emergency care and medicine

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Risk Factors for Emergency Room Visits in Patients with Digestive Bleeding Associated with Direct-Acting Anticoagulants

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Abstract: Gastrointestinal bleeding is the main cause of admission to the emergency services of patients taking direct-acting oral anticoagulants (DOACs). Little is known about the effects of treatment modification on the risk of readmission, especially in elderly patients. This retrospective observational study included elderly patients with atrial fibrillation who were on DOACs and who were admitted to the emergency department due to gastrointestinal bleeding from 2018 to 2023. To evaluate the risk factors for readmission 90 days after discharge, a multivariate analysis was conducted, which included patient comorbidities, concomitant treatment, changes in anticoagulant treatment, and the prescription of DOACs at discharge. One hundred and thirty-nine patients were included. At discharge, anticoagulant therapy was modified in 44 (31.6%) patients, 16 (36.3%) patients were switched from one DOAC to another, 23 (52.2%) to heparins, and 5 (11.3%) to vitamin K antagonists. A total of 21 (15.1%) patients returned to the emergency department within 90 days after discharge due to new bleeding events. No significant differences were observed depending on the modification of treatment at discharge. The presence of cognitive impairment was the only factor associated with readmission at 90 days. Patients who undergo treatment with DOACs and have gastrointestinal bleeding at discharge are at risk of readmission to the emergency room due to new bleeding events. No benefit was observed in modifying anticoagulant treatment at discharge.

Keywords: emergency department; anticoagulation; bleeding; adverse drug reaction

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Citation: Ruiz-Ramos, J.; Pérez-Méndez, M.C.; Socias-Cañellas, C.M.; Lozano-Polo, L.; Plaza-Diaz, A.; Puig-Campmany, M.; Juanes-Borrego, A.M. Risk Factors for Emergency Room Visits in Patients with Digestive Bleeding Associated with Direct-Acting Anticoagulants. *Emerg. Care Med.* **2024**, *1*, 199–209. https://doi.org/10.3390/ecm1030021

Academic Editor: Raimundas Lunevicius

Received: 10 April 2024
Revised: 18 May 2024
Accepted: 28 June 2024
Published: 3 July 2024

Correction Statement: This article has been republished with a minor change. The change does not affect the scientific content of the article and further details are available within the backmatter of the website version of this article.

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1. Introduction

Atrial fibrillation (AF), the most prevalent cardiac arrhythmia, increases in prevalence with age and carries a significant risk of blood clots, hospitalization, and death [1].

It has been estimated that women over 65 years have an incidence exceeding 50 cases per 1000 people per year, while in men over 80 years old, the incidence exceeds 65 cases per 1000 people per year. Interestingly, people of other races experience a roughly 10 case-per-1000-person–year lower incidence compared to white people [2]. Globally, the estimated number of people with AF doubled between 1990 and 2019, reaching 59.7 million in 2019. However, when adjusting for age, the prevalence of AF and death rates from AF showed minimal change worldwide during this period [3]. An aging population is driving a significant rise in non-valvular AF hospital admissions, particularly among the very elderly. A European epidemiology study predicts an 89% increase in elderly AF patients (≥65 years) by 2060 [4]. Notably, the proportion of very elderly patients (≥80 years) with AF is projected to jump from 51.2% in 2016 to 65.2% in 2060. This demographic shift underscores the growing importance of managing AF in elderly and very elderly populations, as older age, especially with AF, carries a heightened risk of stroke and heart failure.

Anticoagulation therapy is one of the main treatments for AF, preventing thrombotic events and reducing the risk of death. However, this benefit comes with a trade-off: an increased risk of bleeding, particularly in the digestive system, is the leading cause of emergency department (ED) visits for patients on these medications [5]. For people 75 or older with AF, the risk of stroke falls between 6.9% and 8.9% over five years. While there's also a risk of gastrointestinal bleeding, ranging from 5.4% to 6.6% over the same timeframe [6], stroke can cause serious disabilities. Therefore, the potential benefits of anticoagulation therapy to prevent stroke usually outweigh the bleeding risks.

For decades, vitamin K antagonists have been the mainstay of thrombotic episode prevention. However, these drugs require frequent monitoring and have various food and drug interactions. These limitations, coupled with the similar effectiveness of newer medications in preventing ischemic events, have fueled the rise of direct oral anticoagulants (DOACs), particularly among elderly patients [7,8].

DOACs offer several advantages over vitamin K antagonists [9]. They directly target specific clotting factors, leading to a more predictable anticoagulant effect, fixed dosing schedules, and less frequent monitoring needs. Additionally, DOACs are less susceptible to interactions with food and drugs. Studies have shown that DOACs are equally or even more effective than warfarin, with a lower risk of major bleeding, especially in brain bleeding [10–12]. Consequently, their use is steadily increasing for stroke prevention in AF, post-surgical clot prevention, and deep vein thrombosis/pulmonary embolism treatment.

Meanwhile, research exists on ED visits for warfarin-related digestive bleeding [13,14], but the impact of DOACs on elderly patients with such bleeding remains unclear. Limited information exists on risk factors for new bleeding episodes in these patients when they switch to a new anticoagulant treatment. These patients are often older with more comorbidities, potentially increasing their risk of bleeding and worsening outcomes. Additionally, data on how clinicians manage anticoagulation therapy after a bleeding episode in real-world clinical settings are limited. The study's findings underscore the necessity for a tailored approach to managing anticoagulation therapy in elderly patients, emphasizing the importance of continuous monitoring and individualized patient care to balance the benefits of stroke prevention with the risks of bleeding. As the elderly population continues to grow, healthcare providers must navigate the complexities of anticoagulation therapy with a nuanced understanding of each patient's unique risk profile. This involves not only the initial prescription of DOACs but also vigilant follow-up care, taking into account the patient's comorbidities, potential drug interactions, and lifestyle factors that may influence their response to treatment. Given the increasing use of DOACs in the elderly population [15,16], identifying such risk factors is crucial.

Our study aimed to address these knowledge gaps by investigating the frequency of emergency room visits and mortality in elderly patients with DOAC-related gastrointestinal bleeding. We also sought to identify factors associated with a higher risk of return visits to the emergency room. This information can help healthcare professionals improve the management of DOAC therapy and potentially reduce the risk of bleeding complications, especially in the growing population of elderly patients on these medications.

2. Materials and Methods

This retrospective single-center observational study included elderly patients (>65 years) who underwent treatment with DOACs and who came to the ED for gastrointestinal bleeding between January 2018 and December 2023. Patients diagnosed with malignant neoplasms were excluded, as were those who died in the ED during the first episode of the ED visit.

This study was carried out in the ED of a third-level reference urban teaching hospital in Catalonia, Spain, with a reference population of 407,000 inhabitants and an annual volume of approximately 150,000 visits to the ED. Of these, 115,000 correspond to adult emergencies, 40% to patients over 65 years of age, and more than 30% are vulnerable patients (those with dementia, dependence, active oncological disease, chronic diseases or comorbidities, or disability). The patients were selected from the database of the adverse

drug events registry of the ED. This database is completed daily by the pharmacists assigned to the emergency department of the hospital based on the data obtained during the visit to the area. The demographic and clinical information of the patients was obtained from the electronic medical records available at the hospital. The comorbidities of the patient and chronic treatment data were obtained from the hospital admission report and the electronic prescription registry in primary care.

To evaluate the risk factors associated with readmission to the ED for new bleeding episodes 90 days after discharge, a multivariate analysis was designed that included variables with a value of $p < 0.2$ in a previous univariate logistic analysis. The factors analyzed included age > 80 years (associated with a higher risk of major bleeding in patients taking oral anticoagulants [17]), sex, and comorbidities, according to the information obtained from the electronic health record (chronic kidney disease, chronic obstructive pulmonary disease, heart failure, diabetes, hypertension, chronic kidney disease Grade III–V [18], and cognitive impairment), severe Charlson Comorbidity Index (>4 points), the presence of major bleeding (symptomatic bleeding in a critical area or organ and/or bleeding causing a fall in hemoglobin levels of 20 g/L or greater or more, or leading to a transfusion of 2 U or more of whole blood or red cells), polypharmacy (>10 drugs) [19], the concomitant use of gastrointestinal drugs (including antiplatelet drugs, corticosteroids and non-steroidal anti-inflammatory drugs) and changes in and the end of prescribed anticoagulant treatment after the first bleeding episode. Treatment with heparin at discharge was considered if the patient continued treatment for more than 7 days after the bleeding episode.

The data analysis was performed using the Stata 13.0 s statistics program (StataCorp, College Station, TX, USA). The quantitative variables were obtained as means (standard deviations) and medians (interquartile ranges [IQRs]), whilst the qualitative ones were expressed as percentages. An analysis of variance (ANOVA) was performed to compare the means of the three groups with the socio-demographic variables and the scores obtained in the items of the scale, using the Bonferroni post hoc test to identify the groups in which significant differences were found. Kaplan–Meier curves were constructed to estimate the survival function of new readmission for new bleeding episodes 90 days after discharge. Patients were censored at ED bleeding episode admission, death, or 90 days after index gastrointestinal bleeding, whichever came first.

This study was approved by the Clinical Research Ethics Committee of Hospital Santa Pau (Reference No: IIBSP-COD-2018-25).

3. Results

A total of 142 patients (85 females) were included during the study period; three (2.1%) patients died during hospitalization and were excluded from the analysis. Of the 139 remaining patients, the mean age was 84.6 (Standard deviation (SD): 7.5) years, and 85 (61.1%) were women. Their characteristics are given in Table 1. Hypertension (presented in 84.1% of the patients included), heart failure (34.8%), and chronic renal failure (31.4%) were the most prevalent comorbidities among the patients included. One hundred and seven (77.0%) patients presented a Charlson Comorbidity Index > 4 points; twenty-eight (19.7%) with edoxaban; and forty-eight (33.8%) with apixaban. Fifty (35.2%) patients experienced major bleeding events. Esophagogastroduodenoscopy was performed in 26 (18.7%) of patients and colonoscopy in 35 (25.1%). A small number of patients (three; 2.2%) were treated with an invasive endoscopic procedure.

Table 1. Characteristics of patients included in the study according to the modification of anticoagulant treatment at hospital discharge.

	Total	No Change (n = 85)	Change (n = 44)	End of Treatment (n = 10)	*p*
Age (Mean; SD)	84.6 (7.5)	85.1 (6.1)	83.6 (6.1)	89.6 (7.1)	0.265
Female (%)	85 (61.1)	50 (58.8)	28 (63.6)	7 (70.0)	0.408
Comorbidities (%)					
Hypertension	117 (84.1)	71 (81.6)	38 (86.4)	8 (80.0)	0.284
Heart failure	54 (38.8)	34 (39.1)	17 (31.5)	3 (30.0)	0.942
Diabetes	36 (25.9)	19 (22.3)	16 (33.3)	1 (10.0)	0.158
COPD	19 (13.8)	13 (14.9)	5 (11.6)	1 (10.0)	0.553
Renal Chronic Failure III–V	44 (31.6)	24 (27.6)	17 (38.6)	2 (20.0)	0.182
Cognitive disorder	37 (26.6)	24 (27.6)	11 (25.0)	3 (30.0)	0.353
Severe CCI (>4 points)	107 (77.0)	66 (77.6)	35 (79.6)	8 (80.0)	0.827
Major bleeding (%)	49 (35.2)	25 (29.4)	20 (45.4)	4 (40.0)	0.027
Destination at discharge (%)					0.197
Home	102 (73.4)	58 (68.2)	38 (86.3)	6 (60.0)	
Nursing home	7 (5.0)	4 (4.7)	1 (2.2)	2 (20.0)	
Long-term hospitalization	30 (21.6)	23 (27.1)	5 (11.4)	2 (20.0)	
Nº Drugs at discharge (Mean; SD)	9.8 (3.4)	9.7 (3.2)	10.1 (3.3)	10 (4.2)	0.663
Severe polypharmacy (>10 drugs) (%)	61 (43.8)	41 (47.1)	17 (38.6)	3 (30.0)	0.319
Antiplatelets (%)	22 (15.9)	18 (20.7)	3 (7.0)	1 (10.0)	0.047
Gastroprotection (%)	62 (44.6)	33 (37.9)	23 (52.2)	6 (60.0)	0.041

CCI: Charlson Comorbidity Index; COPD: chronic obstructive pulmonary disease.

The changes in the antithrombotic treatment prescribed at discharge are shown in Figure 1. Forty-four (31.6%) patients modified their antithrombotic treatment at hospital discharge, and ten (7.2%) patients permanently stopped antithrombotics.

A total of 21 (15.1%) patients presented new visits to the ED within 90 days of discharge due to a bleeding episode. Patients with modified anticoagulant treatment at discharge did not present a lower risk of new visits to the ED [HR: 0.80 (0.32–1.98)] (Figure 2). No significant differences were found between the groups of patients who maintained anticoagulation therapy and those treatment and those who discontinued it upon hospital discharge [HR: 0.75 (0.31–5.72)]. Three (2.1%) patients experienced thromboembolic episodes within 90 days of discharge, two of whom experienced thromboembolic episodes after the suspension of anticoagulant treatment.

On univariate analysis (Table 2), the cognitive impairment and severe Charlson Comorbidity Index were associated with readmission for bleeding or thromboembolic events at 90 days (a *p*-value > 0.200 was obtained for the rest of the variables considered, which were then excluded from the multivariable analysis). In the multivariable analysis, cognitive impairment remains significantly associated with readmission [OR:1.46 (0.46–2.43)]. The change in DOAC treatment at discharge was not associated with a significant reduction in the number of readmission episodes at 90 days.

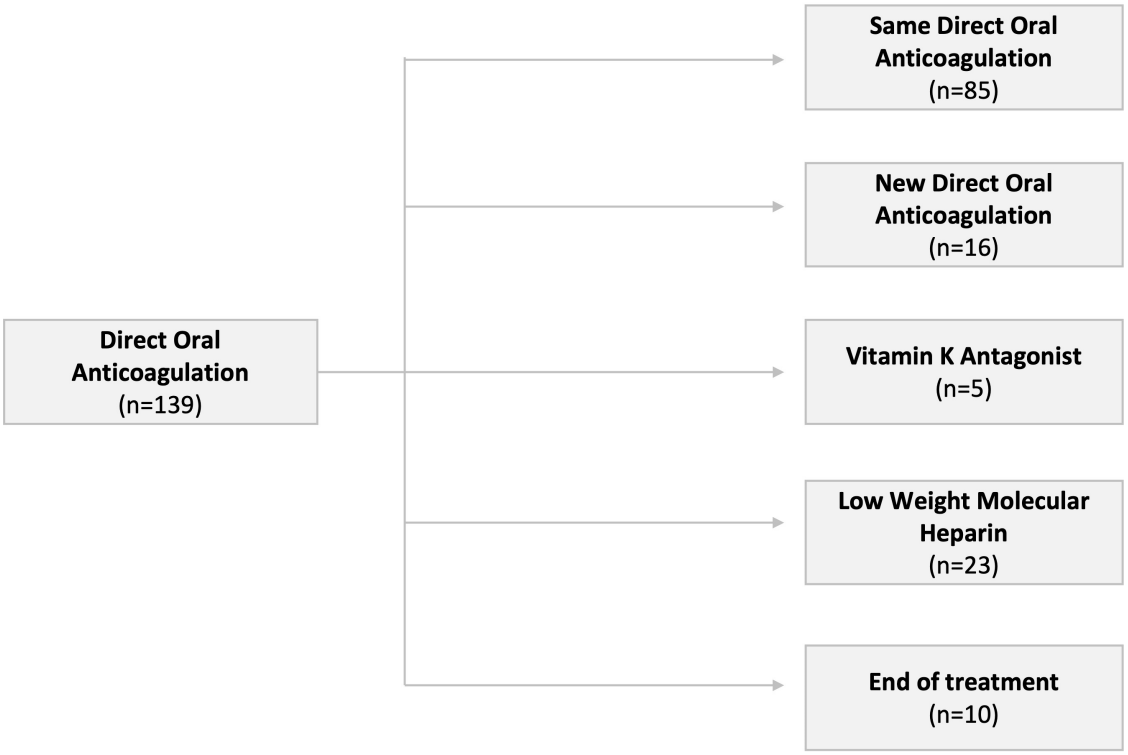

Figure 1. Change in anticoagulant treatment at discharge after the bleeding episode. n: Number of patients.

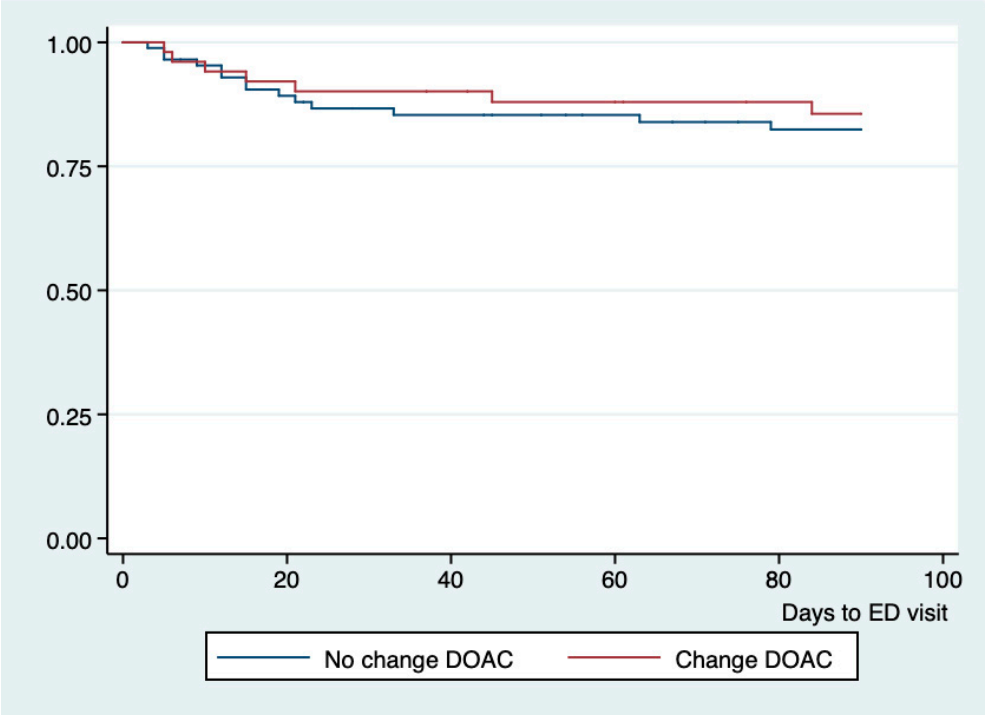

Figure 2. Time until re-consultation due to new bleeding depending on the suspension or change in anticoagulant treatment at discharge. DOAC: Direct-acting anticoagulant.

Table 2. Results of univariate analysis for new bleeding episodes 90 days after discharge.

	Univariate Analysis OR (IC95%)	***p*-Value**
Change in treatment	0.63 (0.21–1.81)	0.485
End of treatment	1.41 (0.28–4.749)	0.655
Age > 80 years	1.44 (0.45–4.64)	0.555
Female	0.82 (0.32–2.10)	0.683
Hypertension	0.76 (0.23–2.54)	0.662
Chronic Heart Failure	1.21 (0.47–3.12)	0.683
Diabetes	1.17 (0.45–3.29)	0.762
COPD	1.15 (0.39–2.13)	0.645
Renal Chronic Failure III–V	1.09 (0.40–2.63)	0.858
Cognitive disorder	2.96 (1.87–7.12)	<0.001
Severe CCI	3.23 (0.71–10.7)	0.128
Major bleeding	0.58 (0.22–2.11)	0.201
Destination at discharge	1.21 (0.29–4.67)	0.863
Severe polypharmacy (>10 drugs)	1.16 (0.46–2.97)	0.751
Antiplatelets	1.29 (0.39–4.29)	0.764
Gastroprotection	1.81 (0.60–4.83)	0.214

CCI: Charlson Comorbidity Index; COPD: chronic obstructive pulmonary disease.

4. Discussion

The impact of changes in antithrombotic treatment after a bleeding episode in ED settings is a critical aspect of patient care, particularly given the complexities of managing anticoagulated patients. The present study shows the impact of changes in antithrombotic treatment with DOACs after a bleeding episode in an ED. Our findings indicate that altering anticoagulant therapy was not associated with a reduction in the risk of new visits to the emergency room within 90 days. Cognitive impairment emerged as the only factor associated with an increased risk of new bleeding episodes.

Gastrointestinal bleeding associated with anticoagulation is a frequent reason for consultation in EDs, ranging from self-limited episodes to life-threatening situations with hemodynamic instability. The overall incidence of major gastrointestinal bleeding in randomized trials of oral anticoagulants ranges from 0.5 to 1.6 events per 100 patient–years for patients treated for venous thromboembolism and from 0.8 to 1.9 events per 100 patient–years for those treated for AF [20]. These rates are higher among patients receiving oral anticoagulants for cancer-associated thrombosis, with incidences ranging from 3.5 to 8.4 events per 100 patient–years. Additionally, the risk of major gastrointestinal bleeding associated with anticoagulation therapy use is affected by the duration of treatment. A Canadian population-based cohort study found a fourfold increase in the incidence of upper and lower gastrointestinal bleeding during the first 30 days of warfarin initiation compared to the subsequent follow-up period over five years [21]. The mortality attributed to these episodes is about 10%, being influenced by the age and comorbidities of the patient [22–26]. The study highlights the complex decision-making process for healthcare professionals managing anticoagulated patients who experience bleeding episodes. Moreover, there is a lack of direct comparative studies on different anticoagulants, making decision-making even more challenging for healthcare providers. Anticoagulant management after these events is complex, given the high risk of new bleeding episodes or thromboembolic episodes after their suspension, and few studies have directly compared the different anticoagulants. Different meta-analyses seem to show that apixaban has a

lower risk of bleeding, although this conclusion is controversial [27,28]. We found no reduction in risk after a change in anticoagulant therapy at discharge.

Most of the included patients stayed on their anticoagulant therapy after bleeding, as it was suspended in only 10 patients; three of them presented a thrombotic episode. This practice is consistent with studies that have shown that maintaining anticoagulant therapy after a hemorrhagic event reduces bleeding episodes and mortality [28]. However, 15% of the patients came back to our ED for bleeding episodes within 90 days after discharge, which is in line with other studies [29,30]. We did not detect a significant association in the multivariate analysis between the suspension or change in anticoagulation agent and the recurrence of bleeding events within 90 days. Given the morbidity associated with a new episode of thromboembolism, the risks of maintaining anticoagulation in our cohort probably outweighed the reduction in the risk of recurrent bleeding. However, the high risk of bleeding in the short term requires multidisciplinary interventions to optimize the dosage and review the concomitant treatments beyond the change in DOAC treatment to avoid new episodes and readmission. Notably, 15.9% of our patients kept their other gastrolesive drugs at discharge, which is a potential point for optimization after discharge from the ED. The use of antiplatelet agents and non-steroidal anti-inflammatory drugs should be carefully reviewed as they are significant risk factors for major gastrointestinal bleeding in patients on oral anticoagulants DOACs. Dual therapies involving both an OAC and aspirin account for up to 40% of patients with anticoagulation-associated gastrointestinal bleeding [20]. Given the common occurrence of coronary and peripheral artery disease, a multidisciplinary approach is essential to determine the appropriate duration of dual and triple therapies, if necessary. Medication reviews should also identify pharmacokinetic drug–drug interactions that could elevate serum DOAC concentrations, thereby potentially increasing bleeding risk. Evaluating renal and hepatic function can guide the selection and dosing of DOACs. Indication-specific approved dose reduction criteria consider various factors such as age, weight, renal function, and drug interactions. It should be noted that empiric dose reductions outside of approved dosing guidelines have been linked to higher rates of stroke, hospitalization, and death in patients with atrial fibrillation [31]; thus, it is not a recommended practice.

Some recent retrospective studies have evaluated the risk of thromboembolism in patients with gastrointestinal bleeding. Sengupta et al. [32], in an analysis of 197 patients, reported that the continuation of anticoagulation therapy was independently associated with a lower risk of major thrombotic events within 90 days without observing a greater risk of recurrent gastrointestinal bleeding at 90 days in patients who continued anticoagulation therapy. A retrospective cohort study of patients with warfarin-associated gastrointestinal bleeding showed that the decision to stop anticoagulation within 90 days of initial bleeding was associated with a higher risk of thrombosis and death [33]. Qureshi et al. [34] also showed that restarting warfarin after a severe gastrointestinal bleeding episode was associated with a decrease in thromboembolism and a reduction in mortality without a significantly increased risk of recurrent gastrointestinal bleeding.

In this study, we observed that the majority of patients experienced recurrent bleeding consultations within the first week after initial hospitalization. This may suggest a strategy of temporarily suspending anticoagulation, if necessary, for less than 7 days to restart treatment after initial discharge. The results obtained are consistent with previous studies, in which the resumption of warfarin therapy between days 1 and 7 following a gastrointestinal bleeding event was associated with a higher risk of recurrent bleeding but a lower risk of thrombosis [33]. A better evaluation of the propensity for recurrent hemorrhage and its severity across the diversity of anatomic lesions involved in the bleeding episode may be used to decide the best time to restart anticoagulation, which is a crucial decision for people at high risk of thrombotic events.

Furthermore, our study found that the presence of cognitive impairment could increase the risk of new consultations for bleeding events and hospital readmission. AF has been linked to a higher risk of memory problems, dementia, and Alzheimer's disease in

different studies. A large Korean study found that people with AF were more likely to develop dementia compared to those without AF. Even those without strokes showed an increased risk of both vascular dementia and Alzheimer's disease. Interestingly, patients with newly diagnosed AF who received anticoagulants had a lower risk of dementia [35]. A European study also showed a strong link between AF and dementia, especially in people without a specific genetic risk factor. This study estimated that 13% of dementia cases could be potentially prevented if AF were addressed [36]. Studies have shown that frail patients with dementia face elevated risks of both emergency department visits and hospital readmissions [37]. Moreover, elderly individuals with atrial fibrillation and cognitive impairment are significantly more susceptible to stroke, major bleeding, and intracranial hemorrhage compared to those with normal cognition [38]. The rise in gastrointestinal bleeding among elderly patients with cognitive disorders may be attributed to specific gastrointestinal ailments prevalent in this demographic, along with co-morbid conditions and polypharmacy. Polypharmacy, a common practice in elderly patients with cognitive disorders, involves increased usage of antidepressants, non-steroidal anti-inflammatory drugs, and other medications that may lead to drug interactions, particularly in patients on DOACs. Additionally, cognitive dysfunction, notably executive dysfunction, has been correlated with increased readmission rates among individuals responsible for self-managing their medications [39].

Frail patients have a higher risk of bleeding associated with anticoagulant therapy [40]. Therefore, it is especially relevant to assess the frailty of patients when choosing whether to continue or suspend anticoagulant treatment at discharge. When managing AF in elderly patients with recurrent bleeding episodes, it is crucial to involve them and their relatives in making treatment decisions. This means understanding their priorities and concerns to choose the best option. The risks and benefits of different medications, such as anticoagulant therapy, should be discussed openly. Some studies are even exploring web-based tools to help patients understand these choices [41].

The limitations of our study include the retrospective nature of the data collection and the lack of information on adequate adherence to anticoagulant treatment. Comorbidities such as cognitive impairment were obtained from the electronic health record, and no prospective confirmation was obtained. The presence of bleeding episodes that did not require a visit to the ED could not be evaluated, either. On the other hand, the study did not prospectively analyze the presence of neoplasms or polyps among the patients included, which factors are responsible for about 10% of gastrointestinal bleeding [42]. Moreover, this study presents a single-center experience managing DOACs after gastrointestinal bleeding, aiming to propose initial hypotheses that warrant confirmation through prospective research. Regrettably, the sample size was not pre-determined, and the current sample size is insufficient to yield definitive results. Likewise, the small sample size makes it necessary to take the results obtained with caution, although, given the scarce information available, they can serve as a basis for proposing future hypotheses to be tested in larger samples.

Compared to upper gastrointestinal bleeding, lower gastrointestinal bleeding poses greater challenges for diagnosis and treatment, especially in patients on anticoagulation therapy. Data on the characteristics, management, and clinical outcomes of patients with acute lower gastrointestinal bleeding while on anticoagulants, particularly DOACs, remains scarce. These patients are typically older and have more co-existing medical conditions, potentially impacting both treatment decisions and overall prognosis. The main sources of gastrointestinal bleeding were not adequately evaluated in the included patients. Additionally, specific interventions aimed at preventing and reducing the risk of new bleeding episodes were not assessed. It is important to note that most of the included population comprises frail patients with minor bleeding, for whom targeted interventions to identify the bleeding source were not conducted. Given the observed significant differences in the risk of rebleeding episodes depending on the initial management of the acute episode [43,44], future studies should consider these variables for a thorough evaluation of bleeding risk in patients undergoing anticoagulant therapy.

Expanding on this study's implications and insights could involve further exploration of specific patient characteristics, detailed analyses of thromboembolic risks versus bleeding risks with different anticoagulants, and recommendations for multidisciplinary interventions to optimize patient outcomes. Additionally, discussing potential areas for future research and implications for clinical guidelines would enrich the discussion on the evolving landscape of anticoagulant management post-bleeding in ED settings. Future research should focus on prospective studies to validate retrospective findings and inform comprehensive guidelines for optimizing anticoagulant therapy in patients with bleeding complications.

5. Conclusions

In conclusion, patients with atrial fibrillation who were anticoagulated with DOACs and who came to the ED for gastrointestinal bleeding presented a high risk of readmission to the ED within 90 days. A change in antithrombotic therapy was not associated with a lower risk of readmission due to bleeding. The study illuminates the complexities of managing anticoagulated patients post-gastrointestinal bleeding and highlights the critical need for evidence-based strategies to guide clinical decision-making in this challenging patient population.

Author Contributions: Conceptualization, J.R.-R., M.P.-C. and A.M.J.-B.; study design, J.R.-R. and M.C.P.-M.; methodology, C.M.S.-C. and J.R.-R.; validation, L.L.-P. and J.R.-R.; formal analysis, J.R.-R. and C.M.S.-C.; resources, A.P.-D.; data curation, A.P.-D. and J.R.-R.; writing—original draft preparation, J.R.-R.; writing—review and editing, M.P.-C. and L.L.-P.; visualization, A.M.J.-B.; supervision, J.R.-R. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: This study was conducted in accordance with the Declaration of Helsinki and approved by the Hospital Sant Pau Ethical Committee (ID: Reference No: IIBSP-COD-2018-25, approved 17 January 2024).

Informed Consent Statement: Patient consent was waived due to retrospective data being collected without personally identifying information.

Data Availability Statement: Data are available under reasonable request.

Conflicts of Interest: The authors declare no conflicts of interest.

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