Current Status of Antithrombotic Therapy in Patients With Breast Cancer and Atrial Fibrillation

Estado actual de la anticoagulación de pacientes con fibrilación auricular y cáncer de mama

To the Editor,

Heart disease associated with cancer and cancer therapies is a growing concern for clinical cardiologists.[1] The European Guidelines for atrial fibrillation (AF) do not recommend differential treatment for cancer patients, and the same anticoagulation criteria are applied as for the general population.[2] The risk of embolism and bleeding can be altered by the presence of cancer, and the CHA_2DS_2-VASc and HAS-BLED risk scales have not been validated specifically in cancer patients.

There is limited evidence supporting use of direct-acting oral anticoagulants (DOACs) in cancer patients with AF. Pivotal trials of DOACs excluded patients with short life expectancy and those with thrombocytopenia (platelets $< 100\,000/\mu L$). Therefore, no specific data have been generated on the safety and efficacy of DOACs in patients with AF and cancer.

Breast cancer is highly prevalent and is often treated with chemotherapy, which has been associated with a higher incidence of AF. The prolonged survival of patients with breast cancer enables extended follow-up.

Our primary objective was to assess whether there are differences in time to onset of ischemic and bleeding events in patients with breast cancer and nonvalvular AF according to risk profile and antithrombotic strategy. Other objectives were to describe our sample and calculate the risk scores to assess their validity for predicting events.

This study was a retrospective, observational, multicenter study in 9 tertiary hospitals in Spain. Patients diagnosed with nonvalvular AF and breast cancer between January 2011 and January 2018 were included from oncology and cardiology clinics (regardless of cancer stage). Valvular AF and/or mechanical prostheses were exclusion criteria. The sample was compared with a cohort of women with AF but without cancer who consecutively attended cardiology clinics. In total, 465 women were included: 312 with AF and breast cancer (cancer cohort) and 153 with AF but no cancer (cancer-free cohort). The 2 groups were compared with the chi-square test or the Student *t* test for categorical or continuous variables with a parametric distribution, respectively. Survival was analyzed using Cox regression to determine the predictive power of the CHA_2DS_2-VASc and HAS-BLED scales in this population. Kaplan-Meier curves were used to compare time to ischemic or bleeding events in patients with cancer and cancer-free patients (Figure 1). Hazard ratios (HR) were analyzed with corresponding 95% confidence intervals (95% CI). Statistical analysis was performed with the SPSS program, version 22.

Clinical data were collected and the risk scores were calculated for both groups. Embolic events included stroke and thromboembolism. Bleeding events included intracranial or gastrointestinal bleeding, epistaxis, and the development of anemia.

The baseline characteristics of the patients are shown in the Table 1. Overall, 97.4% of the patients had an indication for anticoagulation,[2] although 15.5% of the cancer group and 11.3% of the control group were not receiving therapy ($P = .005$). The use of DOACs was lower in the cancer group (16% vs 25.3%, $P = .004$). During follow-up, 26.2% of the patients underwent a switch in antithrombotic treatment (from vitamin K antagonist to DOAC, 15.1%).

The presence of breast cancer was not associated with an increase in embolic or bleeding events. In the cancer group, 11% experienced an embolic event compared with 13.2% in the cancer-free group (log-rank test, 0.71; $P = .72$). In the cancer group, 15.9% experienced a bleeding event compared with 18.2% in the cancer-free group (log-rank test, 0.73; $P = .74$).

No differences were observed between groups in the predictive power of the risk scores. The CHA_2DS_2-VASc score was useful for predicting bleeding events (HR, 1.4; 95% CI, 1.2-1.6; $P < .001$). The discriminatory power, measured by the area under curve, was greater in the cancer group (0.69) than in the control group (0.53), with c-statistic values of 0.67 and 0.56, respectively. The HAS-BLED score was equally useful for predicting bleeding events in the 2 groups (HR, 1.5; 95% CI, 1.3-1.8; $P < .001$). The area under curve in the cancer group (0.67) and the cancer-free group (0.64) were similar whereas the c-statistic was greater in the cancer-free group (0.60 vs 0.75, respectively). These results are in line with similar studies.[3]

In the analysis by subgroups of the ROCKET study[4] and RELY study,[5] bleeding risk was 2 to 6 times higher in cancer patients. Breast cancer does not confer a particular tendency for bleeding, and in these studies, the few patients with cancer included those with

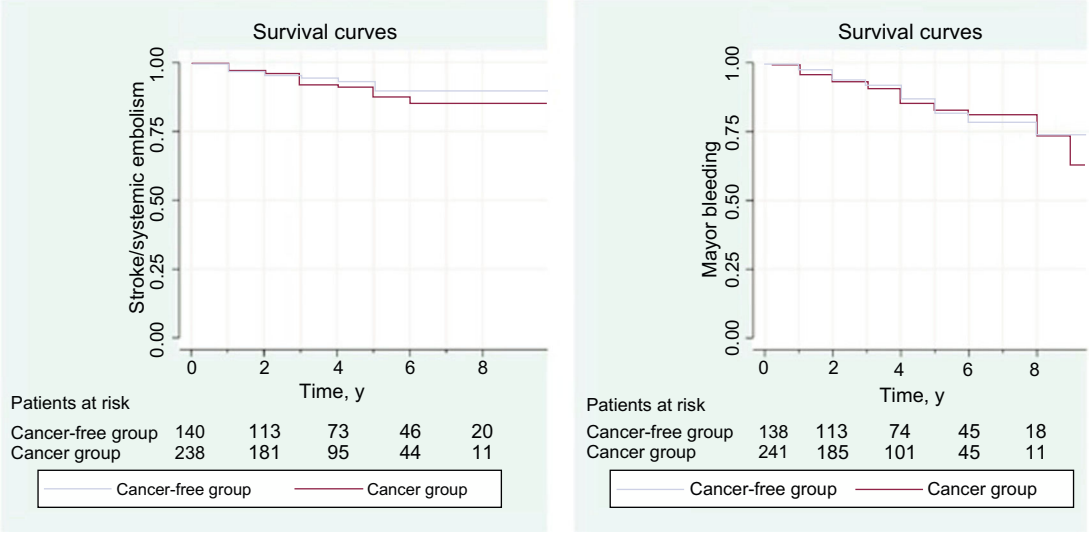

Figure 1. Kaplan-Meier curves for embolic and bleeding events.

Table 1
Baseline Characteristics of the Sample

	Patients With Breast Cancer	Patients Without Breast Cancer	*P*
Age at onset, y	74.17 ± 14.49	73.20 ± 13.46	.48
Duration of follow-up, y	2.98 ± 2.56	4.58 ± 3.51	< .001
Paroxysmal/persistent AF	46.5	47.7	.80
Permanent AF	53.5	52.3	.80
Hypertension	89.4	84.3	.11
Diabetes mellitus	31.1	33.3	.67
Current smoker	1.9	3.3	.52
Exsmoker	4.5	5.9	.52
History of myocardial infarction	6.1	20.3	< .001
History of heart failure	47.8	49	.79
History of stroke	14.1	12.4	.61
History of bleeding	10.3	12.4	.48
History of pulmonary thromboembolism	4.5	1.3	.77
History of vascular disease	4.8	11.1	.01
Liver dysfunction	11.9	2	< .001
Kidney dysfunction	22.1	20.3	.69
Labile INR	45.3	44.6	.91
CHA_2DS_2-VASc	4.48 ± 1.45	4.46 ± 1.54	.86
HAS-BLED	2.29 ± 1.21	2.32 ± 1.29	.79
ATRIA	7.24 ± 2.41	7.48 ± 2.72	.29
SAMETT2R2	2.21 ± 0.47	2.27 ± 0.60	.19
HEMORR2HAGES	2.70 ± 1.33	1.83 ± 1.37	< .001
Metastatic breast cancer	29.2		
Active chemotherapy treatment	15.38		
Hormone therapy	66.9		
Use of anthracyclines	21.8		
Use of taxanes	21.0		
Use of anti-HER-2 agents	12.2		
History of radiotherapy	53.5		

AF, atrial fibrillation.
Values expressed as percentage or mean ± SD.

other cancers such as colorectal cancer, which has a higher risk of bleeding.

Our study has several limitations, as it has an observational design, with data extracted from hospital records. Patients with more advanced cancer are less represented. The group of patients with AF without cancer was selected from cardiology clinics (and so may be subject to selection bias).

In conclusion, the presence of breast cancer was not associated with a higher incidence of embolic or bleeding events in patients with AF. A history of breast cancer did, however, point to worse antithrombotic treatment for patients with AF, that is, lower use of DOAC and a higher percentage of patients without anticoagulation despite having an indication for therapy. The CHA_2DS_2-VASc and HAS-BLED risk scores predict embolic and bleeding events (respectively) in patients with breast cancer and AF, with no differences in predictive power with the general population. These patients should follow the clinical guidelines for the general population in terms of anticoagulation.

FUNDING

Unrestricted grant from Abbott.

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Available online 28 September 2018

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https://doi.org/10.1016/j.rec.2018.06.037
1885-5857/

Classification of Pulmonary Arterial Hypertension by Genetic and Familial Testing

Clasificación de la hipertensión arterial pulmonar basada en el estudio genético y familiar

To the Editor,

Pulmonary hypertension is defined as a mean pulmonary artery pressure $\geq$ 25 mmHg. The pulmonary arterial hypertension (PAH) subtype of this condition is characterized by a pulmonary capillary pressure $\leq$ 15 mmHg and an increased pulmonary vascular resistance ($\geq$3 WU)[1]; untreated PAH has a poor prognosis due to right ventricular failure. Its causes include idiopathic PAH (IPAH), heritable PAH (HPAH), drug- or toxin-induced PAH, and PAH related to other causes such as congenital heart disease (PAH-CHD). It is called HPAH upon identification of a familial pattern or pathogenic mutation; *BMPR2* is the most frequently associated gene, found in up to 75% of patients with HPAH and 25% of those with IPAH.[1–3] Mutations in this gene can also favor the development of PAH in some congenital heart diseases.[4]

A genetic and family study was performed in 8 patients with PAH followed up in our center between 2013 and 2016. Our objective was to determine if the screening results would enable reclassification of the patients. The index cases were studied using massively parallel sequencing with a panel of 16 PAH-linked genes (*ACVRL1*, *BMPR1B*, *BMPR2*, *CAV1*, *EIF2AK4*, *ENG*, *FOXF1*, *GDF2*, *KCNA5*, *KCNK3*, *NOTCH3*, *RASA1*, *SMAD1*, *SMAD4*, *SMAD9*, and *TOPBP1*). Variants were considered pathogenic if they had an allelic frequency $<$ 0.01% in public databases and met the established pathogenicity criteria.[5] Pedigree charts were created and clinical and genetic screening was offered to first- and second-degree relatives.

The patients' characteristics and the genetic and family study results are detailed in Table 1. Of the 8 index cases studied, the family study allowed the identification of 2 patients with HPAH through a family history of PAH. The genetic study found pathogenic or probably pathogenic variants related to PAH in 4 patients: 1 of HPAH, 2 of IPAH, and 1 of PAH-CHD (the last 3 were later reclassified as HPAH). Only mutations in the *BMRP2* gene were detected, all previously described.

We genetically screened 14 relatives of the patients with a confirmed mutation, identifying 1 affected female carrier and 4 healthy male carriers (Table 1).

The following mutations were identified: *a)* case 1: female, 36 years old, classified as HPAH due to the identification of second-degree relatives with PAH; the *p.Cys34Phe* mutation previously described in another Spanish series[6] was found, confirming its cosegregation; *b)* case 2: male, 10 years old, with a small atrial septal defect and severe PAH-CHD disproportionate to the size of the defect; the *p.Arg491Trp* mutation was detected and the patient was considered to have dual-etiology PAH–incidental and hereditary congenital heart disease; the boy's mother had a ventricular septal defect, died during corrective surgery, and possibly had PAH; the maternal branch could not be studied because it did not reside in Spain (Figure 1); *c)* case 3: female, 41 years old, diagnosed with IPAH, with a pulmonary arteriovenous fistula $<$ 1 cm and no other typical findings of hereditary hemorrhagic telangiectasia; the cardiac output was greatly reduced, indicating that this finding had no clinical significance; because the *p.Trp13** mutation was detected in BMPR2 and no mutation was found in the genes related to hereditary hemorrhagic telangiectasia, she was reclassified as having HPAH; her father was not a carrier, and the presence of the mutation in the maternal branch could not be analyzed (Figure 1); *d)* case 6: female, 12 years old, with IPAH; because the *p.Asn442Thrfs*32* mutation was detected, she was reclassified as having HPAH (Figure 1).

Although the development of PAH has been linked to up to 21 genes,[2] our results are consistent with the literature and again show that *BMPR2* is the gene most frequently associated with PAH. Penetrance was higher in women and, due to hormonal factors, was often associated with delivery (cases 3 and 7) (Table 1).[1–3] In addition, a vasodilator response was more frequent in IPAH[6] (cases 5 and 7) (Table 1).

The European Society of Cardiology guidelines recommend the genetic screening of patients with IPAH, HPAH, hereditary hemorrhagic telangiectasia, and pulmonary veno-occlusive disease.[1,2] The genetic study of PAH-CHD patients has not been endorsed, although recent evidence shows its usefulness in this context.[4] Our series included 2 patients with PAH-CHD; 1 of these patient had a pathogenic mutation in *BMPR2*, which could indicate its diagnostic value in this subgroup, particularly when the PAH is disproportionate to the degree of the defect or when it develops after defect repair.

In conclusion, our results show that genetic and family screening of PAH enables the identification of hereditary forms and the correct classification of different subtypes, including patients with PAH-CHD with small defects. This approach not only bolsters disease management, but also genetic counseling in families, which can help to avoid transmission of the disease to offspring. For this reason, we believe that screening should be considered in routine clinical practice.