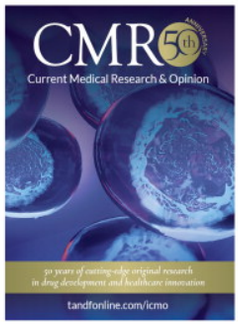

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RESEARCH ARTICLE

Impact of atrial fibrillation and anticoagulation on the risk of death, thromboembolic disease and bleeding in patients with COVID-19: the ACO-VID Registry

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ABSTRACT

Objective: To describe the clinical profile, risk of complications and impact of anticoagulation in COVID-19 hospitalized patients, according to the presence of atrial fibrillation (AF).

Methods: Multicenter, retrospective, and observational study that consecutively included patients >55 years admitted with COVID-19 from March to October 2020. In AF patients, anticoagulation was chosen based on clinicians' judgment. Patients were followed-up for 90 days.

Results: A total of 646 patients were included, of whom 75.2% had AF. Overall, mean age was 75 ± 9.1 years and 62.4% were male. Patients with AF were older and had more comorbidities. The most common anticoagulants used during hospitalization in patients with AF were edoxaban (47.9%), low molecular weight heparin (27.0%), and dabigatran (11.7%) and among patients without AF, these numbers were 0%, 93.8% and 0%. Overall, during the study period (68 ± 3 days), 15.2% of patients died, 8.2% of patients presented a major bleeding and 0.9% had a stroke/systemic embolism. During hospitalization, patients with AF had a higher risk of major bleeding (11.3% vs 0.7%; $p < .01$), COVID-19-related deaths (18.0% vs 4.5%; $p = .02$), and all-cause deaths (20.6% vs 5.6%; $p = .02$). Age (HR 1.5; 95% CI 1.0–2.3) and elevated transaminases (HR 3.5; 95% CI 2.0–6.1) were independently associated with all-cause mortality. AF was independently associated with major bleeding (HR 2.2; 95% CI 1.1–5.3)

Conclusions: Among patients hospitalized with COVID-19, patients with AF were older, had more comorbidities and had a higher risk of major bleeding. Age and elevated transaminases during hospitalization, but not AF nor anticoagulant treatment increased the risk of all-cause death.

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KEYWORDS
Anticoagulation; atrial fibrillation; COVID-19; direct oral anticoagulant

Introduction

Coronavirus disease 2019 (COVID-19) is an acute, complex and highly contagious infectious disease, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that, in severe cases, is associated with the development of interstitial pneumonia and acute respiratory distress syndrome[1,2]. On 11 March 2020, the World Health Organization declared the COVID-19 infection as a pandemic[3]. During the first wave, around 10% of infected patients had a severe condition, requiring hospital admission[4,5]. However, COVID-19 does not only negatively impact on the respiratory system, but also on cardiovascular system. Thus, patients with established cardiovascular disease and COVID-19 infection have a higher risk of complications and death. In addition, COVID-19 is associated with the development of new-onset cardiovascular conditions, such as acute coronary syndrome, cardiac injury, myocarditis, heart failure, arterial and venous thrombosis and arrhythmias, mainly atrial fibrillation (AF)[6,7].

AF is the most common arrhythmia in clinical practice, with an estimated current prevalence of around 2–4% in the adult population. AF markedly increases the risk of developing thromboembolic complications, being anticoagulation the most effective treatment to reduce this risk[8–10]. Patients with severe COVID-19 infection have a higher risk of developing AF. Thus, different studies and meta-analyses have shown that around 8–11% of hospitalized patients with COVID-19 have concomitantly AF, and approximately 3–4% new-onset AF, increasing with age or the severity of COVID-19 infection[11–13]. Different mechanisms have been proposed to explain the relationship between COVID-19 and AF, including dysregulation of metabolism, inflammation, and

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immunity interactions[14]. Of note, previous studies have shown that prior AF and new-onset AF are associated with a higher risk of thromboembolic events, bleeding, all-cause mortality and longer hospital stays[11–13,15,16].

Despite AF is a frequent complication among hospitalized patients with COVID-19, more information is needed about the thromboembolic and bleeding risk of patients with AF compared to those without AF, and the impact of anticoagulation during admission on this population, in order to identify the best therapeutic approach in clinical practice[17–19]. The objectives of this study were to describe the clinical and demographic characteristics of hospitalized patients with COVID-19, the risk of thromboembolic and bleeding complications and mortality, as well as the impact of anticoagulation on these events, according to the presence of prior or new-onset AF.

Methods

Multicenter, retrospective, and observational study that consecutively included adults >55 years old admitted with COVID-19 at University Hospital General Santa Lucia (Cartagena, Murcia) and Hospital Sagrat Cor, Fundació Sanitaria Hospital de Mollet. Barcelona, Hospital Universitari General de Catalunya from March to October 2020. No exclusion criteria were defined. No specific diagnostic or therapeutic actions were taken for participating in the study. Patients were divided in two cohorts according to the presence of AF. In patients with AF, anticoagulation was chosen based on clinicians' judgment. The study was approved by the Ethics Committee of the participating centers. Due to the retrospective design of the study, an informed consent waiver was requested and approved by the Ethics Committee.

Data were collected since admission until 90 days of follow-up (or until the date of the last follow-up) and were recorded in an electronic case report form specifically designed for the study. Data were taken from the medical records of the patients. At baseline, data about biodemographic variables (age, gender), history of AF, comorbidities (previous stroke, bleeding, diabetes, hypertension), and antithrombotic treatment before admission and during hospitalization (i.e. low molecular weight heparin [LMWH] – enoxaparin, bemiparin-, fondaparinux, edoxaban, dabigatran, apixaban, rivaroxaban, and vitamin K antagonist) were recorded. In addition, the dose of the anticoagulants (standard vs reduced) was analyzed, as follows: LMWH 1 mg/kg every 12 h vs other doses; fondaparinux 7.5 mg/daily vs other doses; edoxaban 60 mg vs 30 mg once daily; dabigatran 150 mg vs 110 mg twice daily; apixaban 5 mg vs 2.5 mg twice daily; rivaroxaban 20 mg vs 15 mg once daily[10]. Previous AF was defined as the history of AF, either paroxysmal, persistent or permanent, before admission. New-onset AF was defined as the development of AF during hospitalization. The thromboembolic and the bleeding risk were estimated with the CHA_2D_2-VASc and HAS-BLED scores, respectively[20,21]. Additionally, data from blood tests analysis performed at admission, during the first week of hospitalization, at discharge and within the first 60 days after discharge were also collected. The elevation of transaminases 3 x ULN at any time of admission was considered as clinically relevant. Abnormal kidney function was defined as a creatinine clearance <30 ml/min/1.73 m^2.

Complications that occurred during hospitalization, including admission to the Intensive Care Unit, major bleeding (defined according to the International Society of Thrombosis and Haemostasis)[22], stroke, venous/arterial thromboembolic disease and death (all-cause and COVID-19) were recorded. In addition, outcomes that occurred within 90 days after discharge, including major bleeding, stroke, venous/arterial thromboembolic disease and death were also collected.

Statistical analysis

Qualitative variables were expressed as absolute (*n*) and relative (%) frequencies. Quantitative variables were reported with measures of central tendency (mean) and dispersion (standard deviation). Qualitative variables were compared using the chi-square test or the Fisher exact test, as required. The *t*-test was used to compare two means. Incident rates of complications were calculated according to the history of AF. Multivariate logistic regression analyses were performed to assess predictors of adverse events (i.e. major bleeding, stroke, venous/arterial thromboembolic disease and death). Baseline clinical characteristics, as well as antithrombotic treatment (previous and during hospitalization: type of anticoagulant and the appropriateness of dosage) were considered as independent variables. The multivariate models were constructed by including those factors with $p < .10$ in the bivariate analysis using automatic forward stepwise selection. Only the significant factors were finally included in the model. Statistical significance was set at <.05 for all tests. The statistical analysis was performed using SPSS 21.0 (SPSS Inc., Chicago, IL).

Results

A total of 646 patients hospitalized for COVID-19 were included, of whom 486 (75.2%) had AF. Overall, mean age was 75 ± 9.1 years and 403 (62.4%) were male. Patients with AF were older than patients without AF (>75 years 63.0% vs 25.0%; $p = .001$), had more hypertension (87.2% vs 57.5%; $p = .001$), and more previous bleeding (18.9% vs 5.6%; $p = .001$), but less diabetes (27.4% vs 35.6%; $p = .047$). Among patients with AF, before admission, the most common oral anticoagulant used was acenocoumarol (55.1%). Overall, during hospitalization, only 6 (0.9%) patients did not take any anticoagulant therapy. During hospitalization in patients with AF, edoxaban (47.9%), LMWH (27.0%), and dabigatran (11.7%) were the anticoagulant treatments more used (Table 1).

Overall, during the study period (68 ± 3 days), 97(15.0%) patients died, of which 84 (13.0%)due to COVID-19;53(8.2%) patients presented a major bleeding and 6 (0.9%) patients had a stroke/systemic embolism. Among patients who had major bleeding, no differences were found according to the type of anticoagulant (edoxaban 37.7%; LMWH 35.8%). Only

Table 1. Baseline clinical characteristics.

	No AF ($n = 160$; 24.8%)	AF ($n = 486$; 75.2%)	p
Biodemographic data			
Age (years), *n* (%)			.001
<65	58 (36.8)	55 (11.3)	
65–75	62 (38.8)	125 (25.7)	
>75	40 (25.0)	306 (63.0)	
Sex (male), *n* (%)	105 (65.6)	298 (61.3)	.329
Comorbidities			
Hypertension *n* (%)	92 (57.5)	424 (87.2)	.001
Diabetes, *n* (%)	57 (35.6)	133 (27.4)	.047
Previous stroke, *n* (%)	32 (20.0)	105 (21.6)	.185
Previous bleeding, *n* (%)	9 (5.6)	92 (18.9)	.001
Abnormal kidney function[a], *n* (%)	13 (8)	26 (5)	.055
Antithrombotic treatment			
Treatment before admission, *n* (%)			–
Acenocoumarol	2 (1.2)	268 (55.1)	
Edoxaban (60/30 mg)	0	17/8 (3.5/1.6)	
Dabigatran (150/110 mg)	0	12/7 (2.5/1.4)	
Apixaban (5/2.5 mg)	0	16/10/ (3.3/2.0)	
Rivaroxaban (20/15 mg)	0	19/10/ (3.9/2.1)	
Treatment during hospitalization, *n* (%)			–
Acenocoumarol	1 (0.6)	5 (1.0)	
Edoxaban (60/30 mg)	0	217/16 (44.6/3.3)	
Dabigatran (150/110 mg)	0	42/15/ (8.6/3.1)	
Apixaban (5/2.5 mg)	1/0 (0.6/0)	40/5 (8.2/1.1)	
Rivaroxaban (20/15 mg)	10/ (0.6/0)	14/0 (2.9/0)	
LMWH	150 (93.8)	131 (27.0)	
Fondaparinux	1 (0.6)	0	
None	5 (3.1)	1 (0.2)	

Abbreviations. AF, Atrial fibrillation; LMWH, Low molecular weight heparin. [a]Estimated glomerular filtration rate < 30 ml/min/1.73 m^2.

Table 2. Outcomes during the follow-up according to the presence of AF.

	No AF ($n = 269$; 40.3%)	AF ($n = 399$; 59.7%)	p
Events during hospitalization			
Major bleeding, *n* (%)	2 (0.7)	45 (11.3)	<.01
Stroke/systemic embolism, *n* (%)	0	6 (1.5)	.16
Systemic embolism, *n* (%)	0	1 (0.3)	.81
Thromboembolic disease, *n* (%)	0	7 (1.8)	.13
Death, *n* (%)	15 (5.6)	82 (20.6)	.02
Death for COVID-19, *n* (%)	12 (4.5)	72 (18.0)	.02
Total events			
Major bleeding, *n* (%)	7 (2.6)	46 (11.5)	<.01
Stroke/systemic embolism, *n* (%)	0	6 (1.5)	.16
Systemic embolism, *n* (%)	0	1 (0.3)	.81
Thromboembolic disease, *n* (%)	1 (0.4)	7 (1.8)	.43
Death, *n* (%)	16 (5.9)	82 (20.6)	.036

Abbreviation. AF, Atrial fibrillation.

one patient that presented a major bleeding had to withdraw anticoagulant treatment and no cases of dose reduction were reported. During the follow-up, among AF population who had had major bleeding, 34 (72%) changed to dabigatran after the event and 7 (14%) did not change its treatment. After this last change, only one patient had bleeding and it was treated with LMWH. During hospitalization, compared to patients without AF, patients with AF had a higher risk of major bleeding (11.3% vs 0.7%; $p < .01$), COVID-19-related deaths (18.0% vs 4.5%; $p = .02$), and all-cause deaths (20.6% vs 5.6%; $p = .02$). During the entire study period, there were indeed differences between AF and non-AF groups in all-cause death (20.6% vs 5.9%; $p = .036$) and major bleeding (11.5% vs 2.6%; $p < .01$), but not in the risk of arterial/venous thromboembolic disease, nor stroke/systemic embolism (Table 2; Figure 1).

Among those patients who received full-dose anticoagulation from admission, there was a trend towards a higher risk of events in those patients with AF but did not reach statistical significance. By contrast, among those patients who received reduced-dose anticoagulation from admission, there were more all-cause deaths (63%vs 36%; $p = .001$) and major bleeding (81% vs 19%; $p = .002$), as well as deaths for COVID-19 in patients with AF compared to patients without AF. In the group of patients with AF, no differences in outcomes were observed among patients taking heparin vs other anticoagulants. On the contrary, in patients without AF, the risk of death was higher in non-anticoagulated patients (60% vs 12%; $p = .001$). During hospitalization, among patients with AF, 58 (11%) patients exhibited elevated transaminases 3 × ULN. Those patients with elevated transaminases had a greater mortality risk (30% vs 12%; $p = .01$).

In the multivariate analysis, age (HR 1.5; 95% CI 1.0–2.3) and elevated transaminases 3 × ULN (HR 3.5; 95% CI 2.0–6.1) were independently associated with all-cause mortality and age for COVID-19 related deaths (HR 4.6; 95% CI 1.7–12.7). Additionally, the history of AF was independently associated with the development of major bleeding (HR 2.2; 95% CI 1.1–5.3), after adjustment for gender, age, hypertension, diabetes, previous bleeding, thromboembolic and bleeding risk and anticoagulant treatment during admission (Table 3).The type of oral anticoagulant prior to admission (vitamin K antagonists vs direct oral anticoagulant and among patients taking direct oral anticoagulants: appropriate vs inadequate dosage) did not have an impact on outcomes.

Discussion

In this multicenter study, developed in a wide sample of hospitalized patients with COVID-19, compared to patients without AF, patients with AF were older and had more comorbidities. AF was associated with a higher risk of major bleeding, regardless anticoagulant treatment during admission. Age and elevated transaminases during hospitalization, but not AF nor anticoagulant treatment increased the risk of all-cause deaths.

Patients with severe COVID-19 infection have a higher risk of developing AF and this has been associated with a poorer prognosis. However, taking into account that patients with previous cardiovascular disease have a worse clinical profile, it is important to ascertain whether AF is independently associated with a higher risk of outcomes or it is just a marker of risk[23,24]. This is important, as AF is very common in hospitalized patients with COVID-19. For example, in an international study performed in 76 countries, around one out of five electrophysiology professionals that completed the survey reported cases of AF in this population[19]. Therefore, determining the best preventive approach to reduce the risk of further complications is warranted in these patients. In this context, our multicenter study provided relevant information that could be helpful to clarify this issue.

In our study, patients with AF were older and had more comorbidities, particularly hypertension and previous stroke.

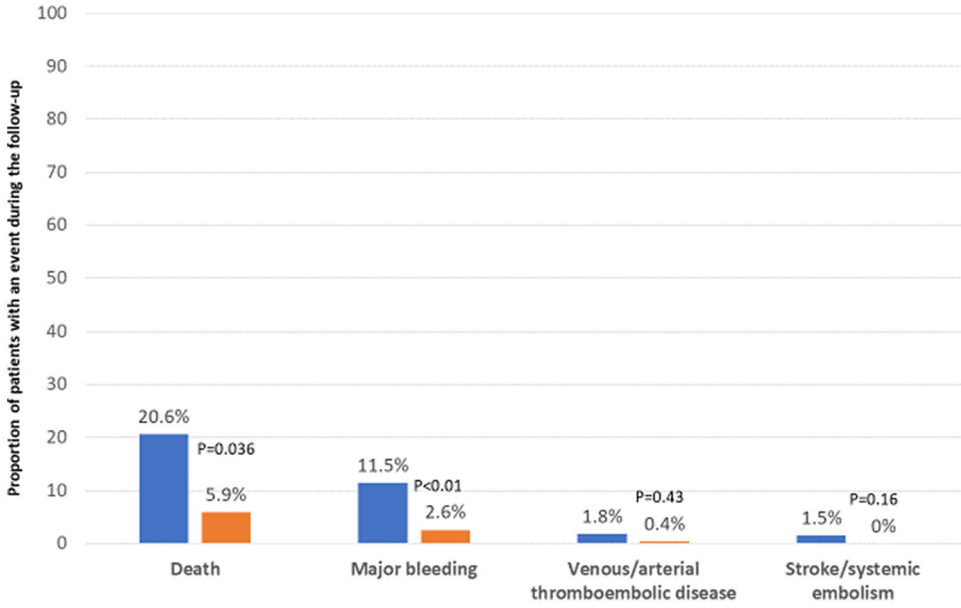

Figure 1. Outcomes during the follow-up in the overall study population, according to AF status. Abbreviation. AF, Atrial fibrillation.

Table 3. Predictors of all-cause death and major bleeding.

	HR	95% CI
All-cause death		
Age	1.5	1.0–2.3
Elevated transaminases 3 × ULN	3.5	2.0–6.1
Death for COVID-19		
Age	4.6	1.7–12.7
Major bleeding		
Atrial fibrillation	2.2	1.1–5.3

Abbreviations. HR, Hazard ratio; CI, Confidence interval; ULN, Upper limit normal.

Previous studies have shown that patients hospitalized for COVID-19 usually have many comorbidities and concomitant treatments, but this is even worse in patients with preexisting cardiovascular diseases, including the presence of AF[25–27]. Therefore, this is in line with our results.

With regard to antithrombotic treatment before admission, in our study, the majority of patients with AF were taking vitamin K antagonists (acenocoumarol). Previous studies have reported that prior oral anticoagulant use could be associated with worse clinical outcomes during COVID-19 hospitalization[28]. We specifically assessed this point according to the type of oral anticoagulant (vitamin K antagonists vs direct oral anticoagulant and among patients taking direct oral anticoagulants: appropriate vs inadequate dosage), but we did not find statistically significant differences between groups. It is likely that in this population it is more important the fact of being anticoagulated, rather than the type of oral anticoagulant. On the other hand in Spain, the introduction of direct oral anticoagulants has been slower than in other European countries due to the restrictions in the reimbursement, as it has been limited to some particular situations, because of the therapeutic positioning report from Spanish competent authorities[29]. Despite that, a decrease in the incidence of AF-related ischemic stroke has been observed during the last years[30]. In addition, during the COVID-19 pandemic, these restrictions have been reduced in order to avoid patients` risk infection, as no anticoagulation control is required with the use of direct oral anticoagulants[31]. As a result, the COVID-19 pandemic provided a window of opportunity to improve the antithrombotic management of patients with AF in Spain. In fact, during hospitalization, whereas LMWH was prescribed for thromboprophylaxis in the majority of patients without AF, in patients with AF, two-thirds were treated with LMWH, followed by direct oral anticoagulants, particularly edoxaban and dabigatran. This is very relevant, as some authors have reported that among patients with AF, previous treatment with direct oral anticoagulants, as well as treatment with these drugs during hospitalization for COVID-19 infection could play a protective role, reducing the risk of complications and death[32–34]. In addition, interruption of treatment with direct oral anticoagulants during admission could be associated with a higher risk of thromboembolic events and death, without reducing the risk of bleeding-related hospitalization[35]. Remarkably, our study showed that the most common antithrombotic therapy used in hospitalized patients were LMWH. Some authors and expert consensus have recommended the use of LMWH instead of oral anticoagulation in hospitalized COVID-19 patients, even in those patients previously treated with oral anticoagulants. This recommendation is well understood in the case of vitamin K antagonists, as anticoagulation control with these drugs markedly worsens during admission. However, in the case of direct oral anticoagulants this recommendation provided from the fact that some treatments for COVID-19 could increase the risk of side effects due to the risk of drug-drug interactions that may modify the blood concentrations of direct oral anticoagulants, leading to a reduction of the protective properties of these drugs or an increase of the bleeding risk[36,37]. However, this has not been confirmed in specific studies[38,39]. In addition, in our study no differences in outcomes were observed in patients taking heparin vs other anticoagulants. All these data suggest that direct oral anticoagulants can be safely used in patients hospitalized for COVID-19.

With regard to AF and the risk of outcomes, although in the univariate analysis, AF was associated with an increased risk of COVID-19-related and all-cause deaths, as well as major bleeding during hospitalization, in the multivariate analysis, AF was an independent predictor only for major bleeding, but not for other outcomes, including thromboembolic complications. Previous studies have reported that in hospitalized COVID-19 patients, AF (previously diagnosed and new-onset) was associated with a higher risk of thromboembolic events, major adverse cardiovascular events (MACE), deaths and longer hospital stay[13,40–42]. Importantly, our study showed that no more adverse events were observed among those patients who received full-dose anticoagulation from admission, but a higher risk of death among those patients who received reduced-dose anticoagulation. Therefore, considering the worse clinical profile of patients with AF compared with non-AF patients and the results of the multivariate analysis, our data strongly suggest that AF could be considered a risk factor in those patients not adequately anticoagulated, but a marker of risk in those who receive the proper anticoagulation, particularly when direct oral anticoagulants are used.

Additionally, AF was associated with an increased risk of major bleeding, and this was independent of the anticoagulant treatment. Other authors have also shown that AF patients admitted with COVID-19 represent a high risk population for bleeding[43]. Therefore, the use of those drugs, particularly direct oral anticoagulants, with a low risk of bleeding, even in elderly or frail patients should be promoted[44].

Treatment for COVID-19 may modify the risk of adverse outcomes in patients with AF. Thus, it has been reported that whereas AF may be associated with a higher risk of in-hospital mortality, the use of remdesivir could improve survival in this population, and this could be related with a better heart rate control, as remdesivir may cause bradycardia[45]. Unfortunately, we could not analyze this point, as the use of remdesivir in Spain at the moment of the study was low.

Finally, elevated transaminases were independently associated with overall mortality in our study. It has been reported that patients with severe COVID-19 are at high risk of hepatotoxicity, not only because of a direct effect of SARS-CoV-2, but also due to the risk of drug-drug interactions and drug-induced hepatotoxicity. In this context, not all drugs would provide the same clinical benefit, being dabigatran and edoxaban the oral anticoagulants with the higher benefit risk profile[38].

This study has some limitations. Due to the retrospective design of the study, data relied on the variables extracted from medical records, which were subject to missing values and could reduce the conclusions' validity. Thus, the history of prior heart failure was not available. In addition, although data about elevated transaminases were available at admission, 3 days and 7 days of hospitalization, we did not have these data before admission. There was a related variable (cirrhosis y/no) in the database. However, no patient had cirrhosis established. On the other hand, although the participation of more sites could have strengthened the study results, the number of patients enrolled was considerably high. Furthermore, the meticulousness of the data recorded, as well as the use of an electronic case report form could reduce potential biases. Finally, our results could be extended only to those patients with a similar clinical profile and healthcare.

Conclusions

In conclusion, among patients hospitalized with COVID-19, patients with AF were older, had more comorbidities and had a higher risk of major bleeding, independently of the anticoagulant treatment taken during hospitalization. Among those patients who received reduced-dose anticoagulation from admission, there were more all-cause deaths and major bleeding, as well as deaths for COVID-19, in patients with AF compared to patients without AF. By contrast, no differences in outcomes were observed in those patients taking full-dose anticoagulation. Age and elevated transaminases during hospitalization, but not AF nor the type of anticoagulant treatment increased the risk of all-cause death. This study allows to identify factors that may have an impact on outcomes, beyond AF and anticoagulation status in patients hospitalized with COVID-19. Further research are needed to determine whether these results can be extended to patients hospitalized due to pneumonia of other origin.

Transparency

Declaration of funding

Funded by the Fundación para la Formación e Investigación Sanitarias de la Región de Murcia, through an unrestricted grant from Boehringer Ingelheim (BI) Spain.BI had no role in the design, analysis, interpretation and publication of the registry. BI was given the opportunity to review the manuscript for medical and scientific accuracy as it relates to BI substances, as well as intellectual property considerations.

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Declaration of financial/other relationships

The author(s) meet criteria for authorship as recommended by the International Committee of Medical Journal Editors (ICMJE). The authors declare not other conflict of interests related to this article that those state in funding source section. Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Author contributions

All authors contributed extensively to the work presented in this paper. All authors have contributed significantly to the conception, design, or acquisition of data, or analysis and interpretation of data. All authors have participated in drafting, reviewing, and/or revising the manuscript and have approved its submission. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

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