ORIGINAL ARTICLE

Study of Dabigatran Use in a Brazilian Public Hospital Specialized in Cardiology

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Abstract

Background: During its commercialization phase, unprecedented effects of new medicaments can be discovered. Dabigatran is an anticoagulant approved by Brazilian National Health Surveillance Agency in 2008.

Objectives: To assess safety, effectiveness adverse event profile and adherence to dabigatran (110 mg and 150 mg) prescribed for patients with non-valvular atrial fibrillation.

Methods: Patients taking dabigatran were subjected to interviews during the first year of treatment, evaluating the prescription depending on the dose, age, gender and risk factors as well as the prevalence of adverse events and the profile of the patients involved.

Results: Between the beginning and the end of the study there was a reduction in the number of subjects using this anticoagulant (10% for the dose of 110 mg and 30% for the dose of 150 mg), without changes in the proportions of individuals regarding to gender (men ≅65%), age (age <75 anos ≅80%), anticoagulation previous history (≅85%) and risk scores for thromboembolic (CHA2DS2 ≥ VASc = 2 ≅80%) and bleeding (HASBLED <3 ≅50% dose 110 mg and ≅85% dose 150 mg) events. The most common adverse event was dyspepsia (≥10%), regardless of gender, but less frequently in patients over 75 years of age (≅20% of cases). Dyspepsia related to dabigatran was mainly associated to its combination with beta-blockers (≅70%), but minoritarily with oral hypoglycemic (≅20%), antiplatelet agents (≅10%), proton pump inhibitors (≅30%) and antagonists H2 (≅3%). Therapeutic adherence was ≅60% regardless of the described adverse events. There were no cases of thromboembolic event and major bleeding.

Conclusions: Dabigatran has shown to be safe and effective in the evaluated conditions. (Int J Cardiovasc Sci. 2017;30(4):334-342)

Keywords: Pharmacovigilance; Anticoagulants; Thrombin; Atrial fibrillation.

Introduction

Atrial fibrillation is a supraventricular arrhythmia associated to several complications, such as systemic thromboembolism, which is responsible for the morbidity and mortality of patients with this arrhythmia. Therefore, treatment includes the use anticoagulants.[1-3]

Dabigatran etexilate, a prodrug, is quickly converted into dabigatran, an anticoagulant that directly and reversibly inhibits thrombin, impeding the conversion of fibrinogen into fibrin.[4-6] Doses of 110 mg and 150 mg of dabigatran etexilate, to prevent stroke in patients with atrial fibrillation, were approved by the FDA in 2010, and by the EMA and ANVISA in 2011.[7,8]

The development of new medication involves the synthesis of molecules with therapeutic potential that are submitted to pre-clinical tests in animals, and then to clinical studies in humans.[9-11] These are divided into four stages, the last of which encompasses post-marketing surveillance to map: adverse and rare effects or those which can only be observed in the long run;

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adherence to the treatment; and drug interaction.[12] In Brazil, dabigatran etexilate is not distributed by the Unified Health System (SUS), nor is it standardized in many hospitals, which hinders the monitoring of its use. Thus, the objective of the present study includes the assessment of safety, effectiveness, and adherence to dabigatran prescribed to non-valvular atrial fibrillation in a public Brazilian hospital, specialized in cardiology, by characterizing the profile of adverse events.

Methods

This pharmacovigilance study was observational, analytical, longitudinal and prospective, to evaluate effectiveness and safety and characterize adverse events associated to a 12-month use of 110 and 150 mg doses of dabigatran in outpatients with non-valvar atrial fibrillation. The drug was obtained with resources from the hospital where the study was developed upon a bidding process and after its insertion on the list of medications standardized by the Institution's Pharmacy and Therapeutics Commission.

The study started with 139 patients, of which 33 received 110 mg. Exclusion criteria included: pregnancy, age < 18 years, and the presence of a heart valve prosthesis. Data collection was done between January 2013 and December 2014 (CAAE 03455512.5.0000.5272). All participants, or legal guardians, signed a free consent form.

Monthly interviews were done, and data were analysed by trimester for the following factors: patients' age and gender, risk scores for bleeding events (HASBLED) and thromboembolic events (CHA_2DS_2-VASc), therapeutic associations, and adverse reactions observed after the beginning of the new anticoagulant pharmacotherapy.

Estimation on patient adherence to the use of dabigatran was done through the method of recording drug removal described by Obreli-Neto et al. (2011),[13] and patients considered as having adhered were those with an agreement level of 80 to 115%.

The study had a few limitations:

- Relatively short follow-up time, small sample for analysis and monitoring of patients in only one health unit;
- Deaths, suspensions, and withdrawals from the treatment;
- Lack of accessibility to data on events that took place outside the health unit since it does not have emergency care.

Statistical analysis

The descriptive statistical analysis was done through SPSS 22.0, with determination of absolute and relative frequency for categorical variables, thus determining a confidence interval of 95% and relative variation.

Results

Table 1 compares the profile of patients who joined the study to those who remained in it for at least one year of treatment with dabigatran. Most patients were under 75 years of age, and, in the case of the higher dose, most of them were male. Regarding risk scores, both the higher and the lower doses of dabigatran were prescribed especially to patients with a high risk of thromboembolic events, which was assessed by the score CHA_2DS_2-VASc. By analysing HASBLED, it was possible to see that the 150 mg dose was prescribed especially to patients at a low risk for bleeding. On the other hand, the frequency of 110 mg prescriptions was similar among patients with high and low risk of bleeding. By comparing the profiles of patients at the beginning and at the end of the study, we can observe that there was no variation of proportions. We can, however, see a reduction of approximately 30% of the number of individuals on anticoagulants in the 150 mg dose group, while that reduction is only of 10% in the 110 mg dose.

Analysis of the data about prescription frequency of 110 mg and 150 mg doses for patients over 75 years of age (Table 1) at the end of the study shows that the lower dose was prioritized for older patients (Relative variation = 0.31; CI – 0.11 – 0.91).

The most frequently reported adverse events during the monthly dispensing of dabigatran are shown in Table 2. It is noteworthy that, in general, dyspepsia was the highest occurrence, with a mean frequency above 10%, followed by minor bleeding. Additionally, we can observe a reduction of adverse events and of the number of patients who remained in the study with each trimester. However, specifically in the third trimester, the number of individuals on the 110 mg dose increased, while the use of the higher dose went down. In the fourth trimester, the number of patients on the 110 mg dose was maintained, while the number of those on the higher dose decreased again.

Table 1 – Comparison between the profiles of patients who entered the study and those who remained for the 1st year of treatment with dabigatran 110 and 150 mg

	Dabigatran 110 mg			Dabigatran 150 mg		
	Beginning of the study (N = 33)	End of the study (N = 30)	Relative variation (CI) Beginning x End	Beginning of the study (N = 106)	End of the study (N = 68)	Relative variation (CI) Beginning x End
Age Group						
< 75 years (%; N)	75.8% (25)	76.7% (23)	1.01 (0.77-1.33)	87.7% (93)	92.6% (63)	1.05 (0.96-1.16)
≥75 years (%; N)	24.2% (8)	23.3% (7)	0.96 (0.40-2.33)	12.3% (13)	7.3% (5)	0.60 (0.22-1.61)
Relative variation (CI) Age Group	0.32 (0.17-0.60)	0.30 (0.15-0.60)	–	0.14 (0.08-0.23)	0.08 (0.03-0.18)	–
Gender						
Female (%; N)	42.4% (14)	36.7% (11)	0.86 (0.47-1.6)	34% (36)	29.4% (20)	0.87 (0.55-1.36)
Male (%; N)	57.6% (19)	63.3% (19)	1.10 (0.74-1.64)	66% (70)	70.6% (48)	1.07 (0.87-1.31)
Relative variation (CI) Gender	1.36 (0.83-2.22)	1.73 (1.00-2.97)	–	1.94 (1.44-2.62)	2.40 (1.61-3.60)	–
CHA_2DS_2-VASc score						
0 – 1 (%; N)	12.1% (4)	16.7% (5)	1.38 (0.41-4.65)	21.7% (23)	26.5% (18)	1.22 (0.71-2.08)
≥ 2 (%; N)	87.9% (29)	83.3% (25)	0.95 (0.77-1.16)	78.3% (83)	73.5% (50)	0.94 (0.79-1.12)
Relative variation (CI) CHA_2DS_2-VASc	7.25 (2.89-18.33)	5.00 (2.21-11.31)	–	3.61 (2.48-5.25)	2.78 (1.82-4.23)	–
HASBLED score						
0 – 2 (%; N)	48.5% (16)	56.7% (17)	1.17 (0.73-1.87)	86.8% (92)	85.3% (58)	0.98 (0.87-1.11)
≥ 3 (%; N)	51.5% (17)	43.3% (13)	0.84 (0.50-1.42)	13.2% (14)	14.7% (10)	1.11 (0.52-2.36)
Relative variation (CI) HASBLED	1.06 (0.65-1.72)	0.76 (0.46-1.28)	–	0.15 (0.09-0.25)	0.17 (0.10-0.31)	–

CI: confidence interval.

Table 3 shows the profile of patients who reported dyspepsia. In general, most individuals were under 75 years of age and presented high risk for thromboembolic events and low risk for bleeding events. No difference was found between genders.

There was a positive correlation between the use of beta-blockers and the occurrence of dyspepsia, as well as an inversely proportional relation between the occurrence of this adverse event and dabigatran association to proton pump inhibitors, histamine H2-receptor antagonists, oral hypoglycemic agents, and antiplatelets (Table 4). The other reported therapeutic combinations did not influence the occurrence of this adverse event (data not shown).

Throughout the four trimesters, most patients adhered to the treatment (Table 5). The occurrence of dyspepsia and minor bleeding did not differ between those who adhered and those who did not. The percentage of individuals that adhered to the treatment was higher among those on dabigatran 110 mg, while in the fourth trimester, the percentage of adherence was higher among those on 150 mg.

No cases of major bleeding or thromboembolic event were recorded during the study.

Discussion

Although the profile of patients at the end of the treatment is similar to that of the beginning, we found a reduction in the total number of individuals on the medication due to treatment suspension or termination and deaths. Such reduction occurred mainly in the higher

Table 2 – Adverse events reported in each of the treatment's four trimesters

Adverse events	1º trimester		2º trimester		3º trimester		4º trimester	
	110 mg N=33	150 mg N=106	110 mg N=27	150 mg N=80	110 mg N=30	150 mg N=71	110 mg N=30	150 mg N=68
Dyspepsia								
% (N)	36.4 % (12)	44.3 % (47)	3.7% (1)	12.5 % (10)	0.0% (0)	16.9% (12)	10.0% (3)	10.3% (7)
IC	22.2-53.4	35.2-53.8	0.7-18.3	6.9-21.5	0.0-11.3	9.9-27.3	3.5-25.6	5.1-19.8
Vomiting								
% (N)	3.0% (1)	4.7% (5)	0.0% (0)	0.0% (0)	0.0% (0)	1.4% (1)	0.0% (0)	0.0% (0)
IC	0.5-15.3	2.0-10.6	0.0-12.5	0.0- 4.6	0.0-11.3	0.2- 7.6	0.0-11.3	0.0-5.3
Dyspnea								
% (N)	12.1 % (4)	4.7% (5)	7.4% (2)	6.2% (5)	10.0% (3)	1.4% (1)	10.0% (3)	1.5% (1)
IC	4.8-27.3	2.0-10.6	2.1-23.4	2.7-13.8	3.5-25.6	0.2- 7.6	3.5-25.6	0.3-7.9
Bleeding								
% (N)	15.1 % (5)	11.3 % (12)	3.7% (1)	10.0% (8)	6.7% (2)	9.9% (7)	13.3% (4)	5.9% (4)
IC	6.6-30.9	6.6-18.7	0.7-18.28	5.1-18.5	1.8-21.3	4.9-19.0	5.3-29.7	2.3-14.2
Edema								
% (N)	3.0 % (1)	1.9% (2)	0.0% (0)	2.5% (2)	3.3% (1)	2.8% (2)	10.0% (3)	2.9% (2)
IC	0.5-15.3	0.5- 6.6	0.0-12.5	0.7- 8.7	0.6-16.7	0.8- 9.7	3.5-25.6	0.8-10.1
Fatigue								
% (N)	6.1% (2)	6.6 % (7)	14.8% (4)	7.5% (6)	10.0% (3)	5.6% (4)	10.0% (3)	2.9% (2)
IC	1.7-19.6	3.2-13.0	5.9-32.5	3.5-15.4	3.5-25.6	2.2-13.6	3.5-25.6	0.8-10.1

CI: confidence interval.

Table 3 – Characterization of patients who presented dyspepsia associated to dabigatran use in each of the four trimesters of follow-up

Dyspepsia	1º Trimester		2º Trimester		3º Trimester		4º Trimester	
	110 mg (N = 12)	150 mg (N = 47)	110 mg (N = 1)	150 mg (N = 10)	110 mg (N = 0)	150 mg (N = 12)	110 mg (N = 2)	150 mg (N = 8)
Age Group								
< 75 years % (N)	83.3% (10)	82.9%(39)	100%(1)	90.0%(9)	0.0%(0)	100%(12)	100%(2)	75.0%(6)
≥75 years % (N)	16.7%(2)	17.1%(8)	0.0% (0)	10.0%(1)	0.0% (0)	0.0% (0)	0.0% (0)	25.0%(2)
Relative variation (CI)	0.20 (0.06-0.73)	0.20 (0.11-0.39)	ND	0.11 (0.17-0.72)	ND	ND	ND	0.33 (0.09-1.18)
Gender								
Female% (N)	58.3%(7)	42.5%(20)	100%(1)	10.0%(1)	0.0% (0)	33.3%(4)	0.0% (0)	50.0%(4)
Male% (N)	41.6%(5)	57.4%(27)	0.0% (0)	90.0%(9)	0.0% (0)	66.7%(8)	100%(2)	50.0%(4)
Relative variation (CI)	0.71 (0.32-1.63)	1.35 (0.89-2.04)	ND	9.00 (1.38-58.44)	ND	2.00 (0.82-4.89)	ND	1.00 (0.37-2.66)
CHA_2DS_2-VASc score								
0 – 1% (N)	8.3%(1)	17.1%(8)	0.0% (0)	20.0%(2)	0.0% (0)	33.3%(4)	0.0% (0)	12.5%(1)
≥ 2% (N)	91.7%(11)	82.9%(39)	100%(1)	80.0%(8)	0.0% (0)	66.7%(8)	100%(2)	87.5%(7)
Relative variation (CI)	11.00 (1.67-72.40)	4.87 (2.56-9.30)	ND	4.00 (1.11-14.35)	ND	2.00 (0.82-4.89)	ND	7.00 (1.10-44.60)
HASBLED score								
0 – 2% (N)	50.0%(6)	89.4%(42)	100%(1)	90.0%(9)	0.0% (0)	100%(12)	100%(2)	100%(8)
≥ 3% (N)	50.0%(6)	10.6%(5)	0.0% (0)	10.0%(1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
Relative variation (CI)	1.00 (0.45-2.23)	0.12 (0.05-0.27)	ND	0.11 (0.02-0.72)	ND	ND	ND	ND

CI: confidence interval; ND: not determinable.

Table 4 – Therapeutic associations to dabigatran in patients who presented dyspepsia in each of the four trimesters of follow-up

Dyspepsia	1º Trimester		2º Trimester		3º Trimester		4º Trimester	
	110 mg (N = 12)	150 mg (N = 47)	110 mg (N = 0)	150 mg (N = 12)	110 mg (N = 0)	150 mg (N = 12)	110 mg (N = 2)	150 mg (N = 8)
Hypoglycemic agent								
Yes% (N)	16.7%(2)	23.4%(11)	0.0%(0)	16.7%(2)	0.0%(0)	16.7%(2)	50.0%(1)	12.5%(1)
No% (N)	83.3% (10)	76.6% (36)	0.0%(0)	83.3%(10)	0.0%(0)	83.3%(10)	50.0% (1)	87.5%(7)
Relative variation (CI)	5.00 (1.38-18.17)	3.27 (1.90-5.62)	ND	5.00 (1.38-18.17)	ND	5.00 (1.38-18.17)	1.00 (0.14-7.10)	7.00 (1.10-44.61)
Antiplatelet agent								
Yes% (N)	8.3%(1)	10.6%(5)	0.0%(0)	40.0%(4)	0.0%(0)	8.3%(1)	0.0%(0)	12.5%(1)
No% (N)	91.7%(11)	89.4%(42)	100%(1)	60.0%(6)	0.0%(0)	91.7%(11)	100%(2)	87.5%(7)
Relative variation (CI)	11.00 (1.67-72.40)	8.40 (3.65-19.35)	ND	1.50 (0.60-3.73)	ND	11.00 (1.67-72.40)	ND	7.00 (1.10-44.61)
Beta-blocker								
Yes% (N)	75.0%(9)	59.6%(28)	100%(1)	80.0%(8)	0.0%(0)	91.7%(11)	100%(2)	62.5%(5)
No% (N)	25.0%(3)	40.4%(19)	0.0%(0)	20.0%(2)	0.0%(0)	8.3%(1)	0.0%(0)	37.5%(3)
Relative variation (CI)	0.33 (0.12-0.94)	0.68 (0.45-1.03)	ND	0,25 (0.07-0.90)	ND	0.09 (0.01-0.60)	ND	0.60 (0.21-1.70)
PPI								
Yes% (N)	8.3%(1)	23.4%(11)	100%(1)	40.0%(4)	0.0%(0)	16.7%(2)	50.0%(1)	12.5%(1)
No% (N)	91.7%(11)	76.6%(36)	0.0%(0)	60.0%(6)	0.0%(0)	83.3%(10)	50.0%(1)	87.5%(7)
Relative variation (CI)	11.00 (1.67-72.40)	3.27 (1.90-5.62)	ND	1.50 (0.60-3.73)	ND	5.00 (1.38-18.17)	1.00 (0.14-7.10)	7.00 (1.10-44.61)
Antagonist H2								
Yes% (N)	0.0%(0)	4.2%(2)	0.0%(0)	10.0%(1)	0.0%(0)	8.3%(1)	0.0%(0)	0.0%(0)
No% (N)	100%(12)	95.8%(45)	0.0%(0)	90.0%(9)	0.0%(0)	91.7%(11)	100%(2)	100%(8)
Relative variation (CI)	ND	22.5 (5.79-87.44)	ND	9.00 (1.39-58.44)	ND	11.00 (1.67-72.40)	ND	ND

PPI: proton pump inhibitors; CI: confidence interval; ND: not determinable

dose, considering also that, in some cases, there was a recommendation to switch to the lower dose of 110 mg.

At the end of the study, the proportion of patients over 75 years of age and on the 110 mg dose was larger in comparison to individuals of the same age on the higher dose. Some studies argue that elderly patients present a decrease in blood flow, kidney mass and function, leading to a reduction of creatinine clearance.[14,15] This, in turn, reflects the clearance of drugs eliminated through urine, such as dabigatran.[4,16] In around 67% of elderly individuals, kidney function decline relative to age was associated to the presence of cardiovascular diseases, among other risk factors.[17] In elderly patients, a great dispositional variability of drugs is particularly prominent; the complexity of interactions between comorbidity, polypharmacy, and changes related to age in drug pharmacokinetics and pharmacodynamics justifies the well-known aphorism: "start low, go slow".[17] Furthermore, age is taken into account for the calculation of the risk score for bleeding.[18]

Data shows that prescription and dose determination for the drug were given based on the risk for

Table 5 – Characterization of patients who did and did not adhere to the treatment with dabigatran in each of the four trimesters of follow-up

Trimester	1º (N=139)		2º (N=107)		3º(N=101)		4º (N=98)	
	% (N)	Relative variation (CI)	% (N)	Relative variation (CI)	% (N)	Relative variation (CI)	% (N)	Relative variation (CI)
Total								
Adherence	56.8% (79)	0.76	59.8% (64)	0.67	62.4% (63)	0.60	63.3% (62)	0.58
No Adherence	43.2% (60)	(0.60-0.96)	40.2% (43)	(0.51-0.89)	37.6% (38)	(0.45-0.81)	36.7% (36)	(0.43-0.78)
110 mg								
Adherence	15.8% (22)	0.50	17.7% (19)	0.42	20.8% (21)	0.43	16.3% (16)	0.87
No Adherence	7.9% (11)	(0.25-0.99)	7.5% (8)	(0.19-0.92)	8.9% (9)	(0.21-0.89)	14.3% (14)	(0.45-1.69)
150 mg								
Adherence	41.0% (57)	0.86	42.0% (45)	0.78	41.6% (42)	0.69	46.9% (46)	0.48
No Adherence	35.2% (49)	(0.64-1.16)	32.7% (35)	(0.55-1.10)	28.7% (29)	(0.47-1.01)	22.4% (22)	(0.31-0.73)
< 75 years								
Adherence	48.9% (68)	0.73	51.4% (55)	0.69	53.5% (54)	0.61	57.1% (56)	0.54
No Adherence	36.0% (50)	(0.56-0.97)	35.5% (38)	(0.50-0.95)	32.7% (33)	(0.44-0.85)	30.6% (30)	(0.38-0.76)
≥ 75 years								
Adherence	7.9% (11)	0.91	8.4% (9)	0.56	8.9% (9)	0.56	6.1% (6)	1.00
No Adherence	7.2% (10)	(0.40-2.07)	4.7% (5)	(0.19-1.60)	4.9% (5)	(0.19-1.60)	6.1% (6)	(0.33-2.99)
Female								
Adherence	19.4% (27)	0.85	16.8% (18)	0.89	19.8% (20)	0.55	18.4% (18)	0.72
No Adherence	16.5% (23)	(0.51-1.41)	14.9% (16)	(0.48-1.65)	10.9% (11)	(0.28-1.09)	13.3% (13)	(0.37-1.39)
Male								
Adherence	37.4% (52)	0,71	43.0% (46)	0.59	42.6% (43)	0.63	44.9% (44)	0.52
No Adherence	26.6% (37)	(0.50-1.01)	25.2% (27)	(0.40-0.87)	26.7% (27)	(0.42-0.93)	23.5% (23)	(0.34-0.79)
Dyspepsia								
Adherence	23.7% (33)	0.79	4.7% (5)	1.20	7.9% (8)	0.50	7.1% (7)	0.43
No Adherence	18.7% (26)	(0.50-1.24)	5.6% (6)	(0.38-3.81)	4.0% (4)	(0.15-1.61)	3.1% (3)	(0.11-1.61)
Minor bleeding								
Adherence	7.9% (11)	0.54	5.6% (6)	0.50	5.9% (6)	0.50	4.1% (4)	1.25
No Adherence	4.3% (6)	(0.21-1.43)	2.8% (3)	(0.13-1.95)	3.0% (3)	(0.13-1.94)	5.1% (5)	(0.34-4.52)

CI: confidence interval.

thromboembolic event and susceptibility to bleeding, respectively.[14] When the risks for stroke and hemorrhage are high, dabigatran seems to offer more clinical benefits than warfarin.[19] However, according to the study RE-LY,[14] the 150 mg dose of dabigatran determined hemorrhagic events in similar proportion, which may justify the inference. It is noteworthy that dabigatran was prescribed to some patients with a CHA_2DS_2-VASc below 2. According to Seno et al. (2014),[19] antithrombotic agents should only be administered under those circumstances, if the patients are male with a risk score of 1.

Adverse reactions to drugs are a type of adverse event considered non-avoidable and are always associated to patient harm.[20] According to Costa (2015),[21] adverse events are in general responsible for non-adherence and/or consequent therapy alteration, and are also related to treatment termination and medical suspension, according to reports. Minor bleedings are predictable adverse events in any anticoagulant treatment;[22] however, in the present study, its incidence decreased considerably throughout the trimesters. Regarding dyspepsia, its occurrence is also described in the literature in relation to dabigatran use, and that is associated to the drug's pharmaceutical formulation.[19] Gastric pH affects the solubility of some drugs and, therefore, their absorption when taken orally.[23] In the present case, the drug consists of hydroxypropylmethylcellulose capsules that hold tartaric acid granules coated with dabigatran etexilate. This medication was designed to promote an acidic microenvironment, favoring dissolution and absorption of the anticoagulant regardless of gastric pH variations.[24]

However, dyspepsia was less frequent among individuals over 75 years of age, which may highlight a mechanism that protects gastric mucosa, due to its atrophy in older patients, that leads to an elevation of the local pH.[25]

Proton pump inhibitors such as omeprazole are largely prescribed for conditions related to an increase in gastric acidity.[26] Some show the association between dabigatran and gastroprotective agents, not only proton pump inhibitors, but also histamine H2-receptor antagonists.[27,28] These therapeutic associations were also observed in the present work and may explain the reduction of dyspepsia occurrences.[27,28] However, changes in gastric pH may alter the drug's solubility, and proton pump inhibitors have proven able to decrease serum concentrations of dabigatran, even though the interaction is not considered clinically significant.[24] Apparently, such associations did not compromise the anticoagulant's effectiveness in the present study because no thromboembolic events were recorded.

Dyspepsia syndrome is expected with the use of antidiabetic[29] and antiplatelet agents, especially those that decrease the biosynthesis of prostaglandins.[30,31] Maybe because of that, patients on such drugs have not associated dyspepsia to the use of dabigratan, as described by Sherid et al. (2014).[32]

Tominaga et al. (2016)[33] reported the association between autonomic activity alterations and dyspepsia symptoms, concluding that Tofisopam, a phosphodiesterase inhibitor that elevates intracellular levels of cyclic nucleotides,[34] can help patients with functional dyspepsia. Since beta-blockers impede adrenergic receptor activation by endogenous agonists, thus decreasing cytosolic levels of cyclic nucleotides,[35] we can relate this mechanism to the higher prevalence of dyspepsia observed in users of this drug class.

In the present study, the occurrence of adverse events does not seem to have influenced adherence to anticoagulant therapy. Literature describes that emotional problems such as depression may be associated to a lack of treatment adherence, and that men are less susceptible to stress and alterations in mental health.[36] That may explain the higher percentage of adherence to treatment among male patients. The literature also suggests that, in general, older patients adhere less to drug treatments.[37,38] Indeed, the proportion of patients who adhered to the treatment was higher than that of those who did not among individuals under 75 years of age. The literature also suggests that the dose of the drug may impact on the patient's decision to adhere or not to a treatment, though the source of this conclusion is not available.[37] In this study, in the first nine months of follow-up, the percentage of those who did adhere to the treatment was higher among users of dabigatran 110 mg. However, in the fourth trimester, the percentage of adherence was higher among those on 150 mg.

Since there was no occurrence of major bleeding or thromboembolic events, this medication can be associated to safety and effectiveness, respectively.[19]

Conclusions

Dyspepsia was observed more frequently than mentioned at literature. The association of dabigatran with medication to protect the gastric mucosa seems to explain the reduction in frequency of this adverse event, while the use of beta-blockers seems to increase it. In this study, dabigatran proved to be safe and effective.

Author contributions

Conception and design of the research: Almeida FVS, Scaramello CBV. Acquisition of data: Martins LB. Analysis and interpretation of the data: Scaramello CBV. Statistical analysis: Scaramello CBV. Writing of the manuscript: Scaramello CBV. Critical revision of the manuscript for intellectual content: Martins ILF, Silva RM.

Potential Conflict of Interest

No potential conflict of interest was reported.

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