Postoperative patients (for elective surgeries) were excluded since they would have the systemic anticoagulation held prior to surgery and in the immediate postoperative period. The data were abstracted using the Mayo Clinic ICU DataMart. The details of Acute Care Datamart and the standardized methods of data abstraction standardized practices are described elsewhere.[15] Systematic patient selection based on the inclusion and exclusion criteria is detailed below in the consort diagram (Fig. 1).

The primary objective of our study was to assess the risk of major bleeding (MB) events in critically ill patients with pre-hospital use of direct oral anticoagulant agents (DOACs) compared to warfarin therapy. Major bleeding was defined as fatal bleeding, bleeding involving a critical organ (i.e., intraspinal, intracerebral, intraocular, retroperitoneal, intramuscular), requires transfusion of ≥ 2 units of blood or causes at least a 2 g/dL drop in hemoglobin level.[16] Our secondary objective was to describe the clinical patient-centered outcomes, including ICU-free days, and hospital length of stay (LOS). We also explored resource utilization needs, such as interventional radiology-guided embolization, endoscopic intervention, and blood transfusion for management of bleeding. Our outcomes of interest included major bleeding events (MB), hospital and ICU LOS, ICU mortality, bleeding event details (including the site of bleeding and management strategies including blood transfusions and endoscopic procedures). Two authors (AW and SL) independently and manually confirmed the details of major bleeding and management strategies required.

Statistical analysis

Categorical variables were summarized as frequency (percentage). Where appropriate, continuous variables were presented as mean ± standard deviation or median with interquartile range (IQR). Fischer exact test or $\chi 2$ test was used to compare the categorical variables among the groups. Normally distributed continuous variables were analyzed using a *t-test*, while non-parametric data were analyzed using the Wilcoxon rank sum test. Measurement of outcomes was initially done by

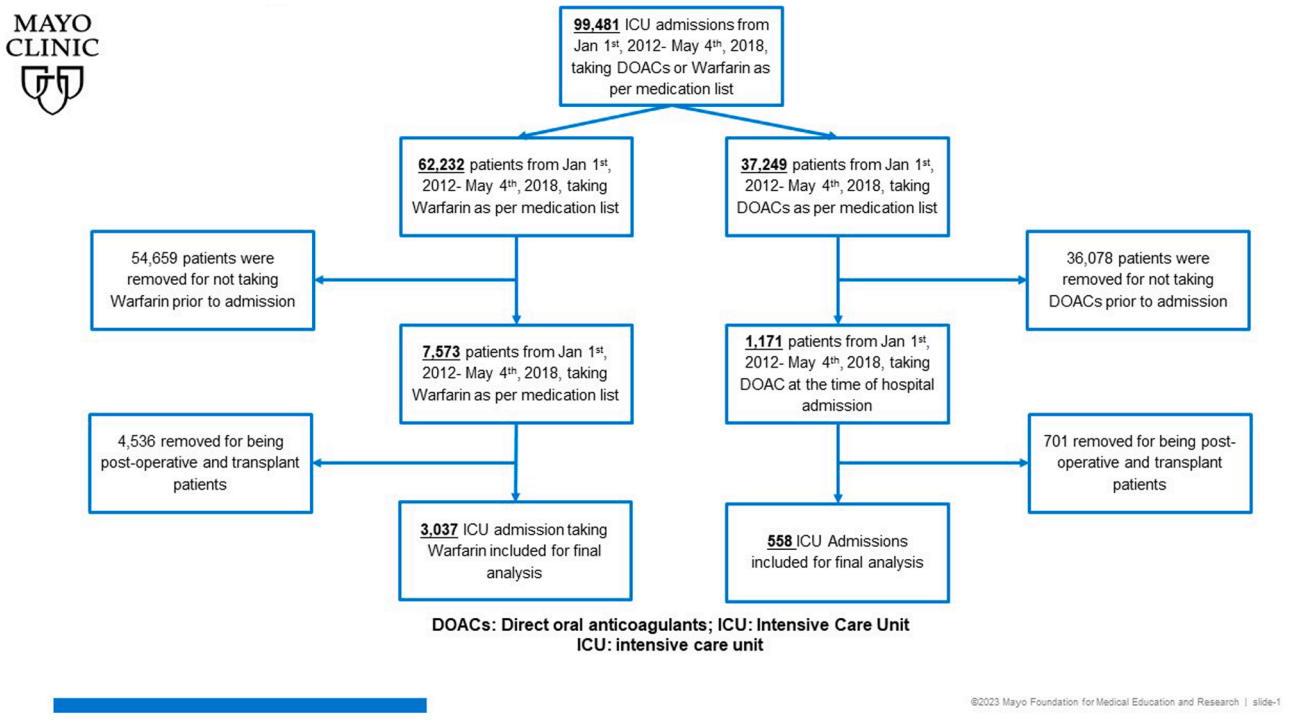

Fig. 1. Consort diagram for patient selection.

comparing the DOACs separately. A *P-value* of < 0.05 was considered statistically significant. Multivariable analysis was done after adjusting for age, sex, race, BMI, comorbidities (CAD, CHF, stroke, chronic pulmonary diseases, COPD, asthma, pulmonary circulatory diseases, history of VTE, diabetes mellitus, chronic kidney disease, chronic liver disease and cirrhosis, peptic ulcer disease, any type of cancer, peripheral vascular disease), and Charlson score.

All statistical analyses were performed using JMP statistical software, version 14.0 (SAS Institute Inc., Cary, NC).

Results

During the study period, 99,481 adult patients required ICU admission and had a pre-hospital prescription of either warfarin or one of the DOACs were identified. Of these, 62,232 had warfarin, whereas 37,249 patients had at least one DOAC on their home medication list. After the application of our exclusion criteria, 36,078 patients were removed for not taking DOACs before the index hospital admission, and 701 patients were excluded for being postoperative or post-transplant. Similarly, 54,659 patients were removed for not taking warfarin before the index hospital admission, and 4536 patients were excluded for being post-operative or post-transplant. Finally, 3037 patients with pre-hospital warfarin and 558 patients with pre-hospital DOAC use were included in the final analysis (Fig. 1).

The frequency of patients on DOAC increased over the years of admission, from 2% in 2012 to 31.8% in 2018 (Fig. 2). Among the patients with pre-hospital DOAC therapy (N=558), 45.9% (N=256) had their DOAC discontinued on admission without transition to an alternative anticoagulation agent, 34.2% (N=191) of patients had their DOACs continued beyond 24 hours of ICU admission and 19.9% (N=111) had the DOAC therapy transitioned to an alternative anticoagulant. Similarly, for the patients with prehospital warfarin therapy (N=3037), 46.3% (N=1406) had warfarin discontinued on admission without transition to an alternative anticoagulation agent, 11.3% (N=343) of patients had warfarin continued beyond 24 hours of ICU admission and 42.4% (N=1288) had the warfarin therapy transitioned to an alternative anticoagulant. With regards to the type of DOACs used, the commonest agent was Apixaban (N=283, 51%), followed by Rivaroxaban (N=225, 40.3%), followed by Dabigatran (N=49, 8.7%) and only 1 patient with Edoxaban.

Baseline patient characteristics of the 2 groups are summarized in Table 1. The patients on the DOAC therapy were younger (69 [59–78] years vs. 72 [62–81], p-value <0.001), had a lower APACHE III score at 24 hours (64[51–78] vs. 67[53–81], p-value 0.007) and a lower Charlson's comorbidity score (4[5–11] vs. 7[5–9], p-value <0.001). Diabetes mellitus (N=1313, 36.5%), any cancer (N=1239, 34.5%), congestive heart failure (CHF) (N=1238, 34.4%), and chronic pulmonary disease (including COPD, asthma, pulmonary hypertension, interstitial lung diseases) (N=1194, 33.2%) were the most common comorbidities. The DOAC group had a higher proportion of patients with cancer (52.2% vs. 31.2%, p-value <0.001). In contrast, the warfarin group had a higher proportion of patients with chronic kidney disease (31.9% vs. 24.9%, p-value <0.001), anemia at the time of admission (11.9% vs. 3.9%, p-value <0.001), peripheral vascular disease (9.1% vs. 6.3%, p-value <0.001), dementia (6.9% vs. 4.1%, p value=0.013) and cirrhosis (4.8% vs. 2.9%, p value=0.04). Overall, the most common indication for anticoagulation was atrial fibrillation (71.7%), followed by a history of DVT (46.2%) and PE (33.4%).

Univariate analysis showed an overall lower major bleeding event rate of 71 (12.7%) vs. 715 (23.5%), p-value <0.01, in the DOAC as compared to warfarin groups. Similarly, the DOAC group also had a shorter ICU LOS (1.40 [0.82–2.32] days vs. 1.49 [0.89–2.74] days, p-value <0.01). DOAC group had lesser GI bleeding events (16 (2.87%) vs. 407 (13.40%), p-value <0.01) but more intracranial bleeding events (6 (1.08%) vs. 5 (0.16%), p-value <0.01), as compared to warfarin group. The two groups had no statistically significant difference in invasive interventions required to control bleeding. Patients with pre-hospital DOAC use suffered lesser episodes of hemorrhagic shock 4 (0.72%) vs. 77 (2.54%), p-value <0.01, and the number of blood product units transfused was higher in the warfarin group, 1111 (36.58%) vs. 163 (29.21%), p-value <0.01 than in the DOAC group (Table 2).

Multivariable analysis showed that the DOAC group had overall

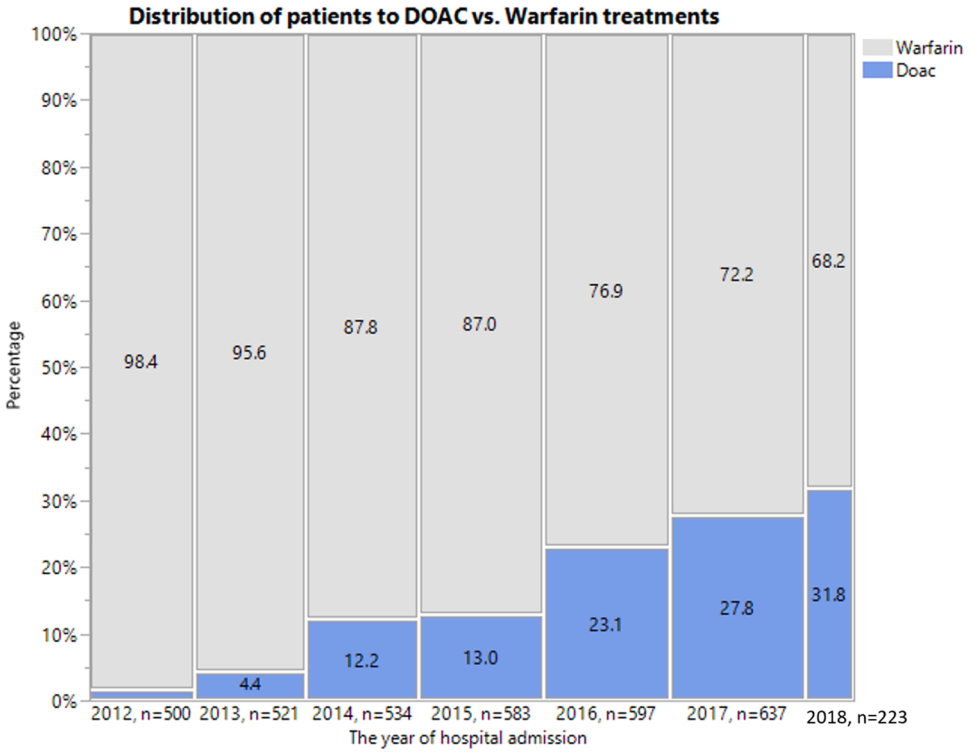

Fig. 2. Distribtuion of patients to DOAC and Warfarin treatment groups over admission years.

Table 1
Baseline characteristics.

Baseline Characteristics	Total ($N = 3595$)	DOAC Group ($n = 558$)	Warfarin Group ($n = 3037$)	p value
Age (years)	72 (61–80)	69 (59–78)	72 (62–81)	< 0.001 *
Sex				0.737
Male	2072 (57.6)	318 (57)	1754 (57.8)	
Female	1523 (42.4)	240 (43)	1283 (42.2)	
BMI (Kg/m^2)	29.6 (24.9–36.1)	29.3 (25–35.6)	29.7 (24.9–36.2)	0.239
Race				0.807
Black	54 (1.5)	10 (1.8)	44 (1.4)	
White	3399 (94.5)	527 (94.4)	2872 (94.6)	
Other/Unknown	142 (4.0)	21 (3.8)	121 (4.0)	
Admission severity of illness				
SAS				
1 hour (points)	26 (17–37)	25 (17–36)	26 (16–37)	0.390
24 hours (points)	49 (38–63)	47 (37–59)	49 (38–63)	0.006 *
APACHE III				
1 hour (points)	43 (31–55)	42 (31–54)	43 (31–55)	0.494
24 hours (points)	66 (53–80)	64 (51–78)	67 (53–81)	0.007 *
SOFA Day 1 (points)	4 (2–7)	4 (2–6)	4 (2–7)	0.010 *
Charlson's Comorbidity Score (points)	7 (5–10)	4 (5–11)	7 (5–9)	< 0.001 *
Comorbidities[€], N (%)				
Cancer	1239 (34.5)	291 (52.2)	948 (31.2)	< 0.001 *
Diabetes mellitus	1313 (36.5)	189 (33.9)	1124 (37)	0.157
Congestive heart failure	1238 (34.4)	183 (32.8)	1055 (34.7)	0.375
Chronic pulmonary disease	1194 (33.2)	172 (30.8)	1022 (33.7)	0.192
Moderate/severe Chronic kidney disease	1109 (30.8)	139 (24.9)	970 (31.9)	0.001 *
Cerebrovascular accident	707 (19.7)	102 (18.3)	605 (19.9)	0.370
Myocardial infarction	534 (14.9)	58 (10.4)	476 (15.7)	0.001 *
Peptic ulcer disease	217 (6)	41 (7.3)	176 (5.8)	0.157
Anemia at the time of admission	382 (10.6)	22 (3.9)	360 (11.9)	< 0.001 *
Peripheral vascular disease	312 (8.7)	35 (6.3)	277 (9.1)	0.028 *
Connective tissue disease	205 (5.7)	31 (5.6)	174 (5.7)	0.871
Dementia	234 (6.5)	23 (4.1)	211 (6.9)	0.013 *
Liver disease/Cirrhosis	163 (4.5)	16 (2.9)	147 (4.8)	0.040 *
Indication for anticoagulation[€], N (%)				
History of Atrial fibrillation	2576 (71.7)	368 (65.9)	2208 (72.7)	0.001 *
History of deep vein thrombosis	1662 (46.2)	220 (39.4)	1442 (47.5)	< 0.001 *
History of pulmonary embolism	1200 (33.4)	167 (29.9)	1033 (34)	0.060
Acute myocardial infarction	593 (16.5)	31 (5.6)	562 (18.5)	< 0.001 *

Continuous variables are presented as median (IQR); categorical variables are expressed as counts (percent).
* Indicates statistical significance (p-*value* < 0.05).
€ categories are not mutually exclusive.

Table 2
Unadjusted outcomes between DOACs and Warfarin groups.

LOS and Mortality Outcomes	**Pre-hospital DOACs ($n = 558$)**	**Pre-hospital Warfarin ($n = 3037$)**	**Total (N=3595)**	**P value**
Major Bleeding Events	71 (12.72%)	715 (23.54%)	786 (21.86%)	**<0.01**
Hospital Length of Stay (LOS)				
Median [IQR]	5.83 [3.62–9.46]	5.98 [3.79–10.51]	5.97 [3.78–10.30]	0.12
ICU Mortality	34 (6.09%)	166 (5.47%)	200 (5.6%)	0.55
ICU Length of Stay in Days (LOS)				
Median [IQR]	1.40 [0.82–2.32]	1.49 [0.89–2.74]	1.47 [0.88–2.68]	**<0.01**
Bleeding Events				
GI bleeding	16 (2.87%)	407 (13.40%)	423 (11.77%)	**<0.01**
Intra-abdominal bleeding	5 (0.90%)	27 (0.89%)	32 (0.90%)	1.00
Retroperitoneal bleeding	2 (0.36%)	27 (0.89%)	29 (0.81%)	0.30
Pulmonary bleeding	2 (0.36%)	11 (0.36%)	13 (0.36)	1.00
Intracranial bleeding	6 (1.08%)	5 (0.16%)	11 (0.31)	**<0.01**
Hemothorax	3 (0.54%)	7 (0.23%)	10 (0.28%)	0.19
Epidural bleeding	1 (0.18%)	0 (0)	1 (0.03%)	0.15
Spinal bleeding	0 (0)	1 (0.03%)	1 (0.03%)	1.00
Intraocular bleeding	0 (0)	0 (0)	0 (0)	-
Hemorrhagic shock	4 (0.72%)	77 (2.54%)	81 (2.25%)	**<0.01**
Bleeding Management				
Need for embolization	7 (1.25%)	15 (0.49%)	22 (0.61%)	0.06
Need for endoscopy (GI bleeding)	10 (1.79%)	101 (3.33%)	111 (3.09%)	0.06
Need for blood transfusion	163 (29.21%)	1111 (36.58%)	1274 (35.44%)	**<0.01**
Need for massive transfusion	3 (0.54%)	7 (0.23%)	10 (0.28%)	0.19

lower odds of major bleeding events (adjusted odds ratio [aOR] 0.46, 95% CI 0.35 to 0.60, p-value <0.01) and hemorrhagic shock (aOR 0.28, 95% 0.10 to 0.78, p-value <0.01). Specifically, the adjusted odds of GI bleeding (aOR 0.19, 95% CI 0.11 to 0.31, p-value <0.01) were lower in the DOAC group when compared to the warfarin group. However, the risk of intracranial bleeding was higher in the DOAC group (aOR 7.20, 95% CI 1.94 to 26.77, p-value <0.01) when compared to the warfarin group. Other major bleeding sites, such as hemothorax, intra-abdominal, retroperitoneal, and pulmonary bleeding, did not differ significantly between the two groups. With regards to the need for intervention and resource utilization, the DOAC group had a lesser need for any blood product transfusion (aOR 0.66, 95% CI 0.53 to 0.81, p-value <0.01) and lesser need for an endoscopic intervention (aOR 0.48, 95% 0.25 to 0.94, p-value 0.02). There was no difference between the groups regarding hospital LOS and ICU-free days (Table 3 and Fig. 3). Since, ours is a large cancer referral center, we observed a large proportion of patients with cancer in our cohort. We conducted a sensitivity analysis on this subset of patient and the results were similar to the larger cohort (Supplement 1).

Discussion

We described the association between pre-hospital anticoagulant use and clinical outcomes of 3595 critically ill patients. Patients with pre-hospital DOAC use had an overall lower major bleeding event rate and needed less blood product transfusions and endoscopic interventions for the management of bleeding during their critical illness. However, the DOAC group had a higher rate of intracranial bleeding than the warfarin

Table 3
Adjusted outcomes between pre-hospital DOAC group versus pre-hospital Warfarin group.

Outcome Variables	Unadjusted HR (95% CI)	*P* value	Adjusted HR (95% CI)	*P* value
Major bleeding events	0.47 (0.36 to 0.62)	<0.01	0.46 (0.35 to 0.60)	<0.01
Need for embolization	2.56 (1.04 to 6.31)	0.04	2.16 (0.84 to 5.57)	0.12
Need for endoscopy (GI bleeding)	0.53 (0.27 to 1.02)	0.06	0.48 (0.25 to 0.94)	0.02
Hemorrhagic shock	0.28 (0.10 to 0.76)	0.01	0.28 (0.10 to 0.78)	<0.01
Need for blood transfusion	0.71 (0.59 to 0.87)	<0.01	0.66 (0.53 to 0.81)	<0.01
Need for massive transfusion	2.34 (0.60 to 9.07)	0.22	2.47 (0.45 to 13.33)	0.31
GI bleeding	0.19 (0.11 to 0.32)	<0.01	0.19 (0.11 to 0.31)	<0.01
Intra-abdominal bleeding	1.01 (0.39 to 2.63)	0.99	1.35 (0.48 to 3.53)	0.61
Retroperitoneal bleeding	0.40 (0.09 to 1.69)	0.21	0.47 (0.11 to 2.04)	0.26
Pulmonary bleeding	0.99 (0.22 to 4.48)	0.99	1.03 (0.21 to 5.14)	0.97
Intracranial bleeding	6.59 (2.00 to 21.67)	<0.01	7.20 (1.94 to 26.77)	<0.01
Hemothorax	2.33 (0.60 to 9.07)	0.22	2.88 (0.68 to 12.21)	0.18
LENGTH OF STAY MEASURES (Days[95% CI])				
Hospital LOS	0.02 (-0.78 to 0.81)	0.97	0.18 (-0.61 to 0.97)	0.65
ICU-free days	-0.43 (-1.10 to 0.23)	0.20	-0.42 (-1.09 to 0.25)	0.22

Multivariable models were adjusted for age, sex, race, BMI, comorbidities (CAD, CHF, Stroke, chronic pulmonary diseases, COPD, asthma, pulmonary circulatory diseases, history of VTE, diabetes mellitus, chronic kidney disease, chronic liver disease and cirrhosis, peptic ulcer disease, any type of cancer, peripheral vascular disease) and Charlson score.

group. This finding is contrary to what is currently known in the literature.[3,17] New findings from our cohort should encourage additional research in the critically ill population to confirm this to improve its external validity.

Phase III trials and observational studies that have evaluated the clinical outcomes in patients on DOAC or warfarin therapy have focused on non-critically ill patients. To the best of our knowledge, this is the largest cohort of critically ill patients for studying the outcomes related to the pre-hospital use of DOAC compared to warfarin. We did not find a statistically significant difference for other patient-centered outcomes such as overall hospital LOS, ICU-free days, need for non-invasive or invasive mechanical ventilation, or need for interventional radiology-guided embolization procedures.

Direct oral anticoagulants (DOACs have been utilized more and more as alternatives to warfarin), due to their mechanism of action as non-vitamin K antagonist oral anticoagulants, have a wide therapeutic window, thereby facilitating fixed dosing in adults without the need for laboratory monitoring, although dose adjustments for body weight and renal function are required. However, warfarin has a proven efficacy track record, low cost, better insurance coverage, and years of post-marketing data compared with DOACs.[18] Most of the previous literature has provided information on the rates of major bleeding and outcomes in the non-critically ill population.[19,20] The main impetus of our study is to assess real-world experience of using DOACs in the critically ill population at a large academic medical center over seven years (2012 through 2018). DOACs are generally considered safer and more effective than warfarin for atrial fibrillation, especially regarding serious bleeding events. Results from the studies from an extensive UK-based database showed that DOACs cause half as much life-threatening bleeding than warfarin.[21] Similarly, the use of apixaban has also been associated with lower risk of GI bleeding in a population-based study and the findings are confirmed by a network metaanalysis.[22–24] Their use is also more convenient to the patients because, compared to warfarin, they don't require frequent blood monitoring and can be given safely in fixed doses. Previously conducted randomized controlled trials have demonstrated the noninferiority of DOACs compared to warfarin.[1,25] Previously published literature has investigated the outcomes in patients with atrial fibrillation.[5,26] A significant weakness of these large studies is the lack of representation of critically ill patients. Our cohort of critically ill

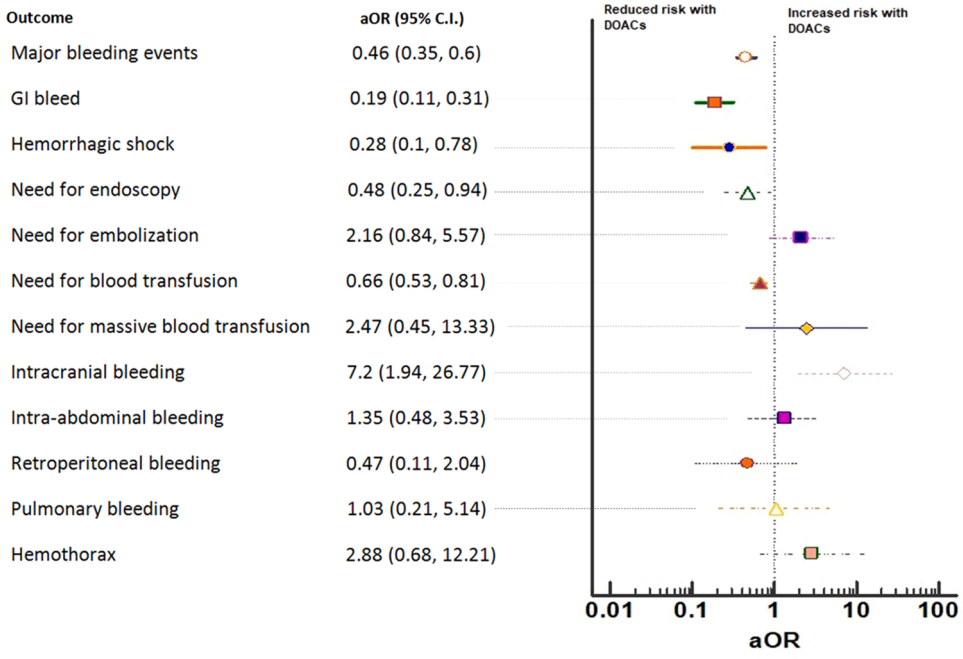

Fig. 3. Forest plot for the outcomes of interest.

patients had DOACs prescribed for multiple indications, with atrial fibrillation being the common reason, but also for other indications such as DVT and PEs. In patients admitted to the ICU, a general approach is to either discontinue the DOAC previously prescribed without transitioning to another agent or use a different agent with a shorter half-life, such as unfractionated heparin or low-molecular-weight heparin, because of practical considerations. Although this approach might appear less risky for the patients, it is based on expert opinion, and there is currently no available literature supporting the hypothesis that the pre-hospital use of DOACs in critically ill patients confers them to a higher risk of bleeding events in the hospital. This strategy has been promoted since critically ill patients might require unanticipated invasive interventions (e.g., central venous catheter insertion, arterial catheter insertion, pleural procedures such as thoracentesis or tube thoracostomy, or other surgical interventions). The high incidence of renal dysfunction and the concomitant use of medications that could have a drug-drug interaction with DOACs are also reasons to withhold DOACs during an acute/critical illness.[27,28] Certain benefits have led to the increased use of DOACs over the last few years. The oral preparation is much more convenient to administer than the injection of heparin analogs. While the use of warfarin has been widespread in the past many decades, the satisfactory level of desired anticoagulation in critically ill populations might be difficult to achieve due to a narrow therapeutic index and large inter-patient variability.

Moreover, warfarin sensitivity in critically ill patients has been associated with worse in-hospital mortality in critically ill population.[29] We also considered the possibility that warfarin when used concomitantly with antiplatelet agents may further increase the risk of bleeding when compared to the DOACs groups, but this hypothesis needs to be confirmed. In our previous work, the concomitant use of DOACs and antiplatelet agents did not significantly increase the risk of bleeding when compared to DOACs alone.[30] Due to the early onset of action, the DOACs rapidly reach a therapeutic level, unlike the vitamin K agonists.[31] Our previously published work described current prescribing practices and preliminary outcomes in ICU patients with pre-hospital use of DOACs. Up to 20% of the patients were transitioned to a different agent within 24 hours of ICU admission, whereas a significant proportion of patients (42%) had anticoagulation discontinued altogether.[12,30] Our previous study highlighted a nonuniform prescribing pattern for DOACs in ICU patients. Since there is no clear guideline, it appears that most of the patients had the DOAC discontinued without switching to an alternate agent. This approach seemed nonuniform without a statistically significant difference between the three approaches (switching anticoagulation from DOAC to an alternative agent, continuing the same DOAC throughout the hospitalization, and discontinuing DOAC altogether). Our current work is focused on creating a body of literature based on which clinicians could make an informed decision about the choice of anticoagulation in critically ill patients. Often changing the medications during the hospitalization and at hospital dismissal could result in non-adherence, which translates into an overall increased risk of adverse events.[32]

Our study has certain limitations. Firstly, we present the outcomes for a cohort from a single large academic center, and the results may vary in the community medical centers. To provide additional validity, these results need to be validated in a larger sample size with the inclusion or large academic centers and community hospitals. Secondly, our cohort spans over a period of several years (2012 through 2018) but needs to be updated with more recent data. This is because of the limitation of our institutional repository, which limited the inclusion of patients until 2018. However, the more recent version of DataMart will have a more up-to-date patient population. In our upcoming work, we intend to update the database with patients beyond 2018 to provide more recent results. In the current work, we only focused on the pre-hospital use of DOACs and warfarin and did not include the change in anticoagulation during the hospital stay (continuation of same anticoagulation, complete discontinuation of anticoagulation or transitioning of anticoagulation to a different agent). Finally, our cohort also included a significant proportion of oncology patients who were critically ill, which is different from the previously studied cohorts. Despite the limitations, our study has many merits. This is the largest cohort of critically ill pents studying the impact of pre-hospital use of DOACs on patient-centered outcomes in ICU patients. With our work, we intend to address the knowledge gap in managing the prescription of anticoagulation agents in the ICU.

Implications on future practice and research:

The exploration of DOACs in this critical cohort of patients presents a paradigm shift. These agents, initially designed for outpatient settings, offer oral administration, standardized dosing, and less frequent monitoring requirements due to their predictable pharmacokinetics. Integrating DOACs into the armamentarium of critical care therapeutics could mitigate the logistical complexities associated with parenteral anticoagulants, ultimately enhancing patient care, and potentially improving clinical outcomes.

By building high-quality literature around this crucial question, we hope to provide more informed decision-making for the bedside clinicians who are coming across this scenario on a day-to-day basis about how to manage the use of DOACs in critically ill patients. In addition to this, we hope to confirm the findings in a prospective manner to assess the safety of continuing the DOACs during the critical illness and during the hospital stay in a protocolized manner. Our results support continuation of the home DOAC therapy, unless there are absolute indications to discontinue the DOACs at the time of hospital admission (increased risk of bleeding, organ failure such as liver and renal, planned procedure). Changes made in the hospital and at the time of dismissal from the hospital have been associated with increased nonadherence and risk of adverse events.[32] Furthermore, the interplay of DOACs with other critical care interventions, such as mechanical ventilation or extracorporeal support, warrants thorough investigation.[33]

In conclusion, our current work shows that the pre-hospital use of DOAC is safe in critically ill patients and is associated with a lower risk of any major bleeding events, including (GI bleeding, hemorrhagic shock, and need for any blood product transfusion) but a higher risk of intracranial bleeding when compared to the group of patients with pre-hospital use of warfarin for anticoagulation. Prospective and multicenter validation is required to confirm these results.

CRediT authorship contribution statement

Amos Lal: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Abdul Wahab:** Data curation, Investigation, Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing. **Aysun Tekin:** Data curation, Formal analysis, Investigation, Methodology, Resources, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. **Simmy Lahori:** Data curation, Investigation, Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing. **John G Park:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

None.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.hrtlng.2023.08.008.

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