Consequences of the poor anticoagulation control of patients with non-valvular atrial fibrillation treated with vitamin K antagonists

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Introduction

- AF is a disabling condition and causes up to 30% of strokes[1]. The prevalence of AF in Spain is 4.4% in people aged >40 years, and most of them suffer non-valvular AF (NVAF)[1-4].
- Vitamin K antagonists (VKA) are effective in preventing cardioembolic complications and have been traditionally used for the treatment of NVAF[5–10] .
- The use of VKA is subject to a high interpatient variability and external factors such as diet, weight changes, diseases, and concomitant medications may influence the coagulation status of patients[11–13].
- The clinical consequences of the poor anticoagulation control include a higher risk of cardiovascular events and deaths[14–17].

Objective

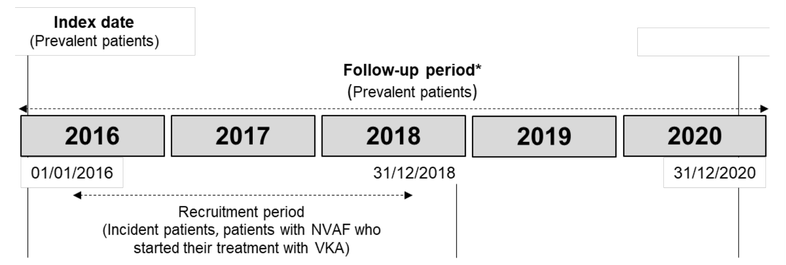
- This study aims to analyze the consequences of the poor anticoagulation control with VKA, in terms of thrombotic events, bleedings and mortality, in patients with NVAF in clinical practice in Spain.

Methods

Design of the study

- This is an observational, retrospective study based on the electronic medical records (EMRs) of the BIG-PAC database[13].
- EMRs undergo rigorous anonymization in the centers of origin, in compliance with Spanish regulations.
- The study considered patients with NVAF who started their treatment with vitamin K antagonists VKA between 01/01/2016 and 31/12/2018 (Figure 1).
  - The index date was the date of the initiation of the VKA treatment, and patients were followed up to 2 years from the index date.
- Poor anticoagulation control was defined using the method of Rosendaal, as having less than 65% of the time in therapeutic range (TTR) or the direct method, having less than 60% of the time in TTR, during the first 6 months of treatment.

Figure 1. Study design



*Patients were followed up to 2 years from the index date

Study variables

- Demographic characteristics, comorbidities, effectiveness, treatment patterns and healthcare resources utilization were analyzed. The results in prevalent patients were compared between, the anticoagulation treatment that led to their inclusion in the study.

Results

Characteristics of prevalent patients

- On average, prevalent patients were 70 years old and 48% of patients were male (Table 1).
- In general, patients with poor anticoagulation control had more comorbidities (2.7 vs. 2.9) and a higher Charlson comorbidity index (p<0.001 in both comparisons). However, the prevalence of comorbidities was similar in both groups, except for peripheral artery disease, which was more frequent in those with poor anticoagulation control (p<0.002).
- NVAF patients with poor control had more minor bleedings than those with adequate anticoagulation control (p<0.003), but a similar history of major bleedings (p=0.250) (Table 1).

Table 1. Characteristics of prevalent patients

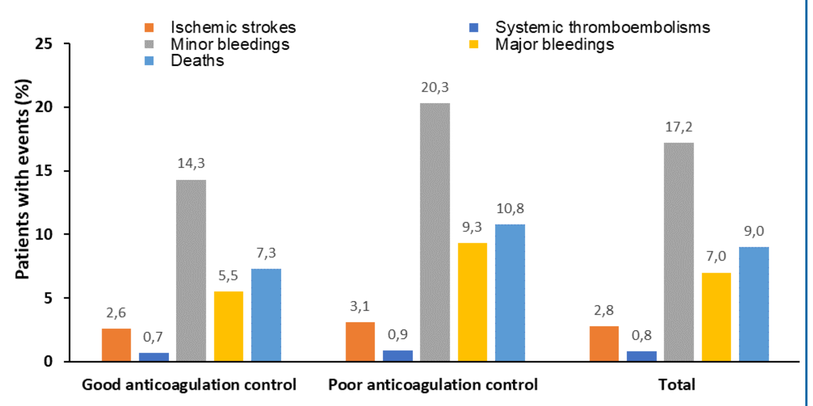
Study groups	Good anticoagulation control	Poor anticoagulation control	Total	p
Number of patients, n (%)	2351 (52.4)	2136 (47.6)	4487 (100)	
Age, years, mean (SD)	69.5 (11.4)	70.6 (7.9)	70.0 (9.9)	<0.001
Gender male, n (%)	1129 (48)	1012 (47.4)	2141 (47.7)	0.666
Scales				
CCI, mean (SD)	1.4 (1.4)	1.6 (1.5)	1.5 (1.5)	<0.001
$CHAS_2DS_2$-VASc, mean (SD)	2.6 (1.6)	3.4 (1.2)	3 (1.5)	<0.001
HAS-BLED, mean (SD)	2.8 (1.0)	3.4 (0.7)	3.1 (0.9)	<0.001
Patients per type of event*, N (%)				
Minor bleeding	159 (6.8)	195 (9.1)	354 (7.9)	0.003
Major bleeding	129 (5.5)	101 (4.7)	230 (5.1)	0.250

CCI: Charlson comorbidity index; SD: standard deviation.

Cardiovascular events and deaths

- Cardiovascular events were more frequent in patients with poor anticoagulation control than in those with adequate control (30.5% vs. 20.7%; reduction: 47.3%; p<0.001).
- Patients with poor anticoagulation control had more cardiovascular events vs. those with good control (p<0,001). Additionally, the mortality rate was also higher in patients with poor control than in those with adequate control (Figure 2).

Figure 2. Incidence of cardiovascular events and deaths



All comparisons Good anticoagulation control vs. Poor anticoagulation control are significant (p<0.05).

Treatment of the study population

- The time from diagnosis to the first prescription was similar in both study cohorts (12.8 years [SD: 23.3]), but the duration of the treatment was longer in those with adequate vs. poor anticoagulation control (Figure 3).
- Acenocoumarol was the most frequently prescribed anticoagulant drug (90.6%) and there were no differences in both cohorts of the study.
- The persistence to the anticoagulant therapy was higher in patients with adequate control (at 12 months: 57.8% vs. 49.3% and at 24 months: 43.8% vs. 34.9%; p<0.001 in both comparisons) (Table 2).
- The main causes of discontinuation were the incidence of new events (25.5%) and the switch of medication (15.4%).
- The use of concomitant drugs was similar in both study cohorts, at the index date and the end of the study, although patients with poor anticoagulation control received more lipid-lowering agents than those with adequate control.

Figure 3. Use of anticoagulant treatments and treatment durations

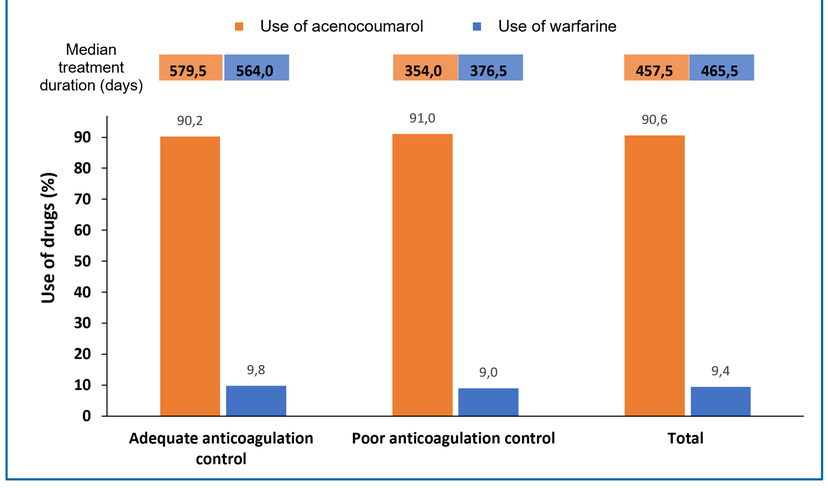


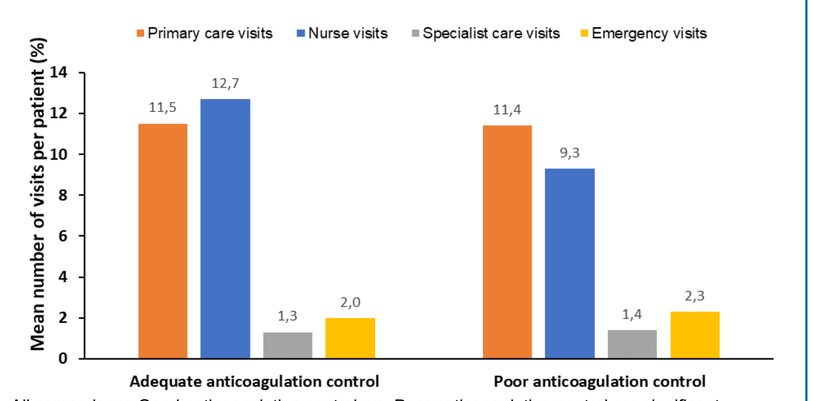
Table 2. Characteristics of prevalent patients

Study groups	Good anticoagulation control	Poor anticoagulation control	Total	p
Number of patients, n (%)	2351 (52.4)	2136 (47.6)	4487 (100)	
Discontinuation, (%)				<0.001
New events	20.7	30.7	25.5	
Medication switch	15.4	15.3	15.4	
Abandonment	13.4	9.1	11.4	
Mortality	6.7	10	8.3	<0.001
Persistence				
at 12 months, (%)	57.8	49.3	53.7	<0.001
at 24 months, (%)	43.8	34.9	39.5	<0.001

Use of healthcare resources in prevalent patients

- The attendance to medical visits (primary care, nursing, and specialist visits) are more frequent in patient with poor anticoagulation control (Figure 4).
- Patients with poor anticoagulation control required more and longer hospitalizations during the follow-up period (p<0.001 in both comparisons).
- The management costs of these patients amounted to €2,232 (SD: 2,340), being higher for patients with poor control (€2,477 [SD: 2,554]).
- It was observed that having an adequate anticoagulation control saved €455 per patient.

Figure 4. Medical visits in prevalent patients



All comparisons Good anticoagulation control vs. Poor anticoagulation control are significant (p<0.05), except for emergency visits (p=0.203).

Conclusions

Poor anticoagulation control in NVAF patients on treatment with VKA was associated with a higher incidence of cardiovascular events, such as major and minor bleedings, ischemic strokes and systemic thromboembolisms. These patients also required more healthcare resources and had higher management costs in comparison to patients with an adequate anticoagulation control. Therefore, the use of other therapeutic alternatives may improve the clinical outcomes in these patients, along with the reduction of the economic burden of NVAF for the National Health System.

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Disclosures

This study was sponsored by Pfizer Inc./Bristol-Myers Squibb. Dr. J. Comín-Colet reports fees as a coordinator investigator of this study by Pfizer and Bristol Myers Squibb. Antoni Sicras is an Atrys Health employee, CRO of the study. Inés Pérez is an Atrys Health employee, CRO of the study. Joel Salazar-Mendiguchía reports that he is a Bristol Myers Squibb employee and has BMS stocks. Isabel del Campo Alonso reports that she is a Bristol Myers Squibb employee has BMS stocks. Ainara Echeto reports that she is a Bristol Myers Squibb employee has BMS stocks. David Vilanova Larena reports that he is a Bristol Myers Squibb employee has BMS stocks. Dra. Olga Delgado Sánchez reports fees as a coordinator investigator of this study by Pfizer and Bristol Myers Squibb.

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