

Presence of Thrombus and Spontaneous Contrast in the Left Atrium of Patients with Atrial Fibrillation Anticoagulated with Dabigatran and Acenocoumarol

Presencia de trombo y contraste espontáneo en la aurícula izquierda en pacientes con fibrilación auricular, anticoagulados con dabigatrán y acenocoumarol

DANIEL A. CHIRINO NAVARTA^{†,1}, ROLANDO PALACIOS², MARIELA S. LEONARDI², GRACIELA TREJO², LORENA BALETTI¹, MARÍA L. RODRÍGUEZ VÁZQUEZ^{MTSAC, 1}, ROGELIO A. MACHADO^{MTSAC, 1}, CLAUDIO DIZEO¹

ABSTRACT

Background: Dabigatran (DAB) has shown similar efficacy to warfarin in the prevention of embolism in patients with atrial fibrillation (AF), but it should be administered with caution in elderly patients. Left atrial thrombus is an important marker of embolism.

Objectives: The aim of this study was to evaluate the presence of left atrial thrombus and spontaneous contrast in patients ≥ 65 years with persistent AF in planned electrical cardioversion, receiving DAB or acenocoumarol (AC) treatment, and to assess the occurrence of thromboembolic and hemorrhagic events at one-month follow-up.

Methods: Patients ≥ 65 years with persistent AF in planned electrical cardioversion and with DAB (110 mg or 150 mg b.i.d. in \geq or < 75 year-old patients, respectively) or AC treatment were prospectively included in the study. Transesophageal echocardiography prior to cardioversion examined for the presence of thrombus and spontaneous contrast in the left atrium. Secondary endpoints were cerebral or systemic thromboembolism and major bleeding at one month follow-up.

Results: A total of 101 patients were included in the study; 45 received DAB (23 at a dose of 110 mg and 22 at a dose of 150 mg) and 56 AC. Left atrial thrombus was found in 8.9% versus 19.6% [RR 0.45 (95% CI 0.15-1.32); $p=0.08$] and spontaneous contrast in 20% versus 44.5% [RR 0.44 (95% CI 0.23-0.86); $p=0.007$] of cases in DAB and AC groups, respectively. Two embolisms were registered at one month, both in the AC group ($p=0.3$) and 4 patients with major bleeding, two in each group ($p=0.5$).

Conclusions: Patients treated with DAB presented with less spontaneous left atrial contrast and lower trend of thrombus than patients with AC. No differences were found in the rate of embolisms and major bleeding at one-month follow-up.

Key words: Dabigatran, Coumarins, Atrial Fibrillation, Heart Atrial. Thrombus

RESUMEN

Introducción: El dabigatrán (DAB) ha demostrado una eficacia similar a la warfarina en la prevención de embolias en pacientes con fibrilación auricular (FA), pero debe administrarse con precaución en pacientes ancianos. El trombo en la aurícula izquierda es un marcador importante de embolias.

Objetivos: Evaluar la presencia de trombo en la aurícula izquierda y contraste espontáneo en la aurícula izquierda en pacientes ≥ 65 años con FA persistente en plan de cardioversión eléctrica que reciben tratamiento con DAB o acenocoumarol (AC). Evaluar además la presencia de eventos tromboembólicos y hemorrágicos al mes de seguimiento.

Material y métodos: Se incluyeron en forma prospectiva pacientes ≥ 65 años con FA persistente en plan de cardioversión eléctrica que se encontraban en tratamiento con DAB (dosis de 110 mg o 150 mg dos veces día en \geq o < 75 años, respectivamente) o AC. Se les realizó ecocardiograma transesofágico previo a la cardioversión en busca de presencia de trombo en la aurícula izquierda y contraste espontáneo en la aurícula izquierda. Fueron puntos secundarios las tromboembolias cerebral o sistémica y el sangrado mayor al mes.

Resultados: Se incluyeron 101 pacientes, 45 recibían DAB (23 con dosis de 110 mg y 22 con dosis de 150 mg) y 56 recibían AC. Se encontró trombo en la aurícula izquierda en el 8,9% versus el 19,6% [RR de 0,45 (IC 95% 0,15-1,32); $p = 0,08$] y contraste espontáneo en la aurícula izquierda en el 20% versus el 44,5% [RR de 0,44 (IC 95% 0,23-0,86); $p = 0,007$] en los grupos DAB y AC, respectivamente. Al mes se registraron 2 embolias, ambas en el grupo AC ($p = 0,3$) y 4 pacientes con sangrado mayor, dos en cada grupo ($p = 0,5$).

Conclusiones: Los pacientes con DAB presentaron menor contraste espontáneo en la aurícula izquierda y una tendencia a menor trombo en la aurícula izquierda que los pacientes con AC. No hubo diferencias en la tasa de embolias ni de sangrado mayor al mes de seguimiento.

Palabras clave: Dabigatrán - Cumarinas - Fibrilación auricular - Trombo en aurícula izquierda

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Address for reprints: Dr. Chirino Navarta, Daniel Agustín - La Rioja 951 - (1221) CABA, Argentina - e-mail: daniel.chirino@hotmail.com

^{MTSAC} Full Member of the Argentine Society of Cardiology

[†] To apply as Full Member of the Argentine Society of Cardiology

¹ Cardiology Service of the Dr. César Milstein Better Health Care Unit

² Coronary Care Unit of Dr. César Milstein Better Health Care Unit

Abbreviations

AC	Acenocoumarol	LA	Left atrium
AF	Atrial fibrillation	LAA	Left atrial appendage
BARC	Bleeding Academic Research Consortium	LAaVel	Left atrial appendage velocity
DAB	Dabigatran	LAT	Left atrial thrombus
ECV	Electrical cardioversion	SpLAC	Spontaneous left atrial contrast
INR	International normalized ratio	TEE	Transesophageal echocardiography

INTRODUCTION

Atrial fibrillation (AF) is the most frequent sustained arrhythmia, with a prevalence of 1.5 to 2% in the general population, that reaches 5%-15% in patients >80 years. (1, 2). Presence of AF is associated with a 5-fold risk of stroke and increased risk of heart failure and mortality. (3) Age is a significant risk factor both for thromboembolic events, (4) as for major bleeding associated to anticoagulant treatment. (5) Moreover, presence of left atrial thrombus (LAT) detected by transesophageal echocardiography (TEE) is also a potent stroke predictor. (6, 7)

It is well known that anticoagulant therapy with vitamin K antagonists (VKA) reduces significantly the risk of stroke in patients with non-valvular AF and increased bleeding. (8) In patients with >48-hour AF, anticoagulation is recommended for 3 or 4 weeks before attempting electrical cardioversion (ECV) to decrease the risk of stroke. (9, 10)

In the last years, new anticoagulants have been developed and approved for the prevention of AF thromboembolic events. (11) Dabigatran etexilate is a prodrug that converts to dabigatran, a direct thrombin inhibitor. (12) At doses of 110 mg b.i.d it has shown to be non-inferior to warfarin with lower risk of bleeding and at doses of 150 mg b.i.d. to be superior to warfarin with similar risk of major bleeding. (13). In patients undergoing ECV, dabigatran (DAB) was similar to warfarin in the rate of stroke and bleeding at one month. (14). Dabigatran should be administered with caution in elderly patients due to the risk of hemorrhage, mainly extracranial ones. (15)

The purpose of this work was to analyze for the presence of LAT and spontaneous left atrial contrast (SpLAC) in a population of patients >65 years of age in planned EC for AF, and with DAB or acenocoumarol (AC) treatment. In addition, the study evaluated for the presence of thromboembolic and hemorrhagic events at one-month follow-up.

METHODS

A prospective registry was performed from October 2012 to March 2015, including ≥65 year-old patients with persistent AF in planned ECV, followed-up by the Cardiology service of a hospital dedicated exclusively to the care of elderly patients. Inclusion criterion was at least 4 weeks of anticoagulant therapy. Patients were divided into two groups: those receiving DAB treatment and those receiving AC. Treatment assignment was performed according to the criteria of the

treating team. In patients receiving DAB, the dose was 150 mg b.i.d. in patients <75 years and 110 mg b.i.d. in those ≥75 years or with creatinine clearance between 50 and 30 ml/min. (15) The AC dose was adjusted to preserve International Normalized Range (INR) >2, performed by the Hematology Service of the hospital.

Inclusion criteria were patients with more than 48-hour AF evolution, who had started with follow-up by the Cardiology service of the hospital within one year prior to referral for ECV. Both hospitalized and ambulatory patients were included. Patients with history of AF and electrical or pharmacological cardioversion with a new episode of AF of >48-hour and <1 year evolution were also included, as well as patients with history of paroxysmal AF, who presented at the moment of ECV decision, episode of AF with >48-hour and <1 year progression.

Patients presenting with renal insufficiency with creatinine clearance <30 ml/min (assessed by the Cockcroft-Gault equation), low platelet count <100,000 per mm, patients with contraindications for anticoagulation, moderate or severe mitral valve disease, or with any other indication for anticoagulation (for example: valve replacement, pulmonary thromboembolism).

Transesophageal echocardiography was performed to all patients before attempting ECV in the echocardiography laboratory of our hospital. Philips HDI 5000 Sono CT equipment, with ATL MPT7-4 multiplanar transesophageal probe was used to look for the presence of left atrial and/or left atrial appendage (LAA) thrombus. Operators were blinded regarding the medication received by patients. The presence LAT and SpLAC was considered both for the LA as for the LAA. Left atrial thrombus was defined as the presence of an echogenic mass of uniform consistency, with different density from the atrial wall and pectineal muscles. Spontaneous left atrial contrast was the presence of echodense images, with a slow vortex motion similar to smoke, identifying them from "noise" images or artifact. (21) Patients not presenting LAT were admitted to the coronary care unit to undergo ECV and those with LAT did not undergo ECV and continued with the anticoagulant treatment they were receiving.

All patients were followed-up by medical interviews during the first month after TEE.

Primary endpoints were presence of LAT and SpLAC detected by TEE. Presence of cerebral or systemic embolic events was secondary endpoint, and major bleeding using the BARC classification was considered safety endpoint. (16) BARC 3 and 5 defined major bleeding and BARC 1 and 2 minor bleeding.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation and categorical variables as percentages. Student's t test or

the Mann-Whitnet test was used to compare DAB and Ac groups for continuous variables, according to normal or nonnormal distribution. Categorical variables were analyzed using Fisher's exact test. Relative risk (RR) for primary (LAT and SpLAC) and secondary (embolism and bleeding) endpoints, and their corresponding 95% confidence interval (95% CI) was calculated using Epi-Info 7 software package.

Multivariate logistic regression analysis was performed to establish primary endpoint LAT and SpLAC predictors using the CHADSVasc score, peal LAA velocity (LAAvel) and DAB treatment.

Kaplan-Meier survival analysis was performed for thromboembolism and major bleeding. The logrank test was used to compare AC and DAB groups during follow-up.

In all cases, a p value <0.05 was considered as statistically significant. Epi-Info 7 and Statistix 7 were used for statistical analyses.

Ethical considerations

The protocol was evaluated and approved by the Institutional Ethics Committee.

RESULTS

Among 140 patients referred for ECV, 125 were >65 years, EET could not be performed in 19 patients and 5 presented with clearance <30 ml/min; thus, 101 patients were included in the analysis. Forty-five pa-

tients received DAB (23 at a dose of 110 mg b.i.d. and 22 at a dose of 150 mg b.i.d.) and 56 AC, 29 of whom presented with INR ≥ 2 (52.7%) at the time of TEE. Mean age was 75 ± 6 years and 41.7% were women. Baseline characteristics are shown in Table 1. The group receiving DAB was more hypertensive (86.6% in the DAB group vs. 67.8% in the AC group, $p=0.02$), without differences in the rest of the variables. As expected, the DAB group presented with higher prothrombin time ($75 \pm 18\%$ vs. $23 \pm 11\%$, $p<0.0001$) and lower INR (0.95 ± 0.15 vs. 2.1 ± 0.5 , $p <0.0001$). Echocardiographic data are shown in Table 2. The DAB group presented with higher LAAvel (0.37 ± 0.16 m/s vs. 0.29 ± 0.12 m/s, $p=0.004$), with similar values for LAAAr (4.7 ± 1.5 vs. 4.3 ± 1.3) and LAAR (27.1 ± 4.5 vs. 28 ± 4.8 cm²).

The primary endpoint for LAT was present in 14.8% (15 patients), 8.9% (4 patients) of cases in the DAB group versus 19.6% in the AC group (11 patients) with RR of 0.45 (95% CI 0.15-1.32), $p=0.08$. Twenty percent of cases (9 patients) in the DAB group presented SpLAC versus 44.5% in the AC group (25 patients), with RR of 0.44 (95% CI 0.23-0.86), $p=0.007$.

Mean follow-up was 39 ± 8 days after TEE. Thromboembolism was present in 1.9% of cases (2 patients), both stroke in the AC group. Among them, one pre-

Table 1. Baseline characteristics of both groups of patients

	DAB (n=45)	AC (n=56)	p
Age	75 \pm 6	74.9 \pm 6	0.85
≥ 75 years - n (%)	23 (51%)	32 (57%)	0.3
Female sex - n(%)	19 (44)	26 (43)	0.54
Hypertension - n (%)	39 (86.6)	38 (67.8)	0.02
Diabetes - n (%)	7 (15.5)	11 (19.6)	0.39
Heart failure - n (%)	10 (22.2)	8 (14.3)	0.15
Previous stroke - n (%)	0 (0)	5 (8.9)	0.02
CHADS2 ≥ 2 - n (%)	29 (64)	32 (58)	0.66
CHADSVasc - n (%)			0.2
0-1	7 (15.5)	12 (21.4)	
2	12 (26.7)	10 (17.8)	
3-9	26 (57.8)	34 (60.8)	
HASBLED - n (%)			0.6
0	2 (4.4)	2 (3.5)	
1	7 (15.5)	13 (23.3)	
2	32 (71.1)	33 (58.9)	
3	4 (9)	7 (12.5)	
4	0 (0)	1 (1.8)	
Days of prior OAC (days)*	42 (32 - 50)	45 (39 - 49)	0.1°
CR CL (ml/min)	80 \pm 40	75 \pm 12	0.38
PT (%)	75 \pm 18	23 \pm 2	<0.0001
INR	1.0 \pm 0.2	2.1 \pm 0.5	<0.0001
Concomitant treatment			
ASA - n(%)	7 (15.5)	6 (10.7)	0.23
Clopidogrel - n(%)	0 (0)	2 (3.5)	0.25

DAB: Dabigatran, AC: Acenocoumarol. OAC: Oral anticoagulation. CR CL: Creatinine clearance. PT: Prothrombin time. INR: International Normalized Ratio. ASA: Acetylsalicylic acid. *: Median (interquartile range). °: Mann-Whitney test

sented LAT and both SpLAC. Conversely, major bleeding appeared in 4 patients (3.9%), two in each group (p=0.5) and minor bleeding in 8 patients (7.9%), three in the DAB group and five in the AC group (p=0.8). Among cases of major bleeding, three patients presented high digestive hemorrhage requiring blood transfusions; one of them, in the DAB group, died. He was classified as BARC-5A. A patient in the AC group presented intracranial hemorrhage. Table 3 shows primary endpoint and event results during follow-up.

Multivariate analysis

Multivariate analysis was performed for the presence of LAT and SpLAC, including LAAVel, CHADSVasc score and DAB treatment. Only the CHADSVasc score was independent predictor of LAT [OR 1.81 (95% CI 1.03-3.34), p=0.04] and SpLAC [OR 2.33 (95% CI 1.38-3.95), p=0.002]. Left atrial appendage velocity was predictor of SpLAC with OR 0.98 (95% CI 0.97-0.99), p=0.02. (See Table 4).

DISCUSSION

Our study is a registry evaluating the presence of LAT and SpLAC in a population of patients >65 years, with persistent AF in planned ECV, treated with DAB or AC. Average age was 75 years, almost 4 years older than that of the RE-LY study, which was 7.5 years (13) and 5 years older than the one of the National Danish Registry. (17) Moreover, in the recently published XIX

CONAREC registry of Argentina, population age was 73 years. (18)

We found a rate of LAT close to 15% and SpLAC of 33%. A study performed in our country, with 129 patients with AF of more than 48-hour evolution, submitted to TEE prior to ECV, found LAT in 16% of cases. (19) In that study, only 29% had INR ≥2, while in our study 51% was in that range. In addition, in the ACUTE study, evaluating the usefulness of TEE versus conventional treatment with warfarin prior to ECV, 14% of patients presented with thrombus. (6) The RE-LY substudy, (14) evaluating 1,270 patients undergoing ECV, 415 of whom underwent TEE, found LAT <2% and SpLAC around 26%. A study analyzing patients with AF referred for ablation, which were in anticoagulation range found 3.6% of thrombus occurrence. (20) Other studies have found around 10% of LAT prevalence. (21, 22)

In our population, patients under treatment with at least one month DAB presented with lower SpLAC than those receiving AC, without significant differences in LAT incidence. In the aforementioned substudy, (14) no significant differences were found in the rate of LAT with warfarin (1.8%) and with both doses of DAB (1.2% with 110 mg and 1.1% with 150 mg). Conversely, the DAB 150 mg group evidenced greater trend to lower SpLAC (21.2% vs.27.3% in the DAB 110 mg group and 31% in the warfarin group). Although age in our patients was almost 4 years older than in the RE-LY study, thromboembolic risk was similar

	DAB (n=45)	AC (n=56)	p
LVDD (mm)	50.3 ± 6	50.2 ± 5	0.9
LVEF <45% - n (%)	11 (24.4)	14 (25)	0.56
LAAr (cm2)	27.1 ± 4.5	28.0 ± 4.6	0.7
LAAAr (cm2)	4.7 ± 1.5	4.3 ± 1.3	0.3
LAAVel (m/seg)	0.37 ± 0.16	0.29 ± 0.12	0.02

DAB: Dabigatran. AC: Acenocoumarol. LVDD: Left ventricular diastolic diameter. LVEF <45%: Left ventricular ejection fraction <45%. LAAr: Left atrial area. LAAAr: Left atrial appendage area. LAAVel: Left atrial appendage peak velocity.

Table 2. Echocardiographic findings

	DAB	AC	RR	95% CI	p
LA thrombus - n(%)	4 (8.9)	11 (19.6)	0.45	0.15 - 1.32	0.9
SpLAC - n (%)	9 (20)	25 (44.6)	0.44	0.23 - 0.86	0.56
Embolism - n (%)	0 (0)	2 (3.4)	---	---	0.7
Major bleeding - n (%)	2 (4.4)	2 (3.5)	1.24	0.28 - 8.4	0.3
Minor bleeding - n (%)	3 (6.7)	5 (8.9)	0.74	0.18 - 2.95	0.02

DAB: Dabigatran. AC: Acenocoumarol. RR: Relative risk. LA: Left atrial. SpLAC: Spontaneous left atrial contrast. Embolism: Cerebral and systemic.

Table 3. Endpoints. Left atrial thrombus, spontaneous left atrial contrast and events at one-month follow-up

	LA thrombus			LA thrombus		
	OR	95% CI	p	OR	95% CI	95% CI
DAB	0.81	0.24 -3,6	0.8	0.57	0.19-1.6	0.19-1.6
Vel OI	0.99	0.98-1.01	0.12	0.98	0.97-0.99	0.97-0.99
CHADSVasc	1.81	1.03-3.34	0.04	2.33	1.38-3.95	1.38-3.95

LA: Left atrial. OR:Odds ratio. DAB: Dabigatran treatment. LAAVel: Left atrial appendage peak velocity.

Table 4. Multivariate analysis for left atrial thrombus and spontaneous left atrial contrast

(CHADS score ≥ 2 in almost 60% of patients in both age groups). In this study, more than 85% of patients presented CHADSVasc ≥ 2 , whereas the RE-LY study did not present this score. Prior anticoagulation time with AC was 45 days, and with DAB 42 days. In the RE-LY substudy more than 75% of patients with both DAB and more than 85% of patients with warfarin received treatment for more than 3 weeks prior to ECV.

The high rate of LAT found in the present study, mainly in patients with AC, might be explained by the low rate of INR ≥ 2 . Several studies have shown that insufficient anticoagulation is associated to higher rate of thromboembolic events (23, 24) and the presence of thrombus and SpLAC, (21, 22) Moreover, patients receiving DAB had better LAA function, evidenced by its higher peak velocity. Other studies have found that LAAVel is a predictor of LAT (25 26) and thromboembolic events. (27) In our study, LAAVel and the CHADSVasc score were predictors of SpLAC, but only CHADSVasc score was predictor of thrombus. This is in agreement with findings from other studies reporting CHADSVasc (19) and CHADS2 (21) as relevant LAT predictors.

Patients in the DAB group received 150 mg b.i.d. and 110 mg b.i.d. according to age $<$ or $>$ 75 years, taking into account the post-hoc RE-LY subanalysis. (15) For this reason they were analyzed together, without discrimination between doses. Our Society guidelines recommend a dose of 110 mg in patients above 80 years. (10, 29) Moreover, a recently published meta-analysis evaluating the efficacy and safety of new oral anticoagulants in patients >75 years, showed that the dose of 150 mg b.i.d. is associated to increased risk of gastrointestinal bleeding and a trend to major bleeding. (28) In our patients the rate of thromboembolic events was 1.9%, higher than that reported in the RE-LY study, (14) where the rate of events was $<1\%$ in all the groups. This could be due to the elevated presence of thrombus and SpLAC (both patients with events presented with one of the two situations). Various works have shown the association between LAT and embolic events. (6, 7, 30)

The rate of major bleeding was less than 5%, without difference between DAB and AC (4.4% and 3.5%). In the ACUTE trial, (6) the rate of bleeding at one month was 2.9% in the TEE group (with lower time of OAC) and 5.5% in the conventional group. In the RE-LY substudy, bleeding at one month was 1.7% in the DAB 110 mg group and 0.6% in the DAB 150 mg and warfarin groups. (14) The fact that our population is older than that of the RE-LY study might explain in part the enhanced bleeding. Age is one of the most important factors associated to bleeding in patients treated with DAB. (31) In the meta-analysis mentioned above, (28) the DAB 110 mg group presented with major bleeding similar to that of warfarin and the 150 mg group a trend to higher bleeding with significant increase in gastrointestinal bleeding. In the Danish registry (17) where more than 80% of patients

>75 years received doses of 110 mg DAB, bleeding with both DAB doses was similar to that of warfarin, with lower intracranial bleeding. Considering the efficacy-safety relationship, a conservative dose of DAB was used in our work showing that DAB was as safe as AC with lower SpLAC and a trend to lower LAT.

Limitations

This is a single-center study, where the use of DAB was registered in patients attending the Cardiology service. It is not a randomized clinical trial; therefore, there may have been biases, and results should be considered in this context. It is an observational study attempting to demonstrate management of this type of patient in our setting. It is a relatively small sample of a subgroup of patients >65 years, and hence there may have been an overestimation of the rate of events. There is no long-term follow-up, but it is adequate considering they are patients in planned ECV, where most events in this subgroup occur in the first month post ECV.

CONCLUSIONS

In our population of patients > 65 years with AF in planned ECV, patients treated with DAB presented with lower SpLAT and a trend to less LAT than patients treated with AC. At one-month follow-up, no differences were found in the rate of embolic events or in major bleeding with both treatments.

Conflicts of interest

None declared

(See authors' conflict of interest forms in the web/ Supplementary Material)

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